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A Holistic Review of COVID-19: Epidemiology, Pathogenesis, Diagnostic Innovations, and Future Treatment Approaches

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Abstract

COVID-19 is still a threat to global health since SARS-CoV-2 mutation and ongoing transmission across the globe. As Covid-19 moves from a pandemic response to an endemic, more research needs to be done in how to manage and develop response strategies for subsequent strains. The present paper offers an extensive literature review regarding the current state of knowledge about COVID-19 epidemiology and pathogenesis, with a focus on the new emerging strains of SARS-CoV-2 and the increasing trend of long COVID, or post-acute sequelae, after infection. Finally, the paper reviews the progress in diagnostics and detection, multiple RT-PCR, which is used to detect multiple genes in SARS-CoV-2 to increase the sensitivity and specificity of the test. Another form of antigen tests, the ELISA-based, used for identification of viral proteins in clinical samples, are also being considered for detection of COVID-19, as easy, quick, and inexpensive diagnostic option, especially in LMICs (low- and middle-income countries). The paper also reviews the present management measures and SARS-CoV-2 vaccine development. These range from discovering new antiviral agents, use of Monoclonal antibodies, modifications needed in vaccine composition as a result of the current emerging forms of the SARS-CoV-2 virus. Booster doses have been of great importance when it comes to continuing protection against variants that show immune escape like Omicron. In addition, more advanced cell therapies, including T-cell and stem cell therapies are in consideration as potential treatments of worse cases of COVID-19 in immunocompromised patients. Due to further mutation and unpredictable transmission patterns of the virus, the development and the actual rollout of vaccines, therapies, and diagnostics are needed to address the consequences of COVID-19 and any descendants. Therefore, the present study supports the hypothesis that the further advance of SARS-CoV-2 warrants a lasting qualitative continuation of investigation and the updating of data pertinent to COVID-19 to enhance the global control of the disease and lessening of infected populations' morbidity and mortality.

Keywords: SARS-CoV-2, SARS-CoV-2 variants, Diagnostic advances, post-pandemic, review

Introduction

Since the peak of the COVID-19 pandemic, there has been a noticeable decline in SARS-CoV-2 infectivity and related mortality rates. This progress is

largely due to public health interventions, medical advancements, and the widespread distribution of vaccines. However, the pandemic is far from over. The emergence of new SARS-CoV-2 variants, such as KP.2, KP.3, and LB.1, presents a serious



threat to global health (CDC, 2020). These variants often carry mutations that could increase their transmissibility, enhance their ability to evade immunity, or potentially reduce the effectiveness of existing treatments and vaccine (Chung *et al.*, 2024).

Additionally, a growing number of individuals are experiencing long-term health issues following recovery from the acute phase of the disease, a condition now commonly referred to as 'long COVID.' Symptoms of long COVID, such as persistent fatigue, respiratory difficulties, and neurological impairments, underline the extended impact of the virus on individuals and healthcare systems worldwide.

While early efforts in developing diagnostic tools, treatments, and vaccines were pivotal in combating the initial waves of the pandemic, the continued evolution of the virus challenges the efficacy of these measures. This highlights the need for ongoing innovation and adaptability.

This paper offers a detailed examination of COVID-19's progression, including advancements in diagnostics, detection techniques, and treatment approaches. It emphasizes the importance of continuous research and updated strategies to mitigate the risks posed by new variants and to better manage the current endemic situation. A vigilant and proactive response remains essential in addressing the long-term challenges of COVID-19 and safeguarding public health.

1. Epidemiology

a) Coronavirus

COVID-19 is an illness resulting from the SARS-CoV-2 virus which is a positive-sense single-stranded RNA virus (Tsang *et al.*, 2020). Coronaviruses are classified into four primary genera: Alpha

(α), Beta (β), Gamma (γ), and Delta (δ) all in lower case letters. Of all these, Alpha and Beta are of clinical importance since they are known to infect humans, while Gamma and Delta mostly infect birds. The experts began to think that Alpha and Beta coronaviruses jumped directly from bats, while Gamma and Delta coronaviruses developed from birds (Woo *et al.*, 2009).

Human coronavirus was first discovered in the mid-1960s with strains of the virus discovered later. To date, seven types of coronaviruses have been identified as having the ability to infect people. These include four common human coronaviruses: Four subtypes recognized include; the Alpha-coronavirus subgenus 229E and NL63 and the Beta-coronavirus subgenus OC43 and HKU1. These seasonally occurring common coronaviruses usually present upper respiratory tract infections, and may present as flu-like symptoms (Ogimi *et al.*, 2020).

However, there are three human coronaviruses that have a reputation for causing dangerous respiratory diseases. Due to scientific classification, they are the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), and SARS-CoV-2. All three are of the Beta genus. Among these pathogens, SARS-CoV-2, which causes COVID-19, seem to be particularly prominent owing to its ability to spread rapidly, high R₀, and ability to cause severe symptoms and death.

These aspects of coronavirus identification and pathogenicity offer core information on the animal-to-human transmission of this virus, its ability to spread and the different clinical presentation of the disease that is associated with it. Such knowledge is paramount in developing ways of managing, treating and preventing coronavirus associated diseases (Peiris *et al.*, 2003).

b) Origin of COVID-19

The COVID-19 can be traced from the last quarter of December 2019 when a number of pneumonia cases of unknown causes surfaced in Wuhan city, Hubei province, People's Republic of China. The first few cases were reported to be associated with the Huanan Wet Seafood Wholesale Market, which sale live animals such as bats and snakes and thus pointed to possibility of zoonotic transmission. First, the outbreak was believed to be caused by viral pneumonia and further studies pointed out that the culprit is the novel coronavirus, now known as SARS-CoV-2 because of its genetic and phylogenetic relationship with SARS-CoV which caused the 2002/2003 SARS epidemic (Ludwig et al 2020). When studying SARS-CoV-2, researchers assumed that it also spread from animals, and the contact with wildlife or consumption of animals could be the ways of transmission. This prompted the Chinese authorities to close wet markets considered unsanitary undertaking that constituted an initial measure to curb the epidemic (Horton *et al.*, 2020). However, the virus remained widespread and went from one being contained in specific geographical regions to being a worldwide pandemic.

COVID-19 cases started to increase earlier in the year 2020 globally thus being declared by the World Health Organization (WHO) a global health emergency. Thus, on March, 11, 2020 the WHO officially defined COVID-19 as a pandemic, and it became an important step generating various attempts to contain a virus presence and impact all over the world.

The Figure 1 shows the world's ten most affected countries by COVID - 19 up to 17 November 2024 based on the information provided to the WHO. In the United States there are 103 million cases while in China there are 99.4 million cases.

India is placed third to report 45 million cases. He explained that other countries with a high number of cases include France 39 million, Germany thirty eight point four million, Brazil thirty seven point five million, Korea thirty four point six million, Japan thirty three point eight million, Italy twenty six point eight million and United Kingdom and Northern Ireland twenty five million. These countries subsequently summarize the situation with the COVID-19 and its impact on the countries worldwide and it is rather negative (WHO, 2024).

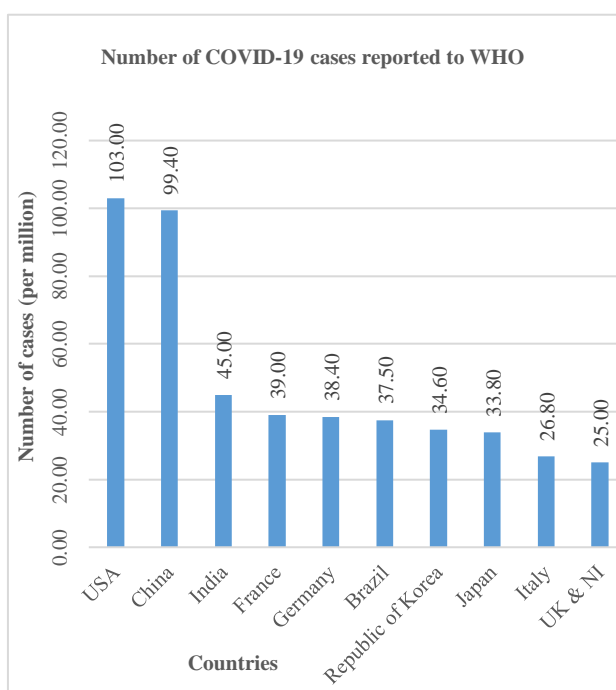


Figure (1): The top 10 countries having the highest number of cases reported to the WHO (cumulative total), as of 17 November 2024

c) Routes of Transmission

SARS-CoV-2, the virus responsible for COVID-19, is primarily transmitted through three major modes: droplets, aerosols, and large droplets that may result from direct or indirect contact. Keeping in view the role during pandemic, each mode contributes much in the transmission of the virus (Belser *et al.*, 2013).



In contact transmission, direct as well as indirect modes are involved. Direct contact transference is informed through the use of contact with body parts and mainly the ocular, auricular or buccal mucous membranes. This was especially quite evident among the health care givers during the pandemic to mention, because they were exposed to the diseases because of contact with their clients. Indirect contact transmission occurs in contact with viruses when an object with infected body fluids is considered as fomites. A person gets infected when he or she comes into contact with the virus on the surface and then touches his or her mucous membranes (Lu and Shi, 2020).

Aerosol transmission refers to a method by which small particles filled with the virus are dispersed through the air. These particles result from actions such as coughing, sneezing, speaking, or even breathing and can remain in the air for longer hours in shut environments, hence posing a great spread of the virus. They found that SARS-CoV-2 can survive in the aerosol form for up to three hours. Correct the chimneying and the air conditioning with good quality filters will help in minimizing the chances of the long range aerosols (Chen *et al.*, 2021).

Droplet transmission takes place through those large droplets that are produced when an individual coughs or sneezes. These droplets usually are emitted short distances and can infect those nearby when one inhales or swallows such droplets. A physical distancing of at least 1.5 meters has been proposed as suitable measure to prevent transmission through this mode. Knowledge of these modes has been valuable in formulating measures to constrain COVID-19 infections within communities (Chen *et al.*, 2021).

d) SARS-CoV-2 Variant

The new coronavirus SARS-CoV-2 is an RNA virus (Denison *et al.*, 2011), which produces a relatively high rate of mutations due to mistakes during replication. Hence, the character produces changes now and then which include the appearance of new strains of the virus. Such last ones are capable of rising the virus's infectivity, transmissibility or ability to evade an immune system. In Shuaibi (2021), the author described five primary types of Covid-19 major variants of concern between 2020 -2022 with unique qualities and consequences.

There are various examples, including the Delta variant, which manifested a rather significant rising in the capacity to overcome neutralizing antibodies (Mlcochova *et al.*, 2021). These antibodies are normally found in those who previously had the COVID illness or those who received the vaccine. This led to increased infections, this time even affecting partially immune groups – this was a new challenge in controlling Covid-19 as the virus persists to mutate.

These mutations prove the need to study these new strains because they inform future course of action for public health interventions as well as the development of vaccines. It also places a lot of importance on the need to work together with other countries in genomic sequencing and research with the view of counter adapting to the virus. Learning how these mutations affect the virus's functions remains central when combating COVID-19 to date.



WHO Label	Pango Lineage	First Outbreak	Number of Cases Worldwide
Alpha	B.1.1.7	United Kingdom	11,41,525
Beta	B.1.351	South Africa	35,651
Gamma	P.1	Brazil	73,495
Delta	B.1.617.2	India	2,88,894
Omicron	B.1.1.529	South Africa	1,895*

Table (1): Five WHO-Labelled Parent Lineage Variants of Concern During 2020–2022 (outbreak.info, 2024)

As new subvariants of SARS-CoV-2, including XBB.1, BA.2.86.1, and JN.1, appear on the scene, COVID-19 has become less deadly than initially feared (Planas *et al.*, 2024). Vaccination has been instrumental in lowering not just the intensity but also the death toll arising from COVID 19. Some through vaccination and others by experiencing the disease, such measures have phased out mortality rates in a step-down formation over the years. Vaccination for instance has been seen to reduce the death toll which has been declining since the first raise of the pandemic (Haider *et al.*, 2023). In addition, the broad variety of diagnostic techniques has advanced and new therapeutic approaches developed to contain the virus and lessen the prevalence of the disease.

Ever since May 5, 2023, The WHO announced that COVID-19 no longer qualifies as Public Health Emergency of International Concern (WHO, 2024). This shift was to open a new phase of long-term management and containment of covid-19. Moreover, due to the ongoing mutations, new types of SARS-CoV-2 virus appear annually. By June 5, 2024, three variants of interest (VOI) has been recognized globally and they are EG.5, BA.2.86 and JN.1 and all the variants originated from the Omicron lineage (B.1.1.529). No Omicron variants were defined as VOCs in 2023 and 2024 as compared to the period 2020–2022, suggesting a reduced capacity of VOCs to

cause significant public health interventions (WHO, 2023). There are mutations that change the pathogenicity of the virus, its ability to invade new susceptible populations and its effect on vaccines, and can propagate across countries (WHO, 2023). Unlike previous VOCs, most Omicron sub-lineages primarily infect the upper respiratory tract, not the lower respiratory tract. Pulmonary diseases especially LRI are generally severe because they may cause pneumonia or affect lung function (Rodriguez *et al.*, 2016).

The new Omicron variants expected to be dominant in America are KP.2, KP.3, and LB.1, all derived from JN.1 (CDC, 2020). These variants are also under observation, because the new mutations may lead to changes in either the severity of the disease, the rate of transmission, or the effectiveness of vaccines. The CDC also proving its proportionate conclusions that by June 2024, at least seventy percent of the total COVID-19 patients will correspond to KP.2, KP.3, and LB.1. Sequence comparison of these variations suggests that KP.2 and KP.3 have evolved the new substitution in the spike protein, LB.1 and KP2.3, have substituted mutated and deleted thirty first position of the spike protein (Kaku *et al.*, 2024). Work employing Lentivirus-based pseudo-virus assays and neutralization tests reveal that these mutations improve

immunodominance and, in certain instances, promotion of pathogenicity. Interestingly, LB.1 and KP.2.3 that has resulted from this lost segment exhibited increased ability to evade the immune response and therefore Still, these variants may pose a significant threat to efforts to manage the current pandemic.

e) SARS-CoV-2 Updated Infection and Mortality Trends in Different Regions

The new COVID-19 cases reported to the WHO from February to November 2024 also depict a shift in the regions obviously due to changes in pandemics behaviour as well as course and measures undertaken to restrict it in a particular region (WHO, 2024). In Africa, actual reported cases of COVID-19 reduced from 501 cases recorded on February 4, 2021, to 78 cases recorded on 3rd of November, 2021, although there are slight variations in the confirming trend (WHO, 2024). The epidemic cases in the Europe was also sawed and saw surge, in February, saw 51,700 then in may saw 16,500 then again rose and in October saw highest 75,400 then in November saw 37,900. The Americas region dipped significantly in the first months – from 21,700 reported in February to 2,100 in May, while the new cases stagnated between 1,200 and 2,800 in the following months. South-East Asia was also low with its record of the number of cases, beginning with 2,700 in February, creeping down to 518 in October then rising slightly in November to 622. The Western Pacific region was also generally downward with cases falling from 23 400 in February to 1500 by November. These trends give a picture of the various trends arising from different regions' vaccination success, measures employed, and the new strains that arise. Higher rates in Europe over the past month demonstrated that focus on new outbreaks can be regional, whereas consistent reduction of daily cases

in Africa and the Western Pacific indicates successful suppression measures can be taken. It therefore becomes important to understand these patterns in order to guide the on-going pandemic management and the specific response in a particular region (WHO, 2024).

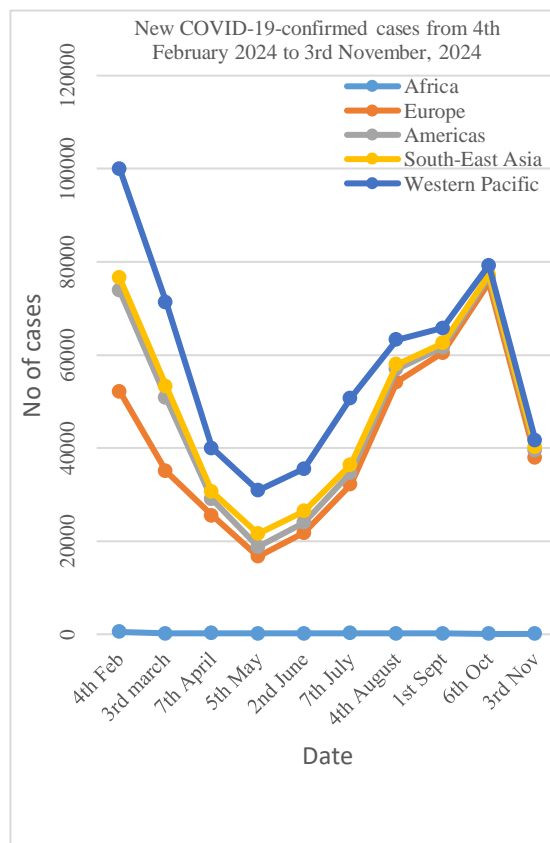


Figure (2): New COVID-19-confirmed cases from 4th February 2024 to 3rd November, 2024

SARS-CoV-2 Updated Mortality Trends

Daily mortality of SARS-CoV-2 from February to November 2024 WHO report demonstrates the geographical differences of the pandemic (WHO, 2024). It is important to mention that the fact reported deaths in Africa were low and constant all year long starting with two in February and went down to zero in September with better control of the disease and control measures.

In Europe, drastic change in the death rate was recorded from 448 deaths in February and 82 in May. This was however succeeded by a rise to 277 in the month of



August and despite dipping to September, subsequent months data showed more than 230 deaths signifying the persistent threat of new variants and possible seasonality.

The region where the worst hit by initial fatalities was the America that showed 1,900 deaths in February but a decline to 358 in June. But it had a spike in August with 1,000 deaths, and again a steep drop again to 575 in November. Such variation persists because of SARS-CoV-2 in the region, even with increased public strategies regarding health.

In South-East Asia the reported deaths were pegged throughout, reducing gradually from 30 in February to 2 in

November as evidence of regional positive pandemic management measures. Likewise in the Western Pacific region, there were steady decrease up to 11 deaths in October with a surge to 14 in November but generally, lowest mortality (WHO, 2024).

These patterns show differential mortality trends by region depending on the vaccination levels, available health care capacity and containment strategies in relation to new variants. The global mortality rates have gradually reduced but occasional milestones in some area reinforce the need for constant surveillance and effective intervention measures program.

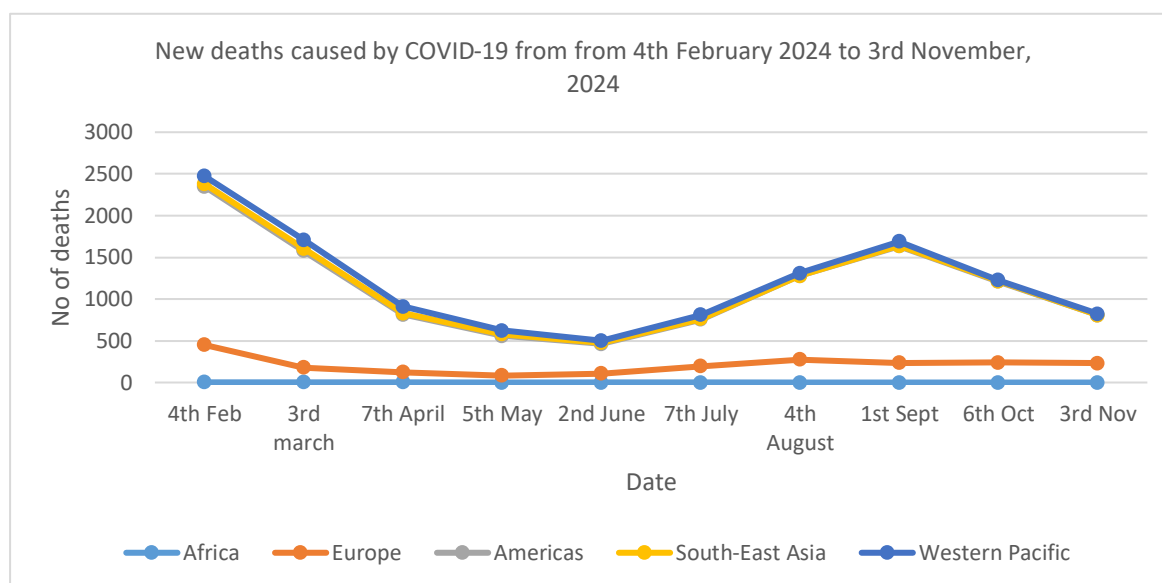


Figure (3): New deaths caused by COVID-19 from 4th February 2024 to 3rd November, 2024.

f) SARS-CoV-2 New Transmission Pattern

The practice is to measure wastewater viral activity in India as it helps identify new infectious diseases such as COVID 19. The move helps health authorities to understand how the SARS-CoV-2 virus is spreading in communities. Figure 4 presents the national trend of SARS-CoV-2 viral precursors in wastewater of Ahmedabad, India along

with the active COVID-19 cases. Two critical metrics are tracked: The two lines on the graph represent cases among active patients (blue line above) and RNA copy levels in the wastewater (red line below). Higher peaks in active case counts can be observed to have a strong positive correlation with rises in wavelengths of RNA in wastewaters proving the existence of a relationship between covid 19 viral genetic material in wastewaters and the number of confirmed cases in the

community. This concern is exemplified by active cases of contagious diseases, which reached a peak in September 2022 and fell afterwards, compared to the over 125000 cases. Outburst two was smaller than the first one and occurred in the last week of July 2022, while another peak in RNA activity was identified in April 2023. Eventually, numerical values of active cases and RNA copy levels decreased, with low viral activity in the course of the

studied period by mid 2024. These trends underscore why surveillance in sewage is an effective, nonintrusive, and low-cost solution to track emerging waves of COVID-19. These two trends are in congruence to the current lack of intense pandemic due to which both of the parameters have declined and thus corroborating the usefulness of WSM specifically in guiding the public health measures (CDC, 2020; WHO, 2024).

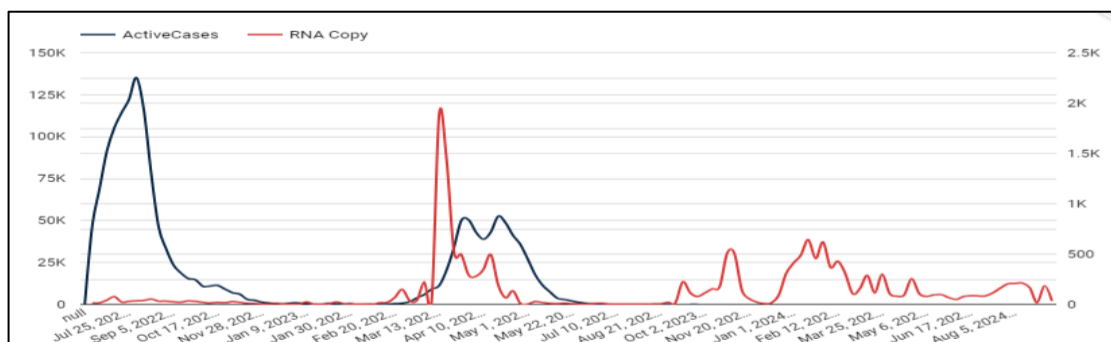


Figure-4: National trends of SARS-CoV-2 viral activity levels in wastewater from the India, Ahmedabad (accessed on 4th December, 2024).

g) SARS-CoV-2 Reinfection Rate

Infection with the same virus had been a worrying factor, even more so with the identification of omicron variants, which are highly infectious and can evade the immune system (Pulliam et al, 2022). Although the total reinfection probability with different variants of the virus is around 0.94 %, it was lower, at a level below 0.6 % until the discovery of Omicron (25). Currently, the reinfection rate has increased to 4.1% that comes from Omicron's multiple mutations particularly in the spike protein that led to the lowered neutralising antibodies. Some of these include mutation of the virus, and decline in immunity after sometime, and the fact that the virus can overcome defences from natural infection and even the vaccines. While vaccination, and more specifically with booster doses, and hybrid immunity help one a degree, still, they cannot shield a person from

reinfection. Higher reinfection rates with Omicron mean that there is a question of public health, having enough hospital beds, adapting testing and isolation measures. All these challenges point to the need for variant-specific vaccines and constant assessment of virus evolution in order to reduce the effects of reinfection (Chen *et al.*, 2024).

2. Pathogenesis

SARS-CoV-2, the virus responsible for COVID-19, is composed of four structural proteins: cleavage and polyprotein precursors, spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins (Akkiz *et al.*, 2021). Spike protein that is necessary for entering the host cells is composed of two major structural domains, S1 and S2. The S1 domain of the spike protein is responsible for the receptor binding and S2 domain is with the



membrane fusion of viral with host cells. In S1Domain, there is a large variation in the Receptor Binding Domain (RBD) that further binds with the host cell receptor. Because of the existence of similarity between SARS-CoV-2 and SARS-CoV, researchers were able to confirm that SARS-CoV-2 requires the receptor, angiotensin-converting enzyme 2 (ACE2) for host cell entry (Jiang *et al.*, 2020). TMPRSS2 helps in the cleavage of the spike protein to enhance membrane fusion and viral entry into the host cells. MERS-CoV prefers ACE2 and these have been reported in varying density in organs such as the lung, hear, kidneys and intestines etc and the region where the virus binds to ACE2 determines the symptoms manifested such as lung inflammation or myocarditis (Wu *et al.*, 2020).

The initial response of the whole organism to combat SARS-CoV-2 is inflammation. Viral entry is sensed by pattern recognition receptors, PRR, detecting pathogen-associated molecular pattern, PAMPs and leads to the release of pro-inflammatory cytokines such as IL-6 and chemokines such as CCL2. IFN-1 is an important element in antiviral activity: enzymes participate in the degradation of viral nucleic acids and proteins and perform the release of viruses. Still, through its non-structural proteins that interfere with signalling pathways while degrading mRNA for IFN-1, SARS-CoV-2 can suppress this response (Chen *et al.*, 2020).

One of the grave immunopathological reactions that occur in the course of SARS-CoV-2 disease include the cytokine storm characterised by elevated levels of IL-6. This is a common with the Acutely Ill clients and if not well managed; it can result in complications such as tissue damage and organs like the heart, liver and kidneys may fail. Macrophages involvement in cytokine storms is suggested by the direct binding of

the viral spike protein to ACE 2 receptors in the cells (Deng *et al.*, 2017).

Regenerative immune responses to SARS-CoV-2 consist of antibody synthesis and T-cell dependent cytolysis. CD4+ lymphocytes are involved in the humoral response and produce IgM, IgG and IgA antibodies. The neutralizing antibodies can also specifically target the S protein or RBD without entry into cells apart from inhibiting viral entry, it can also induce ADCV and ADP. CD8+ lymphocytes are engaged in the destruction of the infected tissues thus shed light on the importance of adaptive immune responses in the regulation of SARS-CoV-2 infection (Channappanavar *et al.* 2017; Zohar *et al.*, 2020).

i. Infection Stage of SARS-CoV-2

SARS-CoV-2 infection has been described in three phases according to the severity of COVID-19 it causes. First stage is the incubation period which starts right from a time an individual contracts the virus and the virus multiplies within the host. In this phase, people are usually asymptomatic and there is no clinical manifestation. The second stage is called the dissemination stage after onset of acute pneumonia and typical manifestations of the disease, such as cough and fever (Vetter *et al.*, 2020). In patients with chronic diseases, such as diabetes or cardiovascular disease, this stage can be accompanied by the development of hypoxia. In case of non-recovery, the disease goes through to the advanced third stage that is dominated by systemic hyper inflammation. This stage can cause multiple organ dysfunction particularly to the kidneys, liver and G.I tract (Mehta *et al.*, 2020; Gupta *et al.*, 2020).

Consideration of comorbidity in COVID-19 patients was attributed to higher death incidences. Co-morbidity means the



pre-existence of another disease apart from the main disease that is diagnosed in a patient. Symptoms of COVID-19 include fever, cough, sore throat, tiredness, chest pain or pressure, loss of smell or taste, difficulty breathing and confusion, muscle or joint pain, skin changes, high blood pressure, kidney problems, and diabetes (Singh *et al.*, 2021). They also greatly raise the risk for severe disease and mortality, because they increase ACE2 expression, thereby vulnerability and disease severity with SARS-CoV-2 infection. For patients with multiple comorbidity, or multimorbidity, are at even higher risk, with mortality rates that are double those of patients without the conditions (Agrawal *et al.*, 2021).

ii. Long COVID

i. Definition of Long COVID

Long COVID also called post-acute sequelae of SARS-CoV-2 infection (PASC) is a condition of ongoing symptoms, new symptoms, or worsening symptoms occurring four weeks or later following the initial phase of COVID-19 (Carfi *et al.*, 2020). These symptoms may persist for anything from weeks and months to years or even indefinitely and recipients continue to suffer from organ dysfunction and decreased quality of life. Long COVID refers to symptomatic COVID-19 within the 4–12 weeks' window and beyond the initial 12 weeks. Some present signs include; dizziness, weakness, general malaise, confusion, chest pain, joint pain and concentration difficulties. Long COVID symptoms can persist irrespective of the form and severity of the primary infection phase and is not limited to specific age demography (Greenhalgh *et al.*, 2020).

ii. Epidemiology of Long COVID

Diagnosis of long COVID also presents a problem due to the fact that it cannot be based on one's viral status because most of the patients who suffer

from this condition test negative when examined with a PCR test (van et al 2019). Recovery time also differs with each person depending on the first attack and response to the disease. For the symptoms were never present, or at least starting from this moment, tests for COVID-19 were not carried out, diagnosis is much more difficult. Long COVID is thought to affect 10–30% of individuals with mild symptoms of the disease and 50–70% of those with severe symptoms. The protected people look completely different: out of 100 immunized patients, only 10-12 get long COVID (Ayoubkhani *et al.*, 2022).

Long COVID is characterized by a wide range of symptoms which affect the respiratory, gastrointestinal, neurological, musculoskeletal, hematopoietic, and endocrine systems. Some may experience one or more of the signs that are, tiredness, headache, and depression. Furthermore, long COVID has overlapping characteristics with post-acute sequelae of SARS-CoV-2 infection (PASC), including ME/CFS, during and after exertion (Singh *et al.*, 2022).

iii. Pathogenesis of Long COVID

This is why fatigue and hypoxia in patients with long COVID can be explained by innate SARS-CoV-2-mediated hypercoagulation (Fogarty *et al.*, 2021). It sparks platelet and endothelial cell activation and causes clotting that leads to blockade of blood vessels and hence poor tissue oxygenation. The SARS-CoV-2 viral spike protein enlarges the inflammation signalling by activating platelets and enhancing the fibrinogen clumping resulting in micro-clots (Grobbelaar *et al.*, 2021). In case these micro-clots do not dissolve through fibrinolysis, hypoxia ensues, decaying tissue function.

Mitochondrial dysfunction is another reason people, experiencing long COVID symptoms, might be facing. There



is a strong association between disease severity and impaired mitochondrial function in PBMCs of COVID-19 patients (Ajaz *et al.*, 2021). This impairment affects ATP generation which in turn affects cellular energy metabolism and as a result various symptoms seen in long COVID.

Neurological signs include loss of smell in patients with damage to the olfactory bulb or the olfactory mucosa. Using MRI, investigations have evidenced that acute COVID-19 leads to stem cell odontology, olfactory stem cells that are developed to accept ACE2 receptors (Vaira *et al.*, 2020). These stem cells become damaged and are unable to help regenerate the olfactory epithelium which leads to anosmia even after the infection has cleared. This reduced regenerative capability is the basis for the chronic loss of sensation that can be seen in some patients.

iv. Treatments for Long COVID

There is no universal cure for long COVID and the treatments depend on the symptoms presented by the patient and therefore should be done clinically. Treatment involves drug therapy, counselling, vocational rehabilitation and physiotherapy. The goal of treatment is to work with given symptoms and try to deal with the reasons for them (Davis *et al.*, 2023).

Preventative remains the most effective measure – cutting the likelihood of contracting long COVID symptoms by a highly significant extent if given prior to SARS CoV2 exposure. However, vaccination does not cure the already existing long COVID symptoms (Watanabe *et al.*, 2023). Various research has proved that early vaccination will reduce the chances of developing long COVID, especially in adults.

The diabetes type drug known as Metformin has also been seen to minimize the possibility of long COVID in patients

diagnosed with COVID-19 and comorbidity of diabetes (Mccarthy *et al.*, 2023). Long COVID is still being researched, and many potential treatments for patients can be found at that institution's RECOVER trial (Mccarthy *et al.*, 2023). For instance, RECOVER-VITAL looks at the use of Paxlovid for long COVID, and RECOVER-NEURO is analyzing approaches for neurological manifestations, including online training and non-invasive brain stimulation. Other trials planned in the future include RECOVER-SLEEP for sleep disturbances, and RECOVER-AUTONOMIC for dysfunction of the autonomic nervous system (Zimmerman *et al.*, 2024).

Thus, long COVID continues to complicate what is already a burden to healthcare systems anywhere in the world. The following should be done in order to reduce the infections, hospitalizations, and long COVID cases which can help to ease this burden; Getting more people for booster doses especially for the new variants.

3. Diagnostic Methods

i. Nucleic Acid Amplification Test (NAAT)

The Nucleic Acid Amplification Test (NAAT), which detects viral RNA and has excellent sensitivity and specificity, is a key diagnostic tool for SARS-CoV-2 infection (Gao *et al.*, 2021; Ravindra *et al.*, 2021). These tests are essential for diagnosing acute COVID-19 and for tracking the existence of the virus in people who may have chronic COVID. RT-qPCR, multiplex RT-qPCR assays, RT-dPCR, and other cutting-edge technologies are important forms of NAATs (Wu *et al.*, 2020).

ii. RT-qPCR

The gold standard to detect SARS-CoV-2 infection is Real-Time Quantitative Polymerase Chain Reaction (RT-qPCR),



which has a high sensitivity and specificity (54). Through the use of reverse transcription (RT) of viral RNA into complementary DNA (cDNA) and real-time PCR amplification, SARS-CoV-2 RNA could be detected and evaluated. It performs most effectively in the very initial stages of infection, when the viral load is at its highest level, which allows prompt action to stop the virus's spread. Samples are first collected, usually from nasopharyngeal or oropharyngeal swabs, which usually have a higher viral load. After extracted RNA is reverse-transcribed to create cDNA, primers and probes that target particular SARS-CoV-2 genes, including the N (nucleocapsid), S (spike), E (envelope), and RdRp (RNA-dependent RNA polymerase) genes, are used to amplify the cDNA. Fluorescent probes enable for real-time measurement during amplification by releasing signals according to the amount of DNA produced. The cycle threshold (Ct) value that RT-qPCR yields helps determine the severity of the disease by reflecting the viral load. RT-qPCR is resource-intensive and depends on the stage of infection, and it may produce false negative results due to poor sample collection, low viral loads, or genetic alterations, despite its quick turnaround time and versatility. However, RT-qPCR continues to be the mainstay of SARS-CoV-2 diagnosis, and new developments are expanding its use in pandemic management (Akkiz *et al.*, 2021).

iii. Multiplex RT-qPCR Assays for Detecting SARS-CoV-2 and Other Respiratory Pathogens

SARS-CoV-2 and other respiratory pathogens can be identified in a single reaction by multiplex RT-qPCR tests, which are technically advanced diagnostics tools. This technique is particularly useful in differential of COVID-19 from other viral diseases such as flu, RSV or adenoviruses which often have similar

symptoms. To identify certain genomic portions of SARS-CoV-2, N, E or S gene or any specific genes associated with the other infections, primers and probes are required. It is the detection of nucleotide sequences within several targets at once at the end of which in a single reaction tube, viral RNA isolated from a patient sample is transcribed into cDNA. Quantification and identification in real-time are possible due to the incorporation of fluorescent labelled dyes which emit different signals that are unique for the pathogen discovered. As a result of our study, it can be concluded that the advantages of multiplex RT-qPCR include the increased epidemiological activity, shorter time to diagnosis, wider possibilities of identifying co-infections, and efficiency. However, there are drawbacks associated with this method; assay design is complex, costs are higher and data interpretation becomes difficult when multiple infections are present. Nevertheless, multiplex RT-qPCR tests have been essential in the COVID-19 pandemic response as it may facilitate faster and accurate diagnosis of respiratory diseases and enhance the care of patients in areas that are afflicted by overbearing respiratory pathogen epidemics (Hashemi *et al.*, 2021).

iv. RT-dPCR (Reverse Transcription Digital Polymerase Chain Reaction)

SARS-CoV-2 RNA may be found and measured using RT-dPCR, a sophisticated and extremely sensitive molecular diagnostic method. By dividing the reaction into thousands of separate droplets or wells, RT-dPCR enables absolute quantification of viral RNA, in contrast to conventional RT-qPCR, which offers relative quantification. Each partition acts as a microreactor containing either zero or one template molecule of the target RNA. Following reverse transcription to cDNA and amplification through PCR,



fluorescence signals are measured for each partition to determine whether the target RNA is present.

This digital strategy has a number of clear benefits. Particularly for samples with low viral loads or when the viral RNA is degraded, it offers remarkable sensitivity and accuracy. The method is very dependable for clinical diagnostics as it also reduces the impact of inhibitors found in patient samples. Additionally, RT-dPCR is less likely to be inconsistent, providing accurate data that are perfect for tracking the dynamics of viral load over time, especially in prolonged COVID cases, or for identifying leftover viral RNA after recovery (Suo *et al.*, 2020).

RT-dPCR has been used increasingly for SARS-CoV-2 research and diagnostic applications, such as determining vaccination response, discovering new variations, and assessing treatment efficacy. Its drawbacks, such as increased expenses, intricate procedures, and the requirement for specialist equipment, might prevent the technology from being widely used in standard diagnostic settings (Shafie *et al.*, 2023). For high-precision viral RNA quantification, RT-dPCR is a potent technology that offers substantial advantages in research and certain clinical applications, notwithstanding these difficulties.

v. Other Nucleic Acid Amplification Tests (NAATs)

In addition to RT-qPCR and RT-dPCR, several other NAAT colourgens have been designed for the identification of SARS-CoV-2 (FDA, 2024). These techniques aim at increasing the usability, modularity and productivity of diagnosis in various care and population health approaches.

A. Loop-Mediated Isothermal Amplification (LAMP):

LAMP is one of the quickest and least expensive NAAT that doesn't expect dynamic thermal cycling since it cycles the viral RNA at a stationary temperature. The assay yields results within one hour using specific primers and a strand-displacing DNA polymerase. For this reason, given that these tests are easy to perform, require little equipment, and are highly sensitive, they are very useful in low resource settings (CDC, 2023; Sagar *et al.*, 2023). Subsequently, to ease interpretation, several LAMP tests undergo further enhancements utilizing colorimetric or fluorometric detection.

B. Transcription-Mediated Amplification (TMA):

Another sensitive and accurate isothermal system targeting SARS-CoV-2 RNA is TMA. It is particularly valuable in the high-throughput testing and is associated with high sensitivity. TMA method can be used extensively in labs and diagnostic centres since it is applied on automated platforms (Dierks *et al.*, 2021).

C. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Based Detection:

CRISPR has been adapted to identify SARS-CoV-2 by applying guide RNA sequences toward viral RNA. A measurable signal is generated when CAS proteins – including Cas12 or Cas13 – bind to the target and activate and digest the reporter (Deol *et al.*, 2022). These assays are ideal candidates for point-of-care testing because they are the following: rapid, adaptable, and selective.

D. Helicase-Dependent Amplification (HDA):

Primers may then attach and amplify DNA or RNA using Helicase enzymes in HDA; an isothermal technique that unwinds DNA. This kind of method is best used in field applications because of its



simplicity and compatibility with simple equipment (Zasada *et al.*, 2022).

E. Nicking Enzyme Amplification Reaction (NEAR):

Enzymes capable of nicking at specific sites help to create single stranded DNA at that locations, NEAR is a very fast nucleic acid amplification method that enables the polymerase to elongate the strand for amplification. The NEAR-based assays are used in many portable diagnostic devices since the results can be obtained in a very short time, in minutes (James *et al.*, 2020).

F. Rolling Circle Amplification (RCA):

Standard Bacterial DNAs are circularized and kept in checked throughout RCA, creating lengthy successive sequences which may be identified through various methods. Other studies have shown that RCA has high specificity and that it is useful when used in multiplex testing but it is not as widely used as other NAATs. All these alternative NAATs offer the following unique and valuable characteristics for SARS-CoV-2 related diagnostics: versatility in terms of platforms, design, equipment, rapidity, and resource requirements (Gu *et al.*, 2018). Each of these methods involves its own optimizing factors and constraints so that healthcare systems can select according to organizational need.

vi. Serological Tests

The existence of antibodies or antigens in blood samples is detected by certain tests known as serological tests. These tests are beneficial in analyzing the immunological reactions, identifying the levels of immunities in a population and in identifying previous infections. In particular, they complement the measurements based on nucleic acids for

the detection of immunological reactions to SARS-CoV-2 (CDC, 2023).

i.RAT

Rapid Antigen Tests (RATs) are rapidly used for screening infected with SARS-CoV-2 antigens which are portions of viral proteins in specimens such as nasal or throat swabs. Antigen tests mainly use what is known as immunochromatographic assays whereby sample is applied on a test device and in presence of the SARS-CoV-2 antigens, a visible signal is generated. RATs have numerous benefits including; being fast with results taking 15-30 minutes, easy to use and inexpensive making them fit for use during mass screening in the community, and at home. They are most useful for the quick identification of persons who have a contagion; which is critical in preventing the spread of an illness. However, their main drawback is suboptimal sensitivity when compared with the increased specificity of other molecular techniques, including RT-PCR. This implies that, compared to RT-PCR, RATs are inclined to deliver negative outcomes even in persons who truly have COVID-19 but with low viral loads inclusive of asymptomatic or early-stage patients (Sagar *et al.*, 2023). In addition, reactions with other coronaviruses or pathogens can lead to false-positive results, as such these tests can be highly inaccurate at times. However, RATs are useful in high throughput testing where speed is of essence, although follow up testing through more precise techniques is advised.

ii.ELISA

Symptoms also have limitations with tests like the PCR test, Antigen test and Enzyme-Linked Immunosorbent Assay (ELISA) which are highly sensitive and specific laboratory tests



that are mostly used for the detection of covert antibodies against SARS-CoV-2. ELISA function in that viral antigens or antibodies are attached to the surface of a plate and then incubated in a medium and reacted with another reagent that produces color change when the target antibodies or antigens are bound. This type of quantitative test has more data outcomes compared to that of antigen tests that separate tests of different antibodies such as IgM, IgG, and IgA that is representing of recent infection and immunity levels. ELISA has been employed usefully in various large-scale epidemiological surveys to identify seropositivity or effectiveness of immunization and the amount of results is useful for a long-term antibody response evaluation. Nonetheless, ELISA and other methods mentioned above have drawbacks as follows: ELISA demands specific equipment and highly professional personnel; it requires much greater reaction time, often measured in hours and days, compared to other techniques, which makes it less appropriate for speedy point of care diagnostics. Also, when comparing ELISA with other types of methods, it should be noted that although this method allows determining the presence of antibodies in samples with high specificity and sensitivity, this method can fail to detect viral infection in patients during the acute phase of viral infection, when titer of detectable antibodies is usually low or absent (Castellanos *et al.*, 2022). Hence ELISA is best used in examining samples collected after infection or after vaccination and not prognostically.

iii. Shortcomings of Antigen Tests

Shortcomings of Antigen Tests are perhaps more observed when compared with the more accurate nucleic acid amplification tests,

(NAATs). Compared to antigen tests, PCR tests, and antibody tests, there are many benefits to tests that use antigens: they are fast and inexpensive, but they are less accurate when the viral load is low, as occurs in asymptomatic patients or those who are beginning to recover from the virus. The minimally derisked RATs enhance the prospects of false negative, a situation which prolongs the time one has to isolating and therefore prolonging transmission. Further, antigen tests are less informative and rarely give quantitative values of viral loads or antibodies indicating severity of the disease or immunity respectively. In addition, there are disadvantages in taking antigen tests which are the ability in identifying the new variants of SARS-CoV-2 in cases there are mutations occur in the viral proteins used in the tests. The fact is that the same antibodies associate with other coronavirus strains, including those potentially causing colds, may give a positive result, making diagnosis more challenging. These weaknesses explain why antigen testing should be complemented by other diagnostics or confirmatory tests when a negative test is given in patients with symptoms or outbreaks in high-incidence areas. Consequently, such tests are less sensitive than more elaborate serologic tests, such as ELISA or molecular tests, such as RT-PCR, even though the antigen tests are relatively faster (Xin *et al.*, 2021).

Molecular tests like RATs and ELISA provide the diagnostic utility and information about immunity to SARS-CoV-2 infection. This is the case since RATs are particularly useful in cases of large-scale screening, avenues with a high population influx besides other large-scale tests; albeit less sensitive than antigen tests. Compared to ELISA, it is more time consuming and expensive, but offers information about



the duration of immunity, which is crucial for the epidemiological observation. However, there are some restrictions of both tests which are important to consider while analysis the results (Johnson *et al.*, 2022). When used alongside molecular testing such as the RT-PCR these serological tools may prove useful in improving diagnostic outcomes as well as assist the public health sectors in addressing COVID-19 pandemic.

4. Ancillary Tests for COVID-19

These additional tests of COVID-19 give valuable information on the virus's genome, mutation, and the immune response to the disease other than basic diagnostic approaches like the RT-PCR and antigen tests. The two key supplementary tests adopted in the detection and management of COVID-19 are Sequencing and Antibody Serology Tests. These tests are central to the characterization of the viral transmission dynamics, identification of emerging strains, as well as antibody response upon recovery or upon vaccination.

i. Sequencing

Sequencing is a visually highly sophisticated method for resolving the genetic map of SARS-CoV-2 viruses, allowing researchers and clinicians to learn more about the pathogens. This test entails identifying the sequence of all nucleotides which make up RNA in the virus' genome. There are two primary types of sequencing used in the context of COVID-19: WGS and targeted sequencing. Sequencing in methods such as whole genome sequencing means decoding all the 6 bases of the virus genome which gives detailed information regarding the virus mutation and variability. This method is invaluable for surveillant viral evolution

and identifying new variants as well as mutations that could alter transmissibility, disease severity, and vaccine effectiveness (El-Daly *et al.*, 2024).

The sequencing efforts are most relevant to new VOCs such as Delta and Omicron variants that emerged and proven to have partial immune breakout and altered disease impact. Sequencing also enables refinement of spike protein or other locations and showcase which mutations can affect recall of vaccines or therapeutic entities. It also tracks transmission of variants and offers epidemiological intelligence that shapes public health approaches on variants and COVID-19 Surges. Although sequencing gives useful data, it has not been applied to daily Covid-19 detection because it is time-consuming, expensive, and not easy to perform. But it is essential for surveillance, studying the way the virus spreads and its effect, as well as for the development of a vaccine and antiviral plan (WHO, 2021).

ii. Antibody Serology Tests

Serology tests are used to diagnosis an antibody in the blood which is an immunoglobulin produced by the body's immune system due to an infection such as COVID-19. These tests are meant to reveal the presence of such proteins as IgM, IgG and IgA that arise at different periods of an infection or after the administration of a vaccine. Detection of antibodies often means that the person experienced and was infected by the virus in the past through natural infection or vaccination, but the results can give some clue about the level of immunity the person has against the virus.

There is no role for serological testing in diagnosis of active SARS-



CoV-2 disease as antibodies take several days to weeks to become detectable. However, they are of greater value in the context of the epidemiological investigations, such as the overall prevalence of COVID-19 antibodies in the given population, the evaluation of the immunogenicity following the COVID-19 vaccine administration, as well as in the development of further public health interventions. These tests are useful to determine a subject that may not show any symptoms or had very mild symptoms that they never took seriously during the pandemic.

Antibody testing is also used in research especially in determining the longevity of protection concerning COVID-19 immunity as well as the effectiveness of vaccines against the virus. For example, it can be used to assess which kind of vaccines are more likely to provoke an immune response in the organism. Nevertheless, serology tests are not ideal for all other forms of SARS-CoV-2; some forms may affect the immune response. However, antibody detection does not preclude subsequent episodes because reinfection may occur, particularly with the circulating strains that have mutations associated with immune escape (Dimech *et al.*, 2024).

5. Treatment Strategies

Despite the spike of the COVID-19 cases, different approaches in treatment have been invented to address the impacts of SARS-CoV-2 virus. The distinctive therapeutic strategies include the possibility of interaction with the virus (antiviral treatment), cytokine storm inhibition (modulation of the immune response), and innate tissue regeneration and immune reinforcement (stem cell therapy). Further below, we

discuss these treatment options in details.

i. Antiviral Therapy

Antiviral drugs are used with the purpose of interfering with the replication of SARS-CoV-2, so that the viral burden does not become too high in the body and therefore does not cause severe and widespread COVID-19. These treatments are very important in the initial phases of the infection because they can possibly lower the chance of serious illness and hospitalization.

i. Remdesivir

Remdesivir is none specific antiviral drug, which belong to class of RNA polymerase inhibitors and acts by blocking RNA dependent RNA polymerase (RdRp) synthesis which is required for the RNA viruses replication including SARS-CoV-2. This inhibition in actuality stops the process of replication and limits the viral quantity that continues vying for tissue possession within the body. Though initially invented to treat Ebola, remdesivir was later used for the treatment of COVID-19 and received authorization as the first antiviral for COVID-19 (Kalil *et al.*, 2021).

Another clinical trial, which has been conducted comparing the effectiveness of remdesivir among patients with Covid-19, demonstrated that the drug was more efficient if it had been used in the initial stage of the disease, during the first week after the beginning of symptoms in particular. That is why its usage was said to have reduced time taken to recover, mainly among the hospitalized patients with moderate symptoms, though its effect on the mortality rates is still undeclared. Remdesivir is given intravenously and is employed mainly on severely affected



patients with COVID 19 that needs oxygen to assist with their breathing but is not used in mild cases or patients with mild symptoms who can take treatment at home. However the drug has some drawbacks, one of which is possible renal toxicity and hence should not be administered to patients with chronic kidney disease (Cao *et al.*, 2023).

ii. Nirmatrelvir–Ritonavir (Paxlovid)

Paxlovid is a combination of two antiviral drugs: nirmatrelvir, a protease inhibitor, and ritonavir, an pharmacokinetic booster of nirmatrelvir because it selectively inhibits the liver enzymes that metabolize the drug. Specifically, Nirmatrelvir work against SARS-CoV-2 main protease (Mpro) enzyme which play vital role in replication process of the virus. This reshape at the end of the polyproteins has been blocked by nirmatrelvir to prevent further development and replication of the virus (Greasley *et al.*, 2022; Takashita *et al.*, 2022; Imai *et al.*, 2023).

Paxlovid is a medicine that is prescribed to patients with mild to moderate COVID symptoms with high risk of developing severe form of the infection. Clinical trials have shown that Paxlovid provides protection against hospitalization and deaths by nearly 88% if administered early within five days of developing symptoms. However, computerized processing is contraindicated in severe renal or hepatic impaired patients due to drug interaction with other drugs especially those that are metabolized by the enzymes in the cytochrome P450 complex. Although Paxlovid has proven highly effective at reducing the risk of severe disease, it does not appear to help patients who are already presenting severe symptoms or those admitted to

hospital with significant organ dysfunction (Perelson *et al.*, 2023).

ii. Immunomodulators

Immunomodulation too targets at controlling immune cascade overdrive to SARS-CoV-2 leading to occurrences of cytokine storms, ARDS and multiple organ dysfunction syndrome. These therapies aim directing the immune system to focus on elements that provoke inflammation thereby enabling body to heal itself from the effects of the infection without having to damage the tissues irreparably.

i. Baricitinib (JAK Inhibitor)

Baricitinib is an orally active Janus kinase (JAK) inhibitor which inhibits the activity of JAK-STAT pathway is known to activate the inflammatory cytokines. This inhibition reduces proinflammatory cytokines in the levels like IL-6, and IL-1 β which are in the inflammatory cascade of COVID-19 especially in severe cases. As JAK inhibitors, baricitinib decreases inflammation that leads to lung injury and organ failure and puts patient at risk of poor survival (Huang *et al.*, 2022).

Baricitinib is indicated for the treatment of COVID-19 in patients with moderate, severe or severe COVID-19 symptoms who will likely require supplemental oxygen or mechanical ventilation. Randomized controlled trials have shown that baricitinib as an adjunct therapy with corticosteroids decreases the mortality and the risk to require invasive mechanical ventilation in severe COVID-19 patients. But it can also lead to infections because it alters the patient's immune system, thus making proper monitoring crucial during treatment. Furthermore, baricitinib is contraindicated in patients with active



infection or with past history of cancer, since the drug increases the risk of malignancy and serious infection (Wolfe et al., 2022).

ii. Tocilizumab (IL-6 Inhibitor)

Tocilizumab is a monoclonal antibody acting selectively on and blocking the IL-6 cytokine molecule, which is released in excessive amounts during a cytokine storm. Increased levels of IL-6 are associated with high inflammation, organ dysfunction, and poor outcome in COVID-19 infected patients. As an 'antagonist' to the IL-6 receptor, tocilizumab works to decrease inflammation and precludes the deterioration of certain organs like the lungs, heart and kidneys in particular (Rezabakhsh *et al.*, 2024; Zhang *et al.*, 2020). Tocilizumab is usually administered to those severe COVID-19 patients admitted to the hospital with elevated IL-6 levels and who need oxygen or mechanical ventilation. It was established that adding tocilizumab to the regimen of high steroid action has a better effect on the treatment of severe COVID-19 cases, decreasing mortality rates and the risk of mechanical ventilation. However, patients treated with tocilizumab should be regularly checked for infections and gastrointestinal perforations and exhibit liver enzyme abnormalities (Lu *et al.*, 2024).

iii. Cell Therapy

Continued discussion has been made on cell-based therapies as an option for critical COVID-19 patients or those with organ injury or no response to conventional interventions. These therapies aims to enhance the immune response mechanisms, treat molecular and tissue injuries and promote healing from viral initiated organ failures.

i. T Cell Therapy

T cell therapy is based on administration of T lymphocytes (T cell), which are among the components of adaptive immunity. These are important in medicating virus infected cells in the body Deng *et al.*, (2006). SARS-CoV-2 clearance by T cells is critical in COVID-19, but T cells are exhausted in critically ill or immunocompromised patients. T cell therapy is the process of augmenting the activity of T cells whether autologous T cells obtained from the patient's blood or allogeneic T cells from a donor, to increase the fight or response to SARS-CoV-2.

The early experiments have indicated that T cell therapy can have benefit in patients with the severe COVID-19, in particular, those who have dangerous prolonged viral replication or immunocompromised condition. This is shown to have an advantage of aiding the body reach a means to clear the virus and avoid reinfection. However, T cell therapy is relatively new today, and more efforts are required in order to establish the best administrations, the safety as well as the efficacy of the therapy (Wang *et al.*, 2023).

ii. Mesenchymal Stem Cell (MSC) Therapy

MSCs (Mesenchymal stem cells) are a type of partially characterized multipotent cell population derived from mesodermal tissues possessing tissue repair/ regeneration capabilities as well as immune regulation. MSCs release molecules that have various effects including promoting tissue remodelling, reducing inflammation and promoting healing of injured organs. This makes MSC therapy appealing to patients with

the severe COVID-19 related injuries like ARDS, myocarditis, or affected liver and kidneys (Sengupta *et al.*, 2020).

In human clinical trials MSC treatment has demonstrated effectiveness in the amelioration of lung pathology and inflammation as well as boosting tissue repair in COVID-19 patients who experience severe pneumonia (Ringden *et al.*, 2022). MSCs are generally given intravenously and in evidence that they are useful in reconstructing damaged lung tissue, shortening time on the ventilator, and increasing overall survival. However, the ongoing studies have reported an immediate benefit of the MSC therapy and there is still so much more to be learned regarding the safety issues, the way MSC therapy works, and the long-term impact it has on COVID-19 (Dilogo *et al.*, 2021).

6. Vaccines

i. Impact of Vaccines on Epidemiology of COVID-19

The current COVID-19 approved vaccines were designed primarily for the basic strain of SARS-CoV-2. For the vaccines, the mRNA vaccine BNT162b2 (Pfizer BioNTech) was 95% effective for preventing symptomatic infections, and the protein subunit vaccine was 90% effective in a study done among participants. Efficacy against both hospitalization and death was near complete for both vaccines. But due to high rates of mutation in SARS-CoV-2, newer strains appeared which lead to so-called breakthrough cases. For instance, these mutation possess the latitude to avoid the neutralizing antibodies like JN.1, which is featured in the Omicron variant (Dunkle *et al.*, 2022).

Essential to vaccine protection are neutralizing antibody titres that, however, wane rapidly and this is why boosters are required. A new mRNA booster for the Omicron XBB.1.5 variant has been endorsed and does certainly enhance the neutralizing antibody titers against the new strains, and hence assists in sustaining the protection. Likewise, the hospitalization and death rates persist at constant levels in vaccinated populations to show that getting vaccinated helps to prevent severe disease sequelae (Wang *et al.*, 2024).

The research has also demonstrated that the proportion of patients more than seventy-five years old and individuals with immunocompromising diseases rose during the Omicron wave; nevertheless, the severity of COVID and mortality dropped thanks to the vaccine. This implies that preventing measures are very important for quantifying the impact of COVID-19 in high-risk populations (Kojima *et al.*, 2023).

ii. Disparities in COVID-19 Response between High-Income and Low-Income Countries

Resource-rich countries in the developed world—say, the United States—were in a position not only financially and infrastructurally to guarantee large-scale vaccination but also to do so where these options have simply not existed for low-resource settings. Developed countries could have huge COVID-19 vaccine inventories, put up large vaccination centres, and use apps to administer vaccines. On the other hand, lower income country especially those in Africa were shaded off due to financial enablers and poor health systems (Zaoui *et al.*, 2023).



To avoid this, COVAX has been developed to distribute vaccines across the globe by the end of 2023 in 2 billion doses to save many lives (Sign *et al.*, 2024). However, there is still an issue of vaccine bequeathal and transportation even in the low income countries after making arrangement of acquiring vaccines. Some of these difficulties have been addressed by solutions such as extension of vaccines to normal immunization schedules, and establishment of mobile immunization stations.

Non-governmental organizations (NGOs) also collaborate with government in delivery of these vaccines to harder to reach areas (Med *et al.*, 2023).

iii. Pfizer-BioNTech COVID-19 Vaccine (mRNA Vaccine)

Pfizer-BioNTech's BNT162b2, introduced in 2020, is an mRNA form of COVID-19 vaccine first to receive an emergency use authorization. BioNTech's Comirnaty works by using adapted mRNA to carry out the genetic plan of the spike glycoprotein of SARS-CoV-2 and delivers it encapsulated in lipid nanoparticles. Early large-scale outcomes exposed the vaccine to have 95% efficacy in stopping symptomatic illness and no severe side effects. Efficacy was found to be reduced gradually, which suggests that booster doses are required (Vogel *et al.*, 2021).

They said that the vaccine has great efficiency against some variants such as the Beta and the Delta, with approximately 90 % effectiveness in preventing hospitalization due to the virus but the efficacy of the vaccine in preventing infection in the first place is lower and wanes over time (Sahin *et al.*, 2020). Research has also indicated that a booster dose increases protection and that it protects especially against serious

outcomes such as hospitalization and death. The research show during the Omicron wave that the booster lessened the effectiveness and substantially hindered developing severe disease but had a comparatively lesser efficiency in preventing breakthrough symptomatic infection. Though it weakens human body more than usual flu, it still afforded substantial degree of safeguard against hospitalization and severe infection (Polack *et al.*, 2020).

To address new variants, Pfizer-BioNTech come up with adapted vaccines, monovalent and bivalent targeting specific Omicron subtypes (BA.1, BA.4/BA.5 and XBB.1.5). The variant-adapted vaccines demonstrated increased immunogenicity compared to the primary titer, and bivalent boosters provided further protection concerning severe diseases and hospitalization (Moreira *et al.*, 2022).

The tolerability of the vaccine is generally acceptable, although some severe side reactions have been noted even though they are rare. This list comprises myocarditis especially in men, coagulation disruptions such as CVT and thrombocytopenia. Nonetheless, the research indicates that vaccine-associated myocarditis often seems to have a more favourable prognosis for the patient than myocarditis with other origins (Martinelli *et al.*, 2023).

The vaccine's safety was comparable to that observed in the general population in immunocompromised populations, including transplant recipients, there were no reports of organ rejection or serious adverse effects. This implies that, there is no harm with regard to increased risk associated with



immunization with patients with compromised immune systems.

iv. Novavax COVID-19 Vaccine (Protein Subunit Vaccine)

The NVX-CoV2373 (Novavax) is a recombinant spike protein COVID-19 vaccine, developed with the Matrix-M adjuvant to promote broad immune response (“Novavax and Serum Institute of India Announce World Health Organization Grants Emergency Use Listing for NVX-CoV2373 COVID-19 Vaccine - Dec 17, 2021). It has been proven very effective in the prevention of COVID-19 disease from the clinical trials because it has overall efficacy of about 89-90% and efficacy against its variants such as Alpha and Delta. It also provided confidence about its ability to act as a booster shot as post-vaccination antibody levels rose sharply against several SARS-CoV-2 variants (Hotez et al. 2022). The data from phase III trials show that NVX-CoV2373 is relatively safe; only minor to moderate side effects such as headache and pain at the injection site. Despite the myocarditis and pericarditis side effects, the number was few than the other vaccines side effects. The vaccine proved real-world efficacy, protection comparing to comparator vaccines depending on variants, NVX-CoV2373 offered generally high protection (Hotez et al. 2022). The new version of the vaccine is NVX-CoV2601 approved for booster dose use in the US and appears to protect against the XBB.1.5 but more research is needed on its ongoing safety and effectiveness. In general, the mainstay is Novavax’s vaccine, which provides an additional non-mRNA way to prevent COVID-19, based on reputable data on its safety and effectiveness (Heath *et al.*, 2021).

Conclusions

Early on in the pandemic, the cooperation of scientists around the globe made it possible to get a clear picture of this new coronavirus. Many new detection techniques and treatment approaches have been developed new and made available thereafter to help contain the spread and enhance management of COVID-19. While continuing the research and controversial COVID-19 is no longer considered a pandemic by the World Health Organisation. They further ensure continued and renewal of vaccines and treatments to counter any new variants of SARS-CoV-2 which will make the current endemicity of COVID-19 worse.

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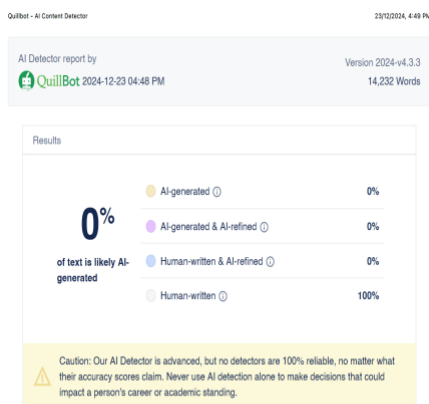
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A Holistic Review of COVID-19: Epidemiology, Pathogenesis, Diagnostic Innovations, and Future Treatment Approaches



Self-Medication with Cannabis

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Abstract

Self-medication utilizing cannabis has collected meaningful attention on account of its perceived healing benefits and developing permissible frameworks. Individuals repeatedly count on cannabis for directing incessant pain, tension, depression, and additional healing conditions, frequently outside adequate counseling from healthcare providers. This practice raises detracting questions about security, efficacy, and the potential for misuse. Although cannabinoids like THC and CBD have proved promise in considering certain environments, discrepancies in product features, drug, and individual reactions present challenges in ensuring optimum effects. This review explores the patterns, ambitions, and risks that guide self-cure using marijuana. Key determinants influencing self-cure contain accessibility, socioeconomic rank, and unhappiness accompanying conventional situations. The impact of authorization on self-medication currents and the populace most affected by marijuana procedures is emphasized. Despite anecdotal evidence upholding allure therapeutic use, strong dispassionate tests are necessary to confirm these claims and address concerns about reliance, cognitive deterioration, and drug interplays. Ethical considerations stand when things use marijuana as a substitute for recommended healing treatments. Public health concerns, containing the normalization of marijuana use and its potential social belongings, are explained in light of changeful public ideas. This review underscores the need for evidence-based directions to guide things self-medicating with marijuana and the healthcare artists advising bureaucracy.

Keywords: self-medication, cannabis, cannabinoids, THC, CBD, chronic pain, anxiety, legalization, public health, dependence

Introduction

The therapeutic use of cannabis is gaining increasing acceptance globally. Countries like Canada (since 2001) and the Netherlands (since 2003) have government-run programs providing quality-controlled cannabis for medical use. Other countries, including Israel, the Czech Republic, and Switzerland, are initiating similar programs, while some nations import cannabis from the Netherlands. In the United States, despite federal resistance, 18

states and the District of Columbia have enacted laws permitting medical cannabis use (Americans for Safe Access, 2012). Self-medication with cannabis is prevalent due to its accessibility and perceived therapeutic benefits. However, this practice is inherently challenging to study, as it occurs outside controlled clinical settings. Limited data is available on medicinal cannabis use and the characteristics of its users. Existing surveys and anecdotal reports highlight the need for controlled



studies to better understand self-medication practices and outcomes.

This review examines self-medication with cannabis, focusing on its patterns, associated risks, and implications for healthcare systems and policies. The discussion also emphasizes the importance of quality control and regulation. In these states, cases evolve on their own or together or obtain from the best growers that present an image of caregivers for groups of patients. In a few states, large-scale movements are authorized to supply the whole demand, but almost no official control of product quality guidelines has existed so far. Nevertheless, in what way or manner marijuana is provided in all of these various programs, it is mostly abandoned until patients themselves rule in what way or manner to execute the herb. Self-drug accompanying marijuana is then probably the ultimate universal habit of utilizing cannabinoids medicinally. Consequently, there grant permission be a lot to gain real experiences of cases of self-medication accompanying marijuana merchandise worldwide.

Self-medication is innately troublesome to study, as it does not occur in the convenient and reserved background of a lab or clinic. Currently, the little published dossier is free in consideration of medicinal marijuana use and the traits of patients complicated in it. The limited survey dossier, case reports, and additional “easy” resources for gathering facts that endure managing hard to draw firm quantitative decisions that can tell dispassionate practice in what way or manner to prescribe marijuana sufficiently. Fortunately, there is an increasing interest in performing controlled studies (Hazekamp and Heerdink 2013; Janicsek and Reiman 2012) and big surveys (Hazekamp and others. 2013) on these patients peoples, to contribute to the understanding of cannabinoid-located cures by querying self-

medicating patients particularized questions about their occurrences.

At the same time, the tactics happenings that are designed to shelter legal and able consumers are fiercely discussed by healing experts, law enforcement instrumentalities, and politicians about the realm, and constantly with good reason. Although marijuana appears to fill a few important medical needs, many current wholes leave enough inducement for relating to sports consumers to act as pseudopatients so that acquire permissible protection for utilizing marijuana. Furthermore, while the security of marijuana is generally accepted and expected inside the range frequently regarded to be agreeable for additional drugs, clinical tests still exist able to supply a clear answer on which are presumed expected the “actual” medical clues for marijuana use. Finally, skilled is still much to gain about the risks of potential contaminations with pesticides, progress-reinforcing chemical compounds, microbes, or weighty metals, exceptionally in the omission of control of product quality. For all these reasons, physicians are often uncertain about playing the part of the prescriber or “watch person,” even in the official administration programs of Canada (Sullivan 2012) and the Netherlands (Hazekamp and Heerdink 2013). Unfortunately, on two together edges concerning this discussion, debates are all also frequently established on personal occurrences, governmental purposes, and feelings, rather than on the increasingly experimental think-insult we have of the cannabis plant. As a result, two together the advantageous and hurtful aspects of marijuana use grant permission to enhance partially inflated, grazing from “marijuana cures tumors” and “it never destroyed anyone” to “marijuana will make you mad and addicted.” The synthetic variety of the great number of assortments of cannabis that are common contemporary assuredly



does little to cause certainty to this discourse. Therefore, the main aim of the conference on the experts and cons of self-medication accompanying marijuana concedes the possibility be to finding a tenable supply model that can fulfill the necessities of healing experts and policymakers (e.g., uniformity, control of product quality, security), in addition to those of patients and their physicians (such as choice of assortment and presidency form, whole plant preparations), while making a powerful but equalized work to underrate diversion and abuse. Finding balance is important, and guaranteeing that we advance our controlled understanding of marijuana use is the key.

This study compiles a few main facets of the medicinal use of marijuana, containing dispassionate data, presidency forms, control of product quality, drugs, and dissimilarities between marijuana types. The outlook of the self-medicating patient will be below discussing appropriate issues to a degree usual user traits, cost, and the public facets of self-drug. Although the term “medicinal/healing marijuana” is frequently secondhand, we prefer to use the wording “curative use of marijuana” in this place book chapter alternatively. While this dissimilarity is only nice, it signifies that marijuana is not innately curative, causing the therapeutic belongings to believe the type used, the medical condition it is secondhand for, and a range of different selections such as presidency form and drug menu. In addition, the term “curative cannabis” can mean that the commodity secondhand is of medical status (condition reserved, patterned, etc.) which is frequently not the case accompanying self-cure. We consider it so more appropriate to consider the use of marijuana to construct healing belongings. Hence, the term: medicinal use of marijuana.

Cannabis and Therapeutic Use: An Evolving Perspective

Cannabis has a long history of use as a medicinal plant. However, its therapeutic potential is often overshadowed by concerns about misuse and abuse. Unlike opioids, cannabis, and cannabinoids are rarely discussed in medical training, resulting in a lack of consensus among healthcare professionals regarding its appropriate use. Despite these challenges, cannabis has demonstrated therapeutic potential in managing conditions like chronic pain, anxiety, and post-traumatic stress disorder (PTSD).

Modern cannabis-based medicines, including synthetic cannabinoids like dronabinol and nabilone, have been developed to address specific medical conditions. However, self-medication with herbal cannabis remains common due to factors like cost, distrust of conventional medicine, and a preference for natural remedies. Addressing these issues requires improved education for healthcare providers and better integration of cannabis into conventional treatment frameworks.

Cannabis and medication an uncomfortable combination

According to a few, herbaceous marijuana, as known or named at another time or place marijuana, is a staff whose abuse potential is well recorded, but whose benefits are poorly distinguished. However, this view over- looks at the reality that the harmfulness of cannabis abuse is not as widely sanctioned as frequently pretended (Nutt and others. 2007) and that few healing belongings claimed by cases are, really, clinically drink- ported and frequently even produced by recorded cures. On the other hand, skilled is still much we need to learn about fields to a degree of dissimilarities between marijuana assortments, cooperation of marijuana components, and the sociocultural function of curative cannabis.



Unlike opioids, another class of reserved substances accompanying long experiences of debate, marijuana, and cannabinoid are exceptionally discussed in healing school or residence. Even the life or function of the ubiquitous endocannabinoid plan appears predominantly mysterious among healing professionals. As a result, hard to reach some wealthy consensus on place foul line grant permission be drawn 'tween the appropriate healing use and the abuse concerning this plant. Instead, what we comment on is an interesting dissemination of belief on marijuana (Ware 2012). Addiction employees, concerned the individual help by increases in moot marijuana use, have on the other hand too stated that marijuana has been used favorably in harm-decline programs meaning more addictive, in the way that opiates (smack), sugar, or alcohol (such as, Reiman 2009). Psychiatrists warned about adolescent marijuana use and psychosis, are again informed about the latest trends and definite belongings of cannabinoids on posttraumatic stress (Passie et al. 2012) and cavities (Mikale and others. 2013). Pain distinctive- ists, attracted by the belongings of marijuana on pain, sleep, and worry, are evenly concerned about Drug-pursuing practice and working impairment. Persons, anxious about the hazardous interest minors show toward marijuana, are together interested in the honest pain remedy that the drug can offer the desired one needs it.

While the reductionist approach of modern cure has previously existed used to marijuana for decades, the after development of cannabinoid-located cure—mainly established accumulation of solid- 9-tetrahydrocannabinol (Δ^9 -THC) and cannabidiol (CBD)—has not happened intelligent to significantly lower the general use of marijuana as a cure. Cannabis appears to implant the middle; on the one help also powerful and expected controlled as an herbaceous (or alternative) medicine, in another way excessively herbaceous is

believed as unoriginal medicine. In general, skilled are diversified reasons that can demonstrate reason folk choose self-cure over more unoriginal analysis, in the way that cost issues, distrust in up-to-date healthcare, or an interest in “green” cure. But in the case of cannabis, we can adjoin a few less prevailing reasons: an off-course choice of synthetic variety with marijuana strains, odd presidency forms, and even interest in the latent marijuana subculture. After all, a far-flung network of information on marijuana lies, contribution-specific magazines, extensive websites, and even worldwide fairs and colloquiums. So even though marijuana and up-to-date cures have an uneasy connection accompanying each one, seemingly the curative use of marijuana is here to stay.

Defining self-Medication

Self-medication usually involves the use of investment in a company or alternative remedies to accomplish pronounced or undiagnosed conditions. When used to marijuana, self-drug often requires the use of the plant or allure products without professional counseling. While self-care can enable patients to take control of their energy, it still poses risks, containing improper drugs, unfavorable belongings, and potential interactions accompanying additional drugs.

The dual type of marijuana as two together relating to sports and medicinal stuff confuses allure use in self-medication. Evidence-located directions are wanted to bridge the gap 'between simple use and clinical practice, ensuring cautious and direct healing outcomes.

In the biography, self-drug mainly refers to one or the other management: (1) the conscious use of the nonprescribed drug (investment in company drugs, alternative situations, etc.) to treat a diagnosed or undiagnosed condition, or (2) the use of a (frequently illegal) drug to consciously or



subconsciously treat a tangible or emotional condition, as bestowed in Khantzian's self-cure theory (Suh and others. 2008) While the former plans an alert exertion to aim a particular affliction state, the latter is frequently secondhand as a clarification for the beginning of an alcohol abuse disorder. Both of these definitions of self-cure have relevance when debating the curative use of marijuana.

Self-drug is visualized by few as a positive habit to enable victims to take better control over their care, and to increase healthcare effectiveness by lowering doctor visits. This has been a reason for exertions to form few formula cures for conditions to the degree of diabetes, asthma, migraines, and hypertension, convenient buyable without a prescription (Woodward and others. 2012). Some nations that turn over one minds medicinal use of marijuana plainly demand "permission" marked by a surgeon to receive guardianship from permissible punishments. The inmates are left to use the marijuana on their own, evaluating for themselves many of the situation environments that are normally confident apiece formal healthcare foundation, to a degree the characteristic and/or dependability of the beginning, correct dosage, routes of presidency, and efficiency in affliction progress. The "tolerant" approach to curative marijuana use that defines these programs offers self-cure as the only alternative for partners. Evidence-located listening of the efficiency of cannabis on the clues that it is secondhand, and even whether it is being secondhand efficiently and responsibly, is almost entirely wanting. Greater addition of specialists in cases of marijuana use, to a degree through actual medicine, commit help to fill that break-in information.

In contrast, in a habit of activity medicine, self-medication grants permission concern relating to sports

dependence on an illegal substance that results in surprising or unacknowledged bettering to a current situation. In this framework, this pattern of dependence on illegal substances grants permission to be the base for a developing hang-up (Hall and Queener 2007). Additionally, studies have proved that curative use of marijuana frequently had a connection with the treatment of an insane condition (Lynch and others. 2006; Prentiss and others. 2004; Reinerman and others. 2011). As Marijuana is by a long way the ultimate widely used illegal drug in Western civilizations, few populations concede the possibility of initially using marijuana recreationally but therefore uncover, intentionally or subconsciously, a bettering of psychiatric manifestations of a recognized or undiagnosed condition. If the primary determinant of dependence on illegal substances is not to treat a medical condition, but significantly for different reasons (public agreement, management, etc.) then the alone use can someday enhance dubious (Henwood and Padgett 2007).

"Self-cure" in both of these frameworks elucidates the significance of an experienced doctor being present and directing patients in their curative use of marijuana, so that decide the ultimate efficacious pattern beneficial, and prevent questions guide becoming worn and/or addiction. Because of the conceivably fine line between correct self-medicating of a healing condition and utilizing cannabis in positions place it grants permission to do more harm than good, a better understanding of the selections, desires, and motivations of sufferers is a good beginning in our investigation of self-medicating accompanying marijuana.

Who and when: distinguishing self-medicating inmates

There are supposed 119–224 heap frequent consumers of cannabis in general



(United Nations Office on Drugs and Crime 2012) but it is immediately imprecise to use what many bureaucracies could be considered, or analyze themselves, as curative consumers. Research from Canada suggests that 1.6–1.8% of the total community may be self-outlined healing consumers, which manages to indicate a healing-use rate of 10% or more with the total marijuana-utilizing state (Ogborne et al. 2000). Still, even though a lot concede possibility understand information from the occurrences of real medicinal consumers of marijuana, there are remarkably few data available on this material. Currently, most facts handy on the belongings of cannabis use arise from studies on the abuse of cannabis as a related to sports drug. As a result, new healing consumers and their physicians are frequently worried about the risk of a habit of activity, overdosing, and inebriation (impression “extreme”). But even though specific studies indeed devote effort to something the alike drug (- nabis), it is important to acknowledge skilled may be big dissimilarities between curative and recreational consumers, for example, in conditions of the goal for us (division 17.1), repetitiveness and size of drug, and route of the presidency.

Randomized, fake pill-regulated, and confused clinical tests (RCTs) are the current golden standard for productiveness and security, allowing us to decide place and when the use of a curative element is medically appropriate. However, the healing belongings of herbal marijuana have straightforwardly distinguished from drug products in various RCTs. Most of these studies distinguished an not listed spoken marijuana extract (Cannador®) to Marinol® (Freeman et al. 2006; Killestein and others.2002; Strasser and others. 2006; Zajicek and others. 2003, 2005) while any remainder of something compared dried cannabis to Marinol® (Haney and others. 2005,2007). Added approaches can command a price of, at least temporary, to

typify self-medicating victims and better believe their selections and preferences.

For this reason, the International Association for Cannabinoid Medicines (IACM) acted a cross-localized survey on the emotional weaknesses of inmates for different presidency forms of cannabinoids, equating self-cure to drug brands such as Marinol®, Nabilone®, and Sativex®. Moreover, a current judgment of the Dutch curative marijuana supports- gram told a money of dossier on consumer traits in a more objective manner, by resolving prescriptions for marijuana dispensed by Dutch pharmacies over diversified age. Both studies are conferred in the following sections (divisions 17.4.1 and 17.4.2). Finally, the dispassionate dossier supports-insult the curative effects of marijuana can be restricted, but they are not missing. A short overview is accordingly likely of the studies advocating few of the differing claims made by subjects (division 17.4.3).

17.4.1 IACM Worldwide survey

The IACM survey was capable of capturing the knowledge and opinions of 953 victims, making it the best worldwide study on consumers bearing experience accompanying diversified cannabinoid-located cures (CBMs) so far (Hazekamp and others. 2013). Although the authors foreshadow the disadvantages of self-picked partnership and point out a potential bias toward herbaceous marijuana, the study pointedout a forceful preference of those scrutinized for herbaceous marijuana commodity and the inhaled route of presidency, as opposedto spoken drug products.Onaverage, players of the survey had occurrence with three to four various CBMs; were current consumers theone had an energy professional complicated in the management of their ailment; and had happened toutilize CBMs for notcompletely various years. The average regular use, established estimates by matters, categorized from2.4g for beverage,



3.0g for smoking and for vaporizing, and 3.4 g for food or tincture. The top five manifestations that cases destined to be treated with CBMs were never-ending pain (29.2% of shareholders), worry (18.3%), eating disorder and/or weight (10.7%), cavity (5.2%), and restlessness or asleep disorder (5.1%). Interestingly, skilled appeared to be no obvious equivalence of the favorite pattern of consumption with the healing condition or syndromes under the situation. Several different studies have labeled the same manifestations, specifically incessant pain, as superior reasons for utilizing CBMs (Canadian Centre on Substance Abuse 2004; Clark 2004; Coomber et al. 2003; Hathaway and Rossiter 2007; Lucas 2012; Ogborne and others. 2000) It endures be eminent that few post- is focused on the strength of marijuana crop to alleviate syndromes, while others were more engaging attention the healing clues of those communicable these merchandise, which can fairly confuse the corresponding of different studies.

When the survey distinguished the benefits of the drug to herbaceous preparations on many various facets (reactions, attack and event of effects, drug, etc.), the latest were favorite private cases. Pharmaceutical commodities were preferred only for their “ease of preparation and consumption,” even though it may be famous that scarcely any of surveyed matters stated real happening accompanying these products. Indeed, herbaceous marijuana output is mainly deficient inconvenient, trustworthy, and patterned presidency forms, opposite to conventional cures. The acquired consumer traits are in bare contrast with the common cure, which is for the most part concentrated on prescribing oral distinct-compound drugs. Perhaps that is to say reason, according to the survey, an increase in cannabis waited widely common even

with those victims the one had access to drug cannabinoid drugs on formula.

17.4.2 The Dutch curative marijuana program

The curative cannabis program of the Netherlands offers drug-grade marijuana on formula to chronically ill subjects (OMC 2013). Although victims are advised to execute the merchandise by utilizing a fine mist or by preparing it as a beverage (Hazekamp and others. 2006, 2007), they are free to select their method of consumption. Presently, most Dutch medical insurance associations indemnify curative cannabis somewhat, and few immediately even cover the Volcano Medic fine mist for healing use (NCSM 2012).

A recent study by Hazekamp and Heerdink (2013), making use of the prescriptions table of the Dutch Foundation for Pharmaceutical Statistics, was the first to use an objective dossier to evaluate bit devouring patterns of arbitrary cannabis use. Covering the ending 2003–2010, the study judged nearly 35,000 prescriptions for curative marijuana by Dutch physicians. Of the 5540 (anonymous) sufferers labeled in the study, more women (56.8%) than men (42.7%) secondhand medicinal marijuana on medicine. The mean (middle) age of the study state was 55.6 (55) age, with a range of 14–93 age. The intentional people took on average 6.4 prescriptions of Curative marijuana accompanies a median of 10 g dispensed per medicine. Overall, curative marijuana was recommended for an average duration of 251 days. Interestingly, this contrasts accompanying different studies that establish marijuana was secondhand medicinally more commonly over an ending of age and even over ten of something (Lucas 2012; Swift and others. 2005).

Although the route of administration taken care of not be judged from the convenient formula dossier, the



average daily use of 0.68 g was considerably inferior to the 3–4 g of the IACM survey. These data point to a reduced potential of misuse, and an apparent dearth of extensive happening of tolerance to marijuana recommended by a specialist. By comparison, an average Dutch marijuana cigarette secondhand for relating to sports purposes holds about 0.26 g of marijuana as opposed to tobacco (Van der Pol and others. 2013). Interestingly, the relative use of various marijuana varieties waited quite constant over the age 2007–2010: about 60% of prescriptions were for an assortment Bedrocan®, accompanying extreme THC (19%); 25% for Bedrobinol®, with lower THC (12%); and 15% for Bediol®, holding two together THC (6%) and CBD (7.5%). By resolving the cure prescribed in the ending right before the first attack of marijuana use,

The study was intelligent in recognizing some healing clues compared to the accompanying cannabis use of the Dutch sufferers. It was established that pain cure was secondhand by 53.6% of all recommended cannabis consumers. Medication arbitrary to treat revulsion was secondhand by 15.5% of all subjects. Although tumor, glauoblivion, and HIV/AIDS are frequently noticed in common media concerning curative marijuana use, oncolytics (2.7%), eye pressure cure (2.2%), and HIV medication (0.9%) were only secondhand by a limited capacity of issues.

Because the study did not cover the entire Dutch public, and a meaningful proportion of inmates is believed to waste marijuana acquired from nonofficial beginnings, the premeditated prevalence rate of 5–8 per 100,000 bear be a very conservative estimate. Prevalence rates (discreetly) stated in some other nations place curative marijuana use is recorded by national experts are 35 (per 100,000) for Canada and 80 for Israel, while in a few US states predominance rates of overflow 100

are claimed (IACM 2012). However, these numbers grant permission to be considerably exaggerated accompanying relating to sports users sitting as curative consumers (Nussbaum and others. 2011).

17.4.3 Clinical research in support of herbaceous marijuana

Clinical studies accompanying distinct cannabinoids (normal or synthetic) or whole plant developments (for example, preserved marijuana, encapsulated extract) have frequently existed stimulated by certain informal experiences of patients utilizing unrefined marijuana output for self-treatment. For example, the antiemetic, longing embellishing, painkiller, and influence sedative effects, and the healing use of cannabinoids in Tourette's condition, were all found or found again in this approach (Hazekamp and others. 2010). This talks about the fault-finding role that accumulating data on current patient presence has played—and can continue to play – in a progressing understanding of marijuana productiveness.

An inclusive summary of dispassionate trials accompanying cannabinoid-located cures was given by two completed review documents (Ben Amar 2006; Hazekamp and Grotenhermen 2010). In the end from 1975–2009, not completely 109 regulated clinical studies were written, evaluating overflow 6500 inmates suffering from an off-course range of sicknesses. Based on the dossier applicable, it is likely to confirm that cannabinoids, still in the form of herbaceous marijuana, exhibit a healing potential mainly as analgesics in never-ending neuropathic pain, as demand stimulants, and as antiemetics in incapacitate afflictions (like, cancer, and AIDS, hepatitis C), and for the situation of differing manifestations of diversified sclerosis. Additionally, cannabinoids may have potential in the indicative situation of sleep-inducing or numbing drug rope



harms, intestinal dysfunction, Tourette's disease, energetic-exercise and worry disorders, allergies, epilepsy, and glaucoma. Perhaps the individual of ultimate inspiring Current verdicts are that cannabinoids grant permission to be effective in the situation of a few forms of malignancy, by not just alleviating symptoms but indeed beating and murdering malignancy cells (Velasco and others. 2012). Nowadays it is better assumed that marijuana elements other than the affecting the mind to produce vivid visions $\Delta 9$ -THC can imitate in healing belongings. Plant cannabinoids such as CBD and tetrahydrocannabivarin (THCV), or the plentifully present terpenes, grant permission to influence the wanted therapeutic belongings in a myriad of ways, containing cooperation, augmentation of rude answer or penetration of the blood-brain hurdle, and doing receptor binding or absorption (Izzo and others. 2009; Russo 2011). Unfortunately, such new intuitions are scarcely mirrored still in our dispassionate understanding of cannabis. Moreover, dispassionate troubles usually devote effort to something isolated cannabinoids likely verbally, while self-medicating cases chiefly use herbal marijuana in inhaled or tasty forms. Those RCTs accompanying cannabis frequently show important disadvantages, containing an anti-discrimination program of cannabis differences (limited to any official beginnings of research-grade cannabis general), drug range (fear of stuff), and presidency form (smoking is powerfully underrepresented in clinical data). In contrast, self-medicating cases can select from an almost constant range of assortments, from what or which place they pick the optimum variety, drug regime, and presidency form by a process of the experimental approach.

17.5 Why: reasons for self-medication

Since the United Nations selected the Single Convention on Narcotic Drugs in

1961, marijuana and allure production have been delineated as "narcotics accompanying an extreme potential for abuse and no recognized curative value." This accurate allowable categorization has efficiently delayed their progress into up-to-date cures, by not only consistently cannabis and cannabinoids to lack the hands of healing consumers, but likewise by depriving investigators of the matters wanted for controlled survey. But despite its lawlessness, big numbers of sufferers have continued to authorize the right to use marijuana, containing for self-cure. Patient-driven lawsuits against their governments have existed the support of the chance of marijuana in Canada, Germany, and Finland, while voter drives have developed in the legalizing of healing pot use in diversified US states. Even in situations place they have an approach to allowable beginnings of herbal marijuana, inmates commonly select to grow their own marijuana (Hazekamp and others. 2013). Besides the (seen) superior productiveness of self-medication, we will survey any potential reasons reason this conceded possibility endures in section 17.5.1.

17.5.1 Choice of differences

As a result of far-reaching works in marijuana breeding and excerpt, an influential range of cultivated assortments (cultivars, as known or named at another time or place strains) has been grown in general. These are commonly outstanding, by plant breeders, relating to sports users, and marijuana cases alike, through the use of interesting names in the way that White Widow, Northern Lights, Amnesia, or Haze. Already, over 700 varieties have been expressed (Snoeijer 2001) and many more are ideas to endure. An important reason for inmates to continue buying fabrics from illicit markets is the experience that, frequently by an experimental approach, they claim to have established particular strains that work optimally for the treatment of their particular syndromes.



In the framework of self-medicating, an understandable question is by what method the chemical elements in the direction of miscellaneous marijuana cultivars reflect characteristic curative features, and what types of marijuana should therefore be vacant to victims. In Canada, a recent review of the social healing pot program pointed out approach to multiple marijuana types is expected a main issue for patients (Health Canada 2011). The most prevalent habit now used to categorize cannabis cultivars is through plant makeup (phenotype) accompanying two main classes usually acknowledged *Cannabis sativa* and *Cannabis indica*. Most modern cultivars are, nevertheless, innately a blend of two together types. It is therefore obscure whether this categorization indicates any appropriate distinctnesses in the synthetic arrangement.

A better understanding of synthetic differences betwixt marijuana cultivars manages help along between the far-flung information on marijuana that lies inside the community of recreational consumers, and the news wanted by curative consumers and health experts. However, it should be more and more clear that parts in cannabis further Δ^9 -THC and CBD, to a degree additional minor plant-cannabinoids and explosive subordinate metabolites called terpenoids, are complicated in the drug's overall effect (Russo 2011). This extreme number of (potential) alive components considerably complicates an unoriginal reductionist approach utilizing examining allure, animal studies, and clinical trials, the place usually a sole alive ingredient is recognized before the review course is attainable.

An alternative approach to this diversified component question may search out together recognize and measure all big components present in differing marijuana types, and therefore use effective statistical tools in the way that principal component study (PCA) to categorize cultivars in a

smaller number of chemically different groups. With this approach it may be attainable to move out marijuana cultivars, accompanying often obscure and unproven traits, toward a new categorization utilizing chemovars with a complex, but however clear synthetic "dab." This methodology has already been favorably used for marijuana for the distinction of cultivars (Hazekamp and Fishedick 2012) as well as control of product quality (Fishedick and others. 2010).

Using an inclusive chemovar approach to concede the possibility helps medicinal consumers and their physicians to favorably switch from an advantageous marijuana sort obtained through unlawful markets to an identical strain that is to say vacant through official state-run programs. It can also help these governmental programs to grow less or make less the follow advantageous cannabis assortments expected patterned and made acquainted as an official cure. Exchange of cultivars and analytical dossier betwixt the miscellaneous marijuana programs worldwide grant permission considerably promote aforementioned a change.

17.5.2 The role of the doctor

Because physicians are the main gatekeepers to the allowable and medically directed use of cannabis, their function and attitudes warrant few further tests. With a climbing interest in, and radio coverage of, curative use of marijuana, victims grant permission to turn toward self-medication when their basic nurse refuses to consider the argument or displays a clear ignorance about it. Unfortunately, physicians often do not visualize themselves correctly outfitted for their watch person act. A survey among US physicians concerning their stances toward allowable medicine of cannabis as a healing remedy erect that a singular-tertiary of surveyed US physicians understand marijuana power has healing value, against the almost two-thirds base of all Americans



(Charuvastra and others. 2005). Safety concerns contained the harms associated with hot, intellectual reliance, and risks of harm due to severe inebriation. Respondents fashioned a clear demand for more research to enact the risks and benefits of cannabis use in particular patient peoples.

Also, a survey by the Canadian Medical Association (CMA) demonstrated that physicians have important concerns about the lack of rigorous research into the drug and their function in prescribing it (Sullivan 2012). Respondents are chiefly anxious that inmates who wanted to heal marijuana actu associates cherished it for recreational purposes, and healing doctors did not have enough information on the risks and benefits or the appropriate use of marijuana for medicinal purposes. The CMA considered upgrading electronics about marijuana, but further developing binding instruction and licensing programs for physicians established the information already feasible. A A survey with classification physicians in Colorado (Kondrad and Reid 2013), the state accompanying the chief written occurrence of medicinal use of marijuana in the US, granted that most physicians trusted marijuana use, even medicinal, bears risks, and nearly half pronounced that physicians should not recom- correct grass as a healing cure at all. But understanding that curative use was before a realism in the United States of america of Colorado, nearly all came to terms with the need for further healing instruction and formal preparation (for example, through the ongoing healing education (CME) scheme) before prescribing or advising it.

Since it is neither certified nor patterned according to Food and Drug Administration (FDA) principles or their equivalent in additional nations, physicians who approve marijuana should be exceptionally scrupulous in their disease and resultant pieces of advice. As a result,

physicians demand clear, definitive directions for curative use, that should raise the appropriate experts and healing associations in different nations. However, this demands a not complete understanding of self-medicating victims, containing a choice of differences, administration forms, dosage, and the main healing environments it is secondhand for. Physicians have few genuine concerns about self-cure accompanying herbaceous marijuana, and it is important to confirm that these concerns are perceived. If unaddressed, the impact conceded possibility to be noticed as specialist frustration or even eluding of positions place their care is critical for patient energy. The main aim of these exertions is to underrate recreation, misuse, and abuse potential while providing enough treatment to all those the one have an authentic need. Recent beliefs freed by various medical partnerships are meaningful to become involved in that direction (American Medical Association 2009; Sullivan 2012).

17.5.3 Social Facets of self-drug

A low link middle from two points those who use marijuana medicinally appear expected that they contract illness conditions that are never-ending and continuous, and they are unhappy with allopathic situations (Hathaway and Rossiter 2007). So even though the dispute on self-medicating accompanying cannabis is generally attracted to healing benefits against pharmacological side effects, supplementary factors can be complicated. A meta-analysis of the emotional belongings of marijuana establishes that the most repeatedly stated belongings were: upgraded mood (that is, drunk, content), improved relaxation, increased awareness of self, and so forth, and revised ideas (Green et al. 2003). This signifies that confirming healing productiveness through clinical wealth uniquely disregards a myriad of psychosocial factors.



The right to drugs accompanying marijuana, as a public justice issue, is individual that growing numbers of North Americans and Europeans appear to support. However, engaging mainly biomedical and mechanics approaches, community health instrumentalities have not historically well-informed enough to combine the aforementioned plans and find it difficult to supply a clear response to this happening. Preconceived whims about cannabis are ever-present, and definitions of marijuana as an instinctive herb remedy as opposed to an artificial drug concede possibility also influence ideas in consideration of allure use (Reiman 2008, 2009; Reinerman and others. 2011). As a result, those who self-drug frequently do so on their conditions, without administration authorization or the counseling of physicians. In this deregulated climate, com- excitement clubs, caffeine shops, dispensaries, and added sorts of collective farms have emerged and been banned to play a lively act in the provision of reliable approaches to, and healing information of, cannabis. Operating on the borders of association, these outlets play a main part in creating a society with humans who are frequently very marginalized themselves. Club participation concedes the possibility provide group correspondence, authorization, and therapeutic support to further the cannabis use itself (Janichek and Reiman 2012).

In a study (Feldman and Mandel 1998) looked at the benefits of enrollment in “marijuana purchasers’ clubs” in the US, the authors decided that such clubs were the soundest option—com- peeled to doctors, pharmacists, lawman, and the dark market—for providing an approach to marijuana as cure. They discuss that the clubs produce the best healing background, a curative surroundings that frequently offer a philosophy of love, humanity, and psychological support in addition to the strong benefits of marijuana itself. A

similar idea was copied in a study by Hathaway and Rossiter (2007), place appendages contrasted their tenderness clubs accompanying situations they taken at the hands of doctors, prosperity instrumentalities, employers, experts, and management officials. A common idea written was that “incessant sickness stigmatizes and cases those the one endures to shame and standardized abuse.” So perhaps the preeminent supporter substance of curative marijuana use is the complete approach that cannot take place alongside the situation accompanying conventional drugs.

Dispensaries can still help to decrease the break essential instruction that many physicians have in danger (visualize portion 17.5.2) and fulfill unmet clinical desires by providing a lucky healing argument offering different duties in consideration of victims. For example, in a study by Reiman (2008), 66% of the subjects surveyed stated that using the whole aids in San Francisco Bay Area healing marijuana abilities containing massage therapy, digestive and herbaceous consultations, peer groups, and acupuncture. On the inconvenience, few dispensaries now offer dispassionate duties connected with the potential disadvantages of cannabis use, in a way that means misuse, reliance, and insane energy duties (Janichek and Reiman 2012).

17.5.4 Costs and Compensation

Because chronically ill cases, as a result of restriction and inaction, are frequently living on a narrow budget, the reason for selecting self-drug grant permission is related to the cost. Indeed, when requested to rate ten various facets of CBM use on a vindication scale varying from 0–10, the determinant cost cut shortest overall, indicating that the cost complicated accompanying utilizing cannabinoid-located drugs, either herbaceous or drugs, is a bigger issue for patients of all training. Of



course, this conceded possibility is not unexpected as most healthcare wholes on the planet do not (still) deal with compensation or health insurance inclusion of CBMs.

The cost determinant power has had a solid influence on the vacant dossier on self-drug, which may be a reason for patients to evolve their marijuana, or to pick weaker-character fruit endangering their fitness. Perhaps patients favoring herbaceous marijuana are those the one need a very extreme measurement of cannabinoids, that cannot be covered by the now usable pharmaceutical cannabinoid arrangements, two together nearly and economically. The US Institute of Medicine then explained this issue in 1999, declaring that for patients outside medical insurance marijuana-

Juana may be more inexpensive than an official beginning of Marinol® (Joy and others. 1999).

However, a few hopeful changes are underway. In 2011, Sativex® was accepted internal reimbursement in Spain from the Spanish Ministry of Health (GW Pharmaceuticals 2011). And in the

The Netherlands' current survey demonstrated that 11 15 important Dutch medical insurance associations evaluated supported not completely few forms of compensation for curative marijuana (NCSM 2012). So even though the a need for more dispassionate data remnants, a fair and complete corresponding on the total costs and benefits of various cannabinoid situations grants permission to be another approach to this complex issue.

17.6 How: The presidency forms and controls product quality

The frequently cited report Marijuana and Medicine: Assessing the Science Base for one US Institute of Medicine (Joy and others. 1999) reminded

the need for active presidency forms for cannabis- goods, asserting that a controlled dossier indicates the potential healing worth of cannabinoid drugs,

Generally Δ 9-THC, for diversified indications, but dried marijuana is an unrefined cannabinoid delivery method that more transfers injurious substances. The report decided that what is wanted for the optimum use of medicinal cannabinoids is a possible, nonsmoked, expeditious-attack delivery order. Self-cure, nearly by definition, is not compelled by controlled observations, and may even energetically fight beliefs articulated by institutional chemists or by associations visualized as “Big Pharma.” As a result, self-medicating subjects may have, by experimental approach, found particular cannabis assortments holding alive components that only currently have enticed the interest of physicists, such as CBD (<http://computer.network.projectCBD.org>), THCV (Izzo and others. 2009), sure types of terpenes (Hazekamp and Fishedick 2012), etc. And possibly they simultaneously have discovered acceptable presidency forms for effective delivery of these compounds. Indeed, diversified odd presidency forms have been grown apiece self-medicating, including reduced extracts popular as marijuana oils, inexperienced juiced buds, marijuana brownies, and a range of fine mist designs.

Although these remedies are sometimes secondhand by abundant groups of sufferers, there is practically nothing-insult in the written literature about bureaucracy in agreements of cannabinoid/terpene arrangement, presence of contaminators, uniformity of quantity, or even their exact development methods. The following divisions will explain a few common presidency forms, and inform the main quality and security facets that guide them (portions 17.6.1–17.6.5).



17.6.1 The biochemistry of presidency forms

Depending on the presidency form, many changes to the original profile of compounds pre-shipped in the new plant material can happen. A common, and frequently missed, function of most presidential forms of (herbal) marijuana is a warming step, that is essential for the conversion of the sour cannabinoids into their, pharmacologically more movement, impartial counterparts. If sufficient heat is used, sour cannabinoids in the way that THC-acid (THCA) and CBD-acid (CBDA) will evolve into their neutral matches by futile the doubtful carboxylic acid group. When cannabis is charred for hot, melted for cookies, or boiled for beverage, nonpsychoactive THCA turns into Δ^9 -THC, and CBDA turns into CBD, thus for all added cannabinoids. This conversion process, famous as decarboxylation, still instinctively takes place in aging marijuana samples, even though at a much more sluggish rate (Veress and others. 1990).

Besides the extent of decarboxylation, additional facets that had a connection with administration form grant permission have a meaningful effect on therapeutic belongings. For example, overheating, in addition to uncovering to light or air, may bring about the establishment of shame products to a degree of cannabitol (CBN) and Δ^8 -THC, accompanying potential pharmacological characteristics of their own (Izzo and others. 2009). Fragile components in the way that the terpenes can leave by evaporation on account of unending depository or preparation patterns that administer heat before devouring (e.g., angered for beverage, evaporating solvent for makinsult extracts). Moreover, each administration form suggests allure own set of distinguishing metabolites formed upon use. As a result of all these determinants linked, a different range of compounds is eventually listing the bloodstream, and

consequently a various type and events of belongings may be noticed with each marijuana cure. The following sections (17.6.2–17.6.5) present a short survey of concerns related to ultimate prevalent presidency forms.

17.6.2 The inhaled route: smoking and vaporizing

Worldwide, hot is without a doubt ultimate commonly secondhand arrangement of absorbing cannabis. The few studies that have straightforwardly distinguished two together forms of THC transmittal show smoking expected com-fable (Haney and others. 2005, 2007) or more effective (Chang and others. 1979; Hepler and Petrus 1976;

Vinciguerra and others. 1988) in attaining adequate ancestry concentrations than spoken presidency. Inhaling is about equal in efficiency to subcutaneous injection, while significantly more practi-U.S. state (Agurell et al. 1986; Ohlsson and others. 1980). A prescription of 2–5 mg of Δ^9 -THC exhausted through smoking dependably produces ancestry concentrations above the persuasive level within any notes of the meeting (Mattes and others. 1994; Wall and Perez-Reyes 1981). As a result, cannabis hot is mainly appreciated by self-medicating inmates as a convenient procedure of presidency, admitting accurate self-titration of the asked belongings (Hazekamp et al. 2013), even though many healing studies utilizing smoked or vaporized presidency of marijuana stated at least a few psychoactivities as a aftereffect (Hazekamp and Grotenhermen 2010). Although the use of smoking should unmistakably not be heartened, possibly relevant to review course either the addition of tobacco to marijuana cigarettes is solely a matter of taste or tendency, or has an actual healing function together accompanying cannabis. At least one individual study has submitted that the occupancy of tobacco releases



comparably more THC from marijuana when cured (Van der Kooy et al. 2009).

Despite the lack of a clear friendship betwixt cannabis use and body part malignancy in dispassionate epidemiological studies (Aldington et al. 2008; Hashibe and others. 2006), breathing poisonous compounds during marijuana hot can pose weighty health hazards (Mehra and others. 2006), presumably even more so for chronically ill and injured patients. This risk is not expected on account of cannabinoids, but rather of deadly pyrolytic by-brand such as sully, colorless odorless toxic gas, and liquid (Hiller et al. 1984; Matthias and others. 1997). Consequently, the weaknesses of cured cannabis have been widely regarded as an important obstacle to the authorization of natural (herbaceous) cannabis as a cure by community health experts (Joy et al. 1999).

Cannabis evaporation, or effervescence, is a method aimed at restraining vexatious respira-conservative toxins by warming marijuana to a hotness where alive cannabinoid vapors are made, but beneath the point of combustion place, pyrolytic poisonous compounds are announced. Vaporization offers the advantages of the pulmonary route of the presidency, that is, brisk delivery into the bloodstream, ease of self-titration, and accompanying belittlement of the risk of over- and underdosing while preventing the respiratory difficulties of hot. Several studies performed in the current age appearance that vaporizing can be thought of as an adept way of cannabinoid administration (Hazekamp and others. 2006; Zuurman and others. 2008) accompanying a bioavailability comparable to hot (Abrams and others. 2007). Because of the hotnesses used for vaporizing (usually in the range of 180–210°C), all range of terpenes present in herbaceous cannabis is capably inhaled, bestmizing healing potential.

17.6.3 The oral route: beverage and food

Herbal marijuana can be wasted in the form of an alcoholic beverage, likewise referred to as a “marijuana beverage.” Although assorted standardized studies have existed accompanying tea developments of marijuana (De Jong and others. 2005; Hazekamp et al. 2007; Steinagle and Upfal 1999), marijuana beverage was raised to be an almost standard arrangement of intake with subjects the one reported to have happening accompanying the spoken use of cannabis cure (Hazekamp and others. 2013). The main benefits associated with allure use include relatively long periods of belonging and low incidence of reactions.

Actual procedures used for marijuana beverage development by patients are broadly mysterious, and many differences may lie. In the Netherlands, cases are considered to prepare marijuana beverages by increasing 1.0 g of cannabis to 1 L of angered water, allowing it to smolder for 15 min, and belatedly leaking out stable parts by using a coil-mesh beverage-mesh (OMC 2013). Even though cannabinoids are notoriously insoluble in water (Hazekamp and Verpoorte 2006) it was raised that marijuana beverage prepared thus allowed meaningful amounts of cannabinoids in a reproducible manner (Hazekamp And others. 2007). Considerably more THCA than Δ 9-THC (percentage about 5:1) was detected, that concede possibility be related by the approximately larger water solubility of THCA distinguished to Δ 9-THC, combined accompanying an almost slow decarboxylation rate of sour cannabinoids in boiling water (Hazekamp and others. 2007). In addition, various cannabinoids were found in their sour form, containing cannabinigerolic acid (CBGA) and tetrahydrocannabivarinic acid (THVA). This grant permission is of particular interest, as most other presidency forms are principally exhausted acidic cannabinoids.



Although usually to some extent known about organic ventures of sour cannabinoids, CBDA was reported to have a powerful antimicrobial project (Leizer and others. 2000) and to show promising antagonistic- -instigative belongings (Takeda et al. 2008), while THCA was erect to have an abundant effect on the human invulnerable system (Verhoeckx and others. 2006).

Self-cure accompanying cannabis in swallowed form, to a degree wafers, brownies, or candies, appears expected specifically popular with North American sufferers (75.6% of survey members; Hazekamp 2013) compared to additional nationalities (46.5% of survey parties). As far as we experience, there now are no justified means available for the study of cannabinoids and/or terpenes in food holding herbal marijuana or extracts. Indeed, fitting a practiced analytical sample appropriate for chromatographic study can be challenging in the appearance of additives to a degree butter, crushed into fine grains, sugars, etc. As a result, no written data appears expected accessible on the composition or regularity of food. Theoretically, issues that are inclined to occur with specific output contain homogenization (ensuring individual biscuit has the unchanging potency as the next), regular decarboxylase- tion (an abundant fairy is baked more protracted than a tinier individual), and shelf-growth support. Consequently, the use of patterned recipes and processes can be situated more important for food than for some different administration forms argued present.

17.6.4 New kids on the block: tinctures, concentrates, and inexperienced juice

According to the IACM survey conferred in division 17.4.1, the ultimate common issues concerning CBMs that cases are engaging attention include distressing taste, lethargy, wild appetite (strong desire), and insane effects (gaining

extreme). It was still suggested that various presidency forms grant permission be preferred in the solitude of an individual's home and honesty (Hazekamp et al. 2013). To address specific issues, self-medicating cases commonly experiment with new presidency forms, few of which may before drawing meaningful popularity. Not unusually, most of these new and odd presidency forms have never been proven for some form of status or safety. When sufferers were asked what new marijuana-based brand bear ought legally applicable (besides herbaceous marijuana itself), tincture established whole marijuana was raised to be the ultimate popular choice (Hazekamp and others. 2013). The main benefit cited was the instability of allure use: as oral drops, in scorched merchandise and beverages, and even for vaporizing or smoking, admitting for maximum bendability of using cannabinoids during the whole of the era. Indeed, a patterned and quality-regulated marijuana coloring would be nearly smooth to produce and would link the modern use of cannabis straightforwardly to the real use of tinctures as interpreted in older merchandise (Zuardi 2006).

In order to “mobilize” the sour cannabinoids, the tincture, or the plant material used to formulate it, must be warmed at some point in the readiness process. Cannabis lubricate is a condensed extract obtained by the fit origin of the buds or leaves of the marijuana plant, deriving its name from its gummy and viscous presence. Various nonpolar solvents have been recommended for this purpose, containing oil heavenly, naphtha, intoxicating, and brownish lubricate. The most well-known marijuana lubricate preparation is known or named at another time or place as “Rick Simpson” lubricate (Simpson 2008, 2013). Part of the self-medicating people firmly trust that these devices are worthy of curing malignancy, a



claim namely moved backward by numerous informal patient news.

However, a current study equating five commonly secondhand development means raises significant distinctnesses in cannabinoid and terpene arrangement of the happening extracts. Also, the demeanor of residual financial sound was established as expected as a meaningful concern, particularly in the case of utilizing oil as the distillation solid. The end of the study searched out gird extracts straightforwardly in olive lubricate, fiery in an angered water soap, for the highest improvement of live compounds, and no risk of basic financially sound residues (Romano and Hazekamp 2013).

Finally, the use of raw marijuana buds and leaves, groomed by excite ruling class in a blender accompanying water or crop liquid squeezed from plants, or by eating bureaucracy straightforwardly as a dish of vegetables, merits some consideration. The demanded, but questionable, healing effects of these brands involve stop of seizures, diabetes, and even helping cure brain tumors in babies (Cannabis International 2013). Different from the different presidency forms said earlier, this preparation does not suffer some form of warming, and then contains all cannabinoids in their native (sour) form (Lee 2013).

17.6.5 Quality and safety

Because the goal of self-cure products is frequently to treat critically ill, or even invulnerable-imperiled, patients, issues concerning synthetic arrangement, quality, and security bear be of the topmost preference. In the absence of clear directions for readiness or chemo- u.s. state description, medicinal consumers of marijuana can carelessly purchase a product that has surprising belongings on their well-being and/or personality. Changes in chemical arrangement grant

permission not only emerge from historical differences betwixt marijuana types, but take care of also come from alternatives, e.g., help conditions, drying, handling, and storage. These determinants concede the possibility of disagreement between various suppliers (coffeehouses, medical centers, compassion clubs), and even between various quantities of the alike marijuana strain (Hazekamp and Fishedick 2012).

For conventional cures, free and verified control of product quality labs play a key role in guaranteeing value and security by operating detailed reasoning of the arrangement of this merchandise. In the social cannabis programs of Canada and the Netherlands, commodities are alone proven for common appearance (that is, color, bud shape, etc.), cannabinoid sketch, terpene sketch (the Netherlands only), and water content. Furthermore, the lack of heavy metals, pesticides, microorganisms, molds, and fungal poisons is settled. Because the self-administration- tion of marijuana most often takes place outside the sphere of permissible cure, guaranteed labs are wary of mastering complicated the reasoning of anything marijuana connected. By need, this void is therefore often suffused by deregulated labs that are started for appearances in the cannabis society, most especially in the US and Canada. However, marijuana is a complex phytomedicine accompanying a wide description of (potential) bioactive parts, that can change in many ways contingent upon the presidency form preferred (as debated earlier in portions 17.6.1–17.6.4). As a result, each type of presidency form needs allure own correctly validated systems for synthetic study. Because these tests are valuable, they are only affordable in the case of abundant bundle sizes. As a result, smaller production sites grant permission to have a basic question accompanying quality control. All these determinants confuse the starting of a trustworthy system



for control of product quality, as was currently proved by an approximate test among ten various California-located labs (Gieringer and Hazekamp 2011). Apart from THC satisfying completely or excessively, diversified case studies have identified the devouring of dangerous marijuana as the cause of therapy, or even death. Among the possible choices, marijuana amounts were erect to contain fungal spores, like, *Aspergillus* or *Penicillium* variety, or injurious microorganisms such as *E. coli* (Hazekamp and others. 2006; McLaren and others. 2008), lead pieces for additional weight.

marijuana is convinced by weight) (Busse and others. 2008), or ground-up cups or talcum to mimic the presence of glandular hairs (“crystal”) thereby suggesting taller effectiveness (Scheel et al. 2012; Van Amsterdam and others. 2007). In the case of pesticides, it is vague that, if any, pose a danger to the energy of customers. As yet, no studies have been administered on the security of pesticides used to inhale or ingest marijuana. Pesticides accompanying known allure grant permission to be changed, destroyed, or performed approximately poisonous in the process of explosion or baking. Although this cannot be a major concern for relating to sports consumers who for the most part inquire about inebriation of their own free will, victims cannot give expected exposure to specific risks. Cannabis devices from a patterned and quality-reserved beginning, if available, concede the possibility and thus be the more reliable choice for medicinal consumers favoring self-cure with herbaceous marijuana.

Prevalence and Demographics

Global estimates suggest that between 119 and 224 million people use cannabis regularly (United Nations Office on Drugs and Crime, 2012). Among these users, a significant proportion report using

cannabis for medical purposes. Studies from Canada indicate that 1.6–1.8% of the population identifies as medical cannabis users, with chronic pain being the most commonly reported condition.

4.2 Motivations for Use

Patients often turn to cannabis due to dissatisfaction with conventional treatments, the high cost of prescription medications, or a preference for natural remedies. The therapeutic benefits of cannabis, including pain relief, improved sleep, and reduced anxiety, are frequently cited as reasons for self-medication.

4.3 Risks and Challenges

Self-medication with cannabis carries inherent risks, including dependence, cognitive impairment, and adverse interactions with other medications. Inconsistent product quality and lack of standardized dosing further complicate its use. Addressing these challenges requires regulatory oversight, clinical research, and patient education.

Research Method

This test applied a blended-techniques method to research self-medicinal drug practices with cannabis. A cross-sectional survey was modified into dispensed to,000 members through online platforms, shooting records on demographics, scientific history, cannabis utilization styles, and perceived efficacy. Qualitative interviews were performed with 30 individuals to find out motivations, demanding situations, and reviews in extra depth. Data evaluation protected descriptive facts for survey responses and thematic coding for qualitative interviews. Ethical approval was obtained, and knowledgeable consent was secured from all contributors.



Results

The survey revealed that sixty eight% of respondents said the use of cannabis to manage chronic pain, was observed through 45% for anxiety and 32% for sleep disturbances. Over half (56%) of participants favored merchandise with a better CBD-to-THC ratio, mentioning fewer psychoactive consequences. Regardless of perceived benefits, 38% of customers said poor results which consist of dizziness, cognitive fog, or dependency problems. Qualitative analysis identified 3 primary problems: dissatisfaction with traditional remedies, the perceived herbal advantages of cannabis, and the challenges of dosing and product variability. Felony access significantly prompted utilization, with contributors in legalized areas demonstrating better delight and reduced stigma in contrast to those in restricted areas.

Discussion

The findings recommend a growing reliance on hashish as a possibility or complementary remedy, driven by its accessibility and consumer-counseled effectiveness. However, the shortage of standardized dosing suggestions and inconsistent products presents dangers. At the same time as legalization improves proper access to and reduces stigma, it can inadvertently inspire unsupervised use. This underscores the pressing need for regulatory oversight and scientific research to set up protection and efficacy benchmarks.

Conclusion

Self-medication with cannabis is increasingly popular among individuals seeking relief from chronic conditions. While promising, its use highlights critical gaps in clinical guidance and regulation. Future efforts should focus on

comprehensive research, public education, and healthcare integration to ensure safe and informed practices.

Self-medication with hashish is big among people searching for comfort from chronic conditions. At the same time as promising, its use highlights critical gaps in clinical steering and regulation. Destiny efforts need to awareness on comprehensive research, public schooling, and healthcare integration to make certain comfortable and informed practices. Self-drugs with marijuana appear to be famous now, and climbing in popularity. The rising interest in learning this wonder has already supported main insight into various facets concerning the medicinal use of marijuana that cases find productive and desirable. Such data is main in judgment of how to increase certain strength outcomes concerning marijuana use, by causing it progressively into the field of up-to-date cure. Ultimately, as official and federally regulated curative marijuana programs stretch to increase in prevalence and intensity, those the one has been pressured into self-drug connected with the unlawful retail grant permission get the opportunity to influence their curative use into the sphere of a regular patient-physician friendship. In the ideal background, physicians should have the news within reach to offer the same care with cannabis as they get by added drug preparations. Self-drug accompanying marijuana may therefore enhance strictly a matter of choice, alternatively essentiality

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Announcement of interest

I at this moment declare that:

I have no pecuniary or other personal hobby, direct or oblique, in any rely that raises or may additionally boost a battle with my obligations as a supervisor of my workplace management

Conflicts of interest: The authors claim that they've no conflicts of Interest.

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Genome wide analysis of growth and development genes in cattle (*Bos taurus*) and Buffalo (*Bubalus bubalis*)

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Abstract

Bos taurus and *Bubalus bubalis* have been major source of meat since about 10000 years. 50 genes associated with growth and development in *Bos taurus* and *Bubalus bubalis* were analyzed integrately by GWAS performing chromosomal mapping, gene structure, conserved motif analysis, gene expression, GO annotation analysis, protein-protein association and phylogenetic analysis, Main bio-informatics tools used were NCBI, Expasy, WebScipio, iTOL, heatmapper, string and MEGA 5. GH, TG and NEB were found as major genes of beef production by visualising expression by heatmapper, motif analysis by MEME and gene structure analysis using webScipio. All other genes were also linked differently with this trait. Each gene had unique structure and discrete role regarding growth. GH affects directly on growth and development. String results revealed that TG associates with other genes in complex networks to stimulate growth. Results of Motif analysis by using MEME and heatmapper showed that NEB has highly conserved domains associated with structural and functional role in skeletal muscle growth and development. Heatmapper analysis showed that CFL1 has role in growth and development of brain, lungs, spleen, colon and testis. ALDH2 showed overexpression in kidney and liver and ACTC1 in heart. Synteny analysis was performed to elucidate syntenic regions between Bt and Bb. Results showed that there is strong similarity and conserved regions. This is due to the strong evolutionary relationship of Bt and Bb. Phylogenetic analysis confirmed strong evolutionary relationship of *Bos taurus* and *Bubalus bubalis*. This comprehensive research could be used by animal scientists to understand growth pattern, association of genes and development of genetic markers to increase beef production to make Pakistan hub of halal food.

Keywords: Gene, GH, growth, development, NCBI

Introduction

Cattle and buffaloes were used as a source of meat and milk production on a global scale about 10000 years ago.

(MacHug *et al.*, 1998). Archeological evidence, historic documents and genetic analysis have recorded the domestication of cattle and buffaloes. Domestication of



cattle and buffaloes occurred autonomously in the Near East and the Indian subcontinent. Human migrations, which advanced the dissemination of domestic cattle over Asia, Africa, Europe and the New World. (Liu *et al.*, 2014) Due to meat production, cattle (*Bos taurus*) and Asian buffaloes (*Bubalus bubalis*) play an essential socioeconomic role. (De Camargo and colleagues, 2015) Meat is a main protein source throughout the world. The meat industry has been rapidly growing to meet the increasing demand for meat, which is one of today's most challenging social issues. (Thornton 2010; Cunningham 1989) The major beef-producing countries in Latin America are Brazil (51.6 %), Argentina (18.5 %) and Mexico (9.4 %). Uruguay, Venezuela, Paraguay, Bolivia, Ecuador, and Chile provide only 1% of regional production. Latin America is a region of the world that boosted supply in response to growing demand for beef. Brazil's beef cattle sector is well-developed, relying primarily on grass-fed cattle such as *Bos taurus*. Beef production in Brazil has grown to become one of the most important sources of job and wealth creation in the last eight years, involving about 200 million head of cattle, 7.5 million jobs, and more than US\$25 billion revenue, with a demand for around 450,000 bulls replacement per year. However, Brazilian beef productivity remains low, and herds require significant improvement (Dunner *et al.*, 2013). There are about 207 million buffaloes in the world, with more than 97 % living in Asia, 2% in Africa, mainly Egypt, 0.7 % in South America, and less than 0.2 % in Australia and Europe. India, Pakistan, China, Egypt, and Nepal are the countries having the most dairy buffaloes. Dairy buffaloes outnumber dairy cows in Pakistan, Egypt, and Nepal. (Vaughn *et al.*, 1999) Pakistan has a diverse range of cattle genetic resources. Buffalo is rightly referred to as Pakistan's "Black Gold" due to their adaptability. The best buffalo animals may be found in the country's

canal-fed districts, where there are enough fodder and crops to consume. With around 250 000 buffalo/cattle, Pakistan's 'Landhi Cattle Colony' has the world's largest concentration (Younas and Yaqoob 2002). In comparison to cattle beef, buffalo meat is slightly dark reddish in colour. As buffalo meat has a reduced cholesterol content, it is of higher quality than cattle beef. Because buffalo meat is devoid of BSE concerns, it is recommended for export to the Gulf countries. (Vaughn *et al.*, 1999; Batzoglou *et al.*, 2000). It is important to recognize that it is our national obligation to change the available genetic resources in a better form for future generations than we received.

Growth and development are economically significant quantitative traits in beef cattle that influence carcass amount. (Kanis *et al.*, 2005; Park *et al.*, 2018) Intramuscular fat deposition, often known as "marbling," contributes greatly to meat production and quality characteristics such as juiciness, flavor, and tenderness. IMF is regulated primarily by genetic variables (breed and sex differences and double-muscling syndrome) as well as age and nutrition. Several number of management elements, including as weaning age, castration, slaughter weight, and environmental conditions also have an impact on IMF. (Wang *et al.*, 2009, Hocquette *et al.*, 2010) Meat production (growth and development) is economically most important trait governed by many genes (Mackay 2001). However, some of these genes may have a major role. These are known as Candidate genes (Mayr 1954). In contrast to natural selection, gene editing and artificial selection favors mutation, which produce "hitch-hiking" effect (Hayes *et al.*, 2009) In subtropical areas, crossbreeding between *Bos taurus* and *Bos indicus* cattle has been used to improve heterosis, growth, and carcass quality. (Davis *et al.*, 2017; Kim *et al.*, 2003).

GWAS (Genome Wide Association Studies) is an authentic method for



connecting traits to its genetics (Korte and Farlow 2013). It has the potential to provide a critical initial look into the genetic architecture and biology of complex characteristics (Belamkar *et al.*, 2011). In beef cattle, GWAS improves the accuracy of genetic predictions for growth, carcasses, reproduction, and health (Kuehn *et al.*, 2011). Dunner *et al.*, (Dunner *et al.*, 2013). The Bovine HapMap Consortium provided the first comprehensive genome-wide investigation of 19 genetically, regionally, and phylogenetically distinct cow breeds in 2009. This was the first study to examine the structure of the bovine genome in different breeds at a high resolution, and it revealed genes involved in production qualities (such as GDF-8 and ABCG2, which are connected to muscle conformation) as well as genes involved in food conversion efficiency (e.g., R3HDM1). Since this initial study, several more have been conducted, all with the same purpose in mind (Silveira *et al.*, 2008; Chung and Kim 2005). CAPN1 (Curi *et al.*, 2009; Tadesse *et al.*, 2006), CAST (Curi *et al.*, 2009, SIRT1) (Tadesse *et al.*, 2006), SIRT2 (GUI *et al.*, 2015), SMO (Zhang *et al.*, 2015), and NEB (Zhang *et al.*, 2015) have all been proposed as functional and positional candidate genes for carcass composition and meat-related production (growth, development) traits (Wyszyska Koko *et al.*, 2006; Davis and Simmen 2000; Herd *et al.*, 1995).

In this study, chromosomal mapping, conserved motif analysis, gene structure, expression analysis, STRING and GO annotation, synteny analysis and phylogenetic analysis were performed to examine 50 genes related with growth and development in *Bos taurus* and *Bubalus bubalis*. The majority of genes for the trait were found in both *Bos Taurus* and *Bubalus bubalis*, but there is difference in chromosome number. Data was collected using various bio-informatics tools e.g. NCBI and Expasy. Web tools used for characterization of genes were iTOL,

WebScipio, heatmapper, string and MEGA 5.

Materials and methods

Sequence Retrieval

Gene bank was searched to identify the growth and development related genes in buffalo and cattle. A query of 50 genes found in various articles was used for this purpose. This was also accomplished with the help of NCBI-BLAsp. Only big open reading frames (ORFs) were employed for further inquiry, such as gene structure determination, phylogenetic analysis, and domain prediction, and only variants of all genes were cross-checked. NCBI was used to obtain genomic sequences, protein length, chromosomal location, and the number of exons in each gene. Using an online tool ([https://web.expasy.org/compute pi/](https://web.expasy.org/compute_pi/)), the isoelectric point and molecular weight of identified proteins were calculated. For further research and characterization, protein sequence data of *Bos taurus* and *Bubalus bubalis* were created.

Chromosomal mapping

File with a map chart NCBI provided an input file with information on growth and development genes. The Map chart programme (<http://www.biometris.wur.nl/UK/Software/MapChart/download>) was used to determine the loci of growth regulating genes (Wheeler *et al.*, 2007; Voorrips 2002).

Gene structure analysis

The coding and genome succession of all predicted genes was downloaded using NCBI. WebScipio was used to get a high-quality gene structure prediction from protein query (<https://www.webscipio.org/>) (Odrionitz *et al.*, 2008).

Conserved motif analysis

In motif analysis, combined information of 50 residues of amino acids



have been subjected to MEME suit server 4.11.2 to compare the orthologous of two species i.e. buffalo (*Bubalus bubalis*) and cattle (*Bos taurus*). The parameters adopted for MEME analysis include number of repetitions, any; protein sequence length 309.5; maximum number of motifs, 10; and optimal breadth of every motif, among 6 and 60 residuals (Cao *et al.*, 2021).

Gene expression analysis

Transcription analysis and putative functions of 50 genes relating to growth and development in different organs of the body of cattle. The expression levels in different organs or tissues based on RNA-seq data (found at <https://www.ebi.ac.uk/gxa/home> in the Expression Atlas database) were downloaded (FPKM values only) (Cook *et al.*, 2019) and analyzed by using Heatmapper at <http://www.heatmapper.ca/> (Babicki *et al.*, 2016). Data comprising RNA sequences from two different experiments showing the expression values in FPKM or TPM for target growth and development related genes in *Bos taurus* and *Bubalus bubalis* (Gonzalez *et al.*, 2018).

GO Analysis

The bioinformatics programme DAVID (Database for Annotation, Visualization, and Integrated Discovery) was used to do the GO annotation study (<https://david.ncifcrf.gov/tools.jsp>) (Huang *et al.*, 2009; Shao *et al.*, 2009; Jiao *et al.*, 2012). growth gene symbol set used as an input source for GO annotation.

Protein-protein association

STRING Ver. 11.0 (<https://string-db.org/cgi/input.pl>) was used to analyze protein-protein association networks (Kim *et al.*, 2021). The STRING programme was used to input the amino acid sequence, and the protein-protein analysis result was downloaded to reflect the gene-gene interaction.

Synteny Analysis

Synteny analysis performed by using TB tool (Chen *et al.*, 2020). Genome file of cattle and buffalo were sequenced aligned with BLAST for synteny analysis (Sun *et al.*, 2019). Identification of tandem and segmental duplication of gene pair based on gene locus.

Phylogenetic Analysis

ClustalW was used to align roughly 50 growth and development-related genes from various families, with gap opening penalty of 10; gap extension penalty of 0.1; gap separation distance of 4; and delay divergence cut-off of 30%. The Neighbor-Joining approach was used to infer evolutionary history (Saitou and Nei 1987). The evolutionary history of taxa studied is represented by the bootstrap consensus tree generated from 1000 replicates (Webb *et al.*, 2008). Branches that correspond to partitions that have been replicated in less than 50% of bootstrap replicates have collapsed. The branch lengths are in the same units as the evolutionary distances used to estimate the phylogenetic tree, and the tree is drawn to scale. MEGA 5 was used to conduct evolutionary analysis. Using a Newick file made with MEGA 5, a phylogenetic tree was created in Interactive Tree of Life (iTOL; <https://itol.embl.de/itol.cgi>). (Hall 2013).

Results

Chromosomal mapping analysis

The results displayed that most genes were located on chromosomes 2 and 4 in cattle while on 2 and 8 in buffalo. Fifty growth and development genes were found on almost all chromosomes except chromosomes # 1, 8, 9, 26 and 27 in cattle and 50 in buffalo on 24 chromosomes except chromosome # 1 and 10. In cattle, Ch#4 had maximum 5 genes CFTR, CRHR2, IGFBP3, LEP and SMO. Ch#2 had second largest concentration of genes of trait with four genes MSTN, NEB,



R3HDM1 and CREB1. Ch#2 in buffalo had six genes of trait MSTN, CREB1 and NEB. ELOVL2, SMIM13 and R3HDM1. Ch# 8 had 5 genes in buffalo but none in cattle. GH1 was located on Ch#19 in but while Ch#2 in Bb. Majority of genes had the same mapping regions and Ch# in both organisms. Chromosome #2 was the largest chromosome in cattle and buffalo among all mapped chromosomes (Figure 1A&1B).

Gene structure analysis

By comparison of sequence and CDS, we determined and examined the structural variation in introns and exons. There were 45 and 38 genes structures analyzed in cattle and buffalo respectively (Figure 2A&2B). Red segment showed the gap region while red thin line indicated mismatch and blue line for sequence shift. In cattle, DGAT1, IGFBP3, MMP1 and MYOZ1 had long gap regions. CRTC2 and GH1 had spliced introns. NEB had very complex structure with large number of small size exons followed by introns. In buffalo, ALAS1, CHRNE, MSTN, SNC 29 and CRTC3 possessed long gap regions. DGT1 and LHX6 had two introns separated by small exotic regions. ALDH2, RORA and STAT6 had single long introns. Each of DGAT1 and IGFALS contained 3, ABCG2, ADMST4, CAST ELOVL2, IGFBP3 had 2 and CPN2, GPX8 SIRT1, STAT6 and WRD7 had 1 mismatch region. CAST, CRTC3, DGAT1, STAT6 and TCF12 contained one additional codon. The number of exons and introns in cattle of almost all genes were greater as in buffalo.

Motifs analysis

This analysis depicted the motif location, motif consensus and graphical representation of motif. Conserved motifs are involved in action of growth and developmental proteins. The top 10 motifs were predicted. Motif 1 was most prominent out of the top 10 motifs. (Shown figure 5). Motif 1 was highly expressed in

buffalo and *Bos taurus* having frequency 222 and 217 respectively. Motif analysis revealed that the top 10 motifs are located on 25 genes. In cattle, motif-1 was located on 6 gene namely. Motif-10 had the least f value 12 and was present on ADMST4, TG and NEB. Motif -5 was located on just two genes ADMST4 and NEB. In buffalo, Motif-1 was located on 9 genes CHRNE, NEB, SIRT1, STAT6, MYF5, HSD17B7, WRD7, LHX6 and CAST. This motif was present in these six genes in cattle also. Motif-9 and MOTIF-10 had the least frequency 2. Motif-9 was present on IGFALS, CFTR, NEB and STAT6 while motif -10 on NEB only. Motif-5 was present on PLTP in addition to NEB in place of ADMST4 as in cattle. STAT6 had 3 motifs (motif-1, 6 and 10) but only one in cattle (motif-3). Motif -7 was present only on NEB both in cattle and buffalo. TG had two motifs (motif-9, 10) in cattle but none in buffalo. NEB had all motifs showed it is highly conserved for production (Figure 3A&3B).

Gene expression analysis

Heatmapper was used to analyze the expression of growth and development genes in several organs such as the brain, colon, heart, kidney, liver, lung, skeletal muscles, spleen, and testis (Bakhtiarizadeh *et al.*, 2018). In the heat map red colour showed up regulation and blue colour to down regulation. Results revealed NEB up-regulation in skeletal muscle tissues (high expression). The top Up-regulation of CFL1 was seen in brain, lungs, spleen, colon and testis. ALDH2 showed up regulation in kidney and liver and ACTC1 in heart (Figure 4A&4B).

GO annotation analysis

This analysis results revealed annotation. Plotted graph (Figure 5A) showed that fifteen genes CRTC3, IGFBP3, TCF12, PAX6, RORA, SIRT2, FOXO1, GH1, CREB1, MYOD1, CAPN2, LHX6, STAT6, ABCG2, MYF5 were



involved in GO terms for nucleus with P-Value 0.0059 E-21 followed by cellular compartment. Plotted graph (Figure 5B) showed that nine genes ADAMTS4, GH1, TG, SMO, MSTN, MMP1, IGFBP3, LEP and CHRNE were involved in disulfide bond with P-Value 0.0057 E-21 followed by functional category. Plotted graph (Figure 5C) showed that five CREB1, LHX6, PAX6, RORA, FOXO1 genes were involved in sequence-specific DNA binding for cytokine activity with P-Value 0.0239 E-22 followed by molecular function. The plotted graph (Figure 5D) revealed that eight genes, CRT3, SMO, TCF12, STAT6, RORA, SIRT1, SIRT2, FOXO1 played a part in positive transcription regulation from the RNA polymerase II promoter with P-Value 0.0011E-20, followed by biological process. Blue bar indicated gene count while Black lines indicated the P-Value in graphs.

Protein-protein association

Protein control biological function solely or by association with other proteins. Empty nodes indicated the unpredicted 3D structure while filled structure indicated predicted 3D structure like TG consists of predicted 3D structure (filled node). The thickness of line showed degree of interaction of one gene with others. TG showed first shell of interaction with ten predicted functional partners that were included MB, LRP2, TTR, NKX2-1, SLCA5, TSHR, ASGR2, ASGR1 and ALB genes in cattle (Figure 6A). Strongest interaction indicated in cattle than buffalo. TG gene had high association with the LRP2 gene. All genes were involved in first shell interaction also showed strong second shell interaction. In buffalo, TG gene showed first shell of interaction with ten predicted functional partner TTR, LRP2, CD44, PDIA4, ASG, ASGR2, MB, TSHR, TPO and DIO2. TTR, LRP2, ASG, ASGR2, TSHR, TPO and DIO2 nodes also showed second shell of interaction. TTR, LRP2,

ASG, ASGR2, TSHR, TPO and DIO2 showed the strong interaction with TG. (Figure 6B). TG gene had most association with the LRP2 gene. Filled nodes consisted of known 3D protein structures found in PDB database.

Synteny Analysis

In synteny analysis, ninety-six gene pairs showed duplication of gene pair in cattle and buffalo. Synteny revealed amino acids sequence duplication on paralogous as well as orthologous chromosomes. All ninety-six showed segmental duplication in synteny graph. Genes located on Bt 4 chromosome were duplicated on Bb8 chromosome while genes present Bt5 were duplicated on Bb 4 (Figure 7). For gene expansion mechanisms of cattle and buffalo species in evolution from diploid to tetraploid, gene duplication events analyzed in mastitis resistant genes. Tandem duplication arose resulting because of tight linking of gene to the same chromosome (Wei *et al.*, 2007; Zhang *et al.*, 2011).

Phylogenetic Analysis

Phylogenetic genetic analysis showed the evolutionary link between the Cattle and Buffalo. The evolutionary link between these genes in buffalo and cattle was expressed through phylogenetic trees, which was found by constructing a phylogenetic tree (Figure 8). Protein sequence of growth and development related genes belonging to different families were used to construct phylogenetic trees and to measure the evolutionary relationship between growth and development related genes in buffalo and cattle. Phylogenetic tree showed the 4 clades consist of 50 genes. Most of genes were in first clade while clade #4 contains only two genes. Resembling genes were grouped in same clade while diversified in different clades. Genes at first nodes e.g. BtIGFALS and BbCHRNE were conserved



and important to show evolutionary relationship

Discussion

Bubalus bubalis and *Bos taurus* are economically important due to meat production. We used chromosomal mapping to find location of genes affecting meat production. Our result also revealed that *Bubalus bubalis* and *Bos taurus* have similarity in mapping regions. This enabled us to develop genetic markers that could be used to induce positive mutations via gene editing. Genetic changes are viewed for growth regulation (Vaughn *et al.*, 1999). Based on genetic studies, Atchley and colleagues came to the same conclusion. (Vaughn *et al.*, 1999) This genome scan method enables us to identify genes that influence body composition and meat production features. (Gordo *et al.*, 2012)

Gene structure analysis was performed to elucidate different functional portions (exon, intron, mismatch, codon etc.) as activity of gene is attributed to its parts mainly exon. There were 45 and 38 genes structures analyzed in cattle and buffalo respectively. All genes in cattle showed a greater number of exons and introns as compared to corresponding gene in buffalo. NEB exhibited an extremely complicated and distinctive structure in cattle, with multiple exons and introns. Conserved sections are most likely found in this sort of gene. Our findings also revealed that *Bubalus bubalis* and *Bos taurus* are related. Batzoglou *et al.*, (2000) used analysis to predict the degree of similarity in the number, size, and sequence of exons and introns in humans and mice. Although it has long been considered that numerous genes govern meat output and quality, there is growing evidence that single genes account for a significant amount of variance in some respects (Warner *et al.*, 2010). Myostatin is highly expressed in the

developing somite and skeletal muscles of mice. (Maccatrozzo *et al.*, 2001).

The goal of motif analysis was to find conserved domains. Variations in conserved motifs had the potential to be fatal. The number of conserved motifs in NEB was the highest. The presence of all ten motifs in NEB exhibited it as unique and highly conserved. Interestingly TG had two motifs in cow and none in buffalo probably may be due to its specialty toward species. Existence of motif-1 on six common genes CAST, LHX6, WRD7, HSD17B7, MYF5 and NEB showed that these genes remained conserved over time. Motif 1,5,7 and 8 had about same value in Bt and Bb showed they were more conserved than others. The STAT motif region is an important transcriptional mediator of GH's sex-dependent effects in the mouse liver (Zhang *et al.*, 2012). SOCS2 inhibits the action of growth hormone in vitro and in vivo. In SOCS2-deficient mice, the magnitude of organ and tissue growth in response to GH was significant in SOCS2-deficient mice. SOCS2 levels and timing are a GH-controlling factor. (Greenhalgh *et al.*, 2005). AP-1-like motif regulates insulin-like growth factor I (IGF-I). The STAT gene is involved in growth hormone signaling (Herrington *et al.*, 2000). The PKC motif may possibly be implicated in GH action signaling, as well as STAT transcription activators. The human IGF-I gene is also a target for estrogen regulation, and disorders like osteoporosis may be linked to the development of the regulating machinery. The pufferfish (*Fugu*) genome has been classified as a compact vertebrate genome (Brenner *et al.*, 1993). Because it contains around 90% of all mammalian genes and is largely conserved among mammalian species and chicken, the Pufferfish genome, *Fugu rubripes*, was chosen as a model of the mammalian genome (Brenner *et al.*, 1993).

NEB was found to be upregulated in skeletal muscle tissues (high expression).



CFL1 was up regulated in the brain, lungs, spleen, and testis and colon. ALDH2 was regulated in the kidney and liver and ACTC1 in the heart. Cattle cloning using somatic cell nuclear transfer (SCNT) is a common agricultural practice that also serves as a model system for researching mammalian development and gene expression (Biase *et al.*, 2016). Gene expression can be utilized to detect molecular changes in bovine muscle that are related with marbling (Wang *et al.*, 2009). Furthermore, the genes shown to be significantly expressed during the formation of marbling could be exploited to generate genetic indicators or biomarkers to improve beef production tactics (Wang *et al.*, 2009). Both myostatin1 and myostatin2 expression peaked at the 140-g stage, indicating that muscle growth in poultry may be restricted at this period (Johansen and Overturf 2005). Collagen isoforms are expressed during bovine adipogenesis (Tahara *et al.*, 2004). Adipocyte fatty acid binding protein (FABP4), an adipogenesis-related gene, is continuously expressed in buffalo and is involved in intracellular transport and fatty acid metabolism, as well as differentiation (Rump *et al.*, 1996) and signal transduction (Glatz *et al.*, 1993; Veerkamp *et al.*, 1993). (Borchers and Spener 1994).

Our GO analysis showed that MYOD1 and MYF5 positively regulated skeletal muscle fiber development, SMO, MYOD1 skeletal muscle fiber development, and SMO, MYOD1, GH1, CREB1 and SMO in positive regulation of multicellular organism growth, IGFBP3, RORA, and SIRT1 were involved in the regulation of the glucose metabolic process. Hepatocyte growth was regulated by CREB1 and SIRT2. The transcription from the RNA polymerase II promoter was positively regulated by CRTC3, SMO, TCF12, STAT6, RORA, SIRT1, SIRT2, and FOXO1. IGFBP3, MYOD1, MYF5 in positive regulation of myoblast differentiation, and MSTN, MYOD1 in

negative regulation of myoblast proliferation. RORA, SIRT1 and SIRT2, FOXO1 in negative regulation of fat cell differentiation, IGFBP3, MYOD1, MYF5 in positive regulation of myoblast differentiation, and MSTN, MYOD1 in negative regulation of myoblast proliferation. Brown fat cell differentiation was aided by LEP and SIRT1, while transcription was regulated by PAX6, STAT6, RORA, and FOXO1. HSD17B7 and CFTR are involved in the biosynthesis of cholesterol. SIRT2 regulated negatively autophagy, LEP MSTN, GAA had effect in muscle cell cellular homeostasis and LEP, RORA, SIRT1 in angiogenesis. MYOD1, CAPN2 regulated myoblast fusion, MYOD1, MYF5 positively regulated myoblast fusion, SIRT1, PLTP positively regulated cholesterol and TG, MYOD1, MYF5 negatively regulate myoblast fusion, MYOD1, MYF5 negatively regulate myoblast fusion, MYOD1, MYF5 negatively regulated myoblast fusion, MYOD1, MY DGAT1, SIRT1 fatty acid homeostasis, SIRT2 myelination Nucleus formation and function was controlled by CRTC3, IGFBP3, TCF12, PAX6, RORA, SIRT2, FOXO1, GH1, CREB1, MYOD1, CAPN2, LHX6, STAT6, ABCG2, MYF5. In DNA binding, CREB1, LHX6, PAX6, RORA, and FOXO1 were involved. The AMPK signaling pathway includes CREB1, LEP, SIRT1, FOXO1, and CFTR. SOCS2, GH1, LEP, and STAT6 were involved in the Jak-STAT signaling pathway; TG, CREB1, and GPX8 were involved in thyroid hormone synthesis; PAX6, STAT6, RORA, and FOXO1 were involved in transcription; and CHRNE, KCNK2, and CFTR were ion channels. Multi gene expression was involved in the majority of biological processes and structures. A single gene can influence multiple traits. GH was discovered as a potential gene that affects goose growth and development after a transcriptome investigation of the pituitary gland (Tang *et al.*, 2020).



Protein association analysis was used to look into gene interaction. Genes usually work together to produce a phenotype. Our findings revealed that TG is the most important gene in gene networking. In beef cattle, the association of the thyroglobulin gene with other genes was investigated for carcass and meat qualities (Gan *et al.*, 2008). The thyroglobulin gene is connected to other genes that regulate meat output in beef cattle. Multi-breed and multi-trait co-association analyses were used to investigate meat production features in three beef cow breeds. Caldas *et al.*, (Caldas *et al.*, 2016). Three genes, DGAT1, TG, and FABP4, were studied to see if they were linked to varying amounts of IMF. There was no indication of a link between DGAT1 and FABP4 in this study (Nasser *et al.*, 2021). Polymorphisms in the leptin and thyroglobulin genes have been linked to beef cow meat and carcass qualities (Carvalho *et al.*, 2012). The LEP gene has been related to CFT in beef cattle (Li *et al.*, 2013). In beef cow populations, the genes DGAT1, leptin, SCD1, CAPN1, and CAST show a high connection. In beef cattle, the LEP, SCD1, and CAPN1 genes demonstrate networking in meat characteristics (Li *et al.*, 2013). Commercial tests for TG5, CAPN, and CAST gene association with marbling are currently available under the GeneStar trademark (Sosnicki and Newman 2010).

Synteny analysis was performed to elucidate syntenic regions between Bt and Bb. Results showed that there is strong similarity and conserved regions. This is due to strong evolutionary relationships of Bt and Bb. Strong segmental duplication is due to high evolutionary relationships. Genes present on same chromosome in Bt and Bb are highly conserved while present on different chromosomes depict variations over time. The GAPD-IGF1 loci are substantially conserved in chickens and other vertebrates, according to genetic maps of the insulin-like growth factor 1

gene (Amills *et al.*, 2003). Synteny conservation between humans and pigs is three times higher than between humans and mice, resulting in fewer but larger conserved segments (Rettenberger *et al.*, 2003).

Synteny Using the Mouse Genome Database (MGD), Genome Database (GDB), and Online Mendelian Inheritance in Man (OMIM) websites, a systematic review identified approximately 400 mouse mutations, reviewed approximately 250 of these for vertebral phenotypes, and assessed 45 of these for synteny conservation between mouse and man. Some mouse mutants show traits that are similar to human phenotypes (Cooper *et al.*, 1998).

The evolutionary relationship between these genes in buffalo and cattle was determined by constructing a phylogenetic tree. Genes paralogues were close to each other in tree. paralogues emerging from the same node had structural similarity and known as sister paralogues for example BtGH1 and BbGH1 were paralogues. Distance of node from centre showed that during the evolutionary process, these genes underwent greater diversification in the progenitor species. Most of the genes of buffalo and cattle grouped together revealed their strong evolutionary relationship. The buffalo HSP gene family was found to be more closely linked to *Bos taurus*, goats, and sheep, as well as the common clade of horse and camel, when each HSP family gene was clustered together in one group (Figure 2). Buffalo is also distantly related to other mammals such as pigs, dogs, rats, mice, and zebra fish (Nadeem *et al.*, 2020). The role of MSTN in this model organism (zebrafish) must be investigated further (Acosta *et al.*, 2005). Many of the disparities between zebrafish and mammalian studies could be explained by the combined influence of zfMSTN-1 and -2, which diminish MSTN-1 mRNA levels in fish (Kerr *et al.*, 2005) while raising MSTN expression in humans



and rats (Shmelkov *et al.*, 2005). This was previously seen as evidence of differences in expression regulation between fish and mammals. The myostatin (MSTN 1, 2)-null phenotypes in mammals and zebrafish are characterized by dramatic increases in skeletal muscle mass, also known as "double muscling" (Kerr *et al.* 2005). There is no apparent phylogenetic relationship between IGFBPs and IGFBP-rPs, nor between the three different IGFBP-rPs, which contradicts their evolutionary relationship. (Rodgers *et al.*, 2008).

Conclusions

With the increasing pressure of quality food with population explosion, the world has moved towards JWAS for study and introduction of constructive mutations in a short span. This research was conducted to elucidate the integrated role of various genes. Each gene has a unique structure and discrete role regarding growth. GH affected directly on growth and development. TG associated with other genes in complex network to stimulate growth as depicted in association analysis. Results of heatmap, motif and gene structure analysis showed NEB had highly conserved domains for structural and functional role in skeletal muscle growth and development. CFL1 had a role in growth and development of brain, lungs, spleen and testis. ALDH2 showed up regulation in kidney and liver and ACTC1 in heart. *Bubalus bubalis* and *Bos taurus* had strong evolutionary relationships as shown by synteny and phylogenetic analysis. This study may be helpful to resolve the problem of under nutrition. This will lead to entry into a new era of artificial selection. Pakistan has a wealth of cattle genetic resources, with tremendous phenotypic and genetic variety. Efforts to effectively manage and use these resources, on the other hand, are limited due to a lack of understanding as well as the fragility of government institutions. Animal scientists could use this information to design genetic

markers to boost cattle output (Wu *et al.*, 2015). To better understand the structure and function of NEB in buffalo, further research is required.

Conflict of interest statement

This research was not funded by anyone. There was no involvement of a corporation in the study design, data collection, analysis, or interpretation, or the decision to submit the paper for publication. There are no other financial or personal links between the authors that could improperly affect or distort the content of the study. This is entirely and equally for the benefit of all human beings.

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Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi: ...

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Table 1

Agreement between the ELISA antibody test results reported using a semi-quantitative evaluation scheme and canine parvovirus (CPV) hemagglutination titers/canine distemper (CDV) serum neutralization titers performed at a reference laboratory.

	CPV r^2 (n)	CDV r^2 (n)
Point-of-care testing using manufacturer-recommended protocol ^a	0.67 (199)	0.71 (200)
Point-of-care testing using extra wash	0.64 (103)	0.73 (104)
Synbiotics laboratory-performed testing using manufacturer-recommended protocol	0.56 (153)	0.72 (153)
Optical density (OD) measurement	0.51 (153)	0.63 (153)

^a As per Synbiotics TiterCHEK CDV/CPV direction insert

Figure legends

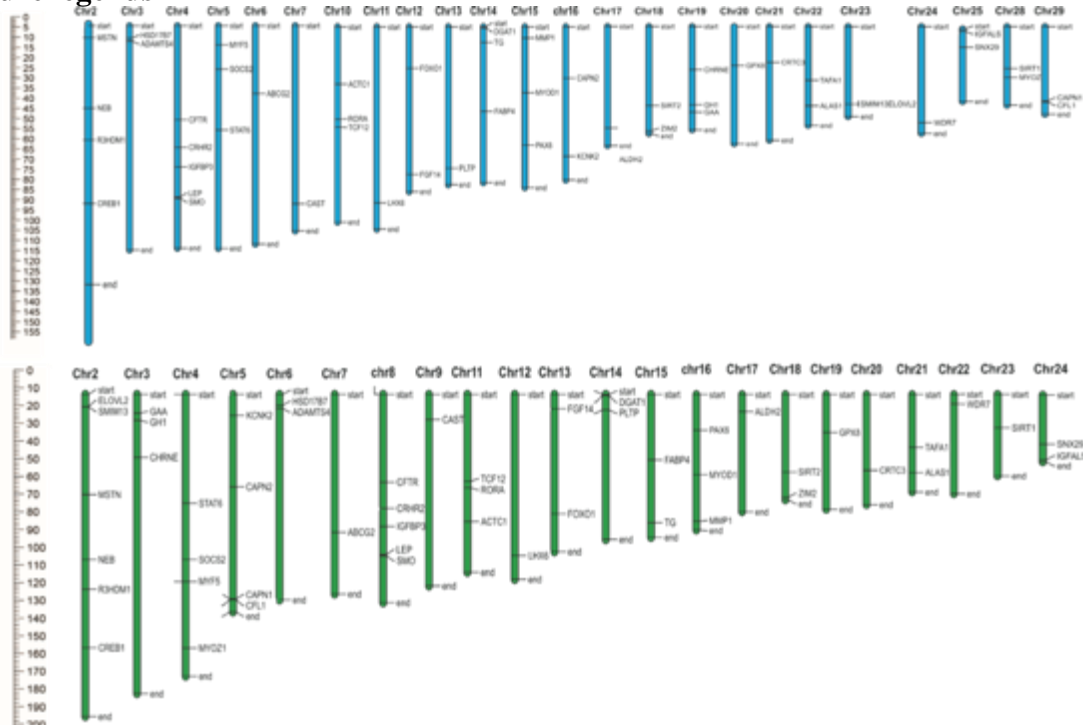


Fig. (1): chromosomal mapping in buffalo (A) and cattle (B).

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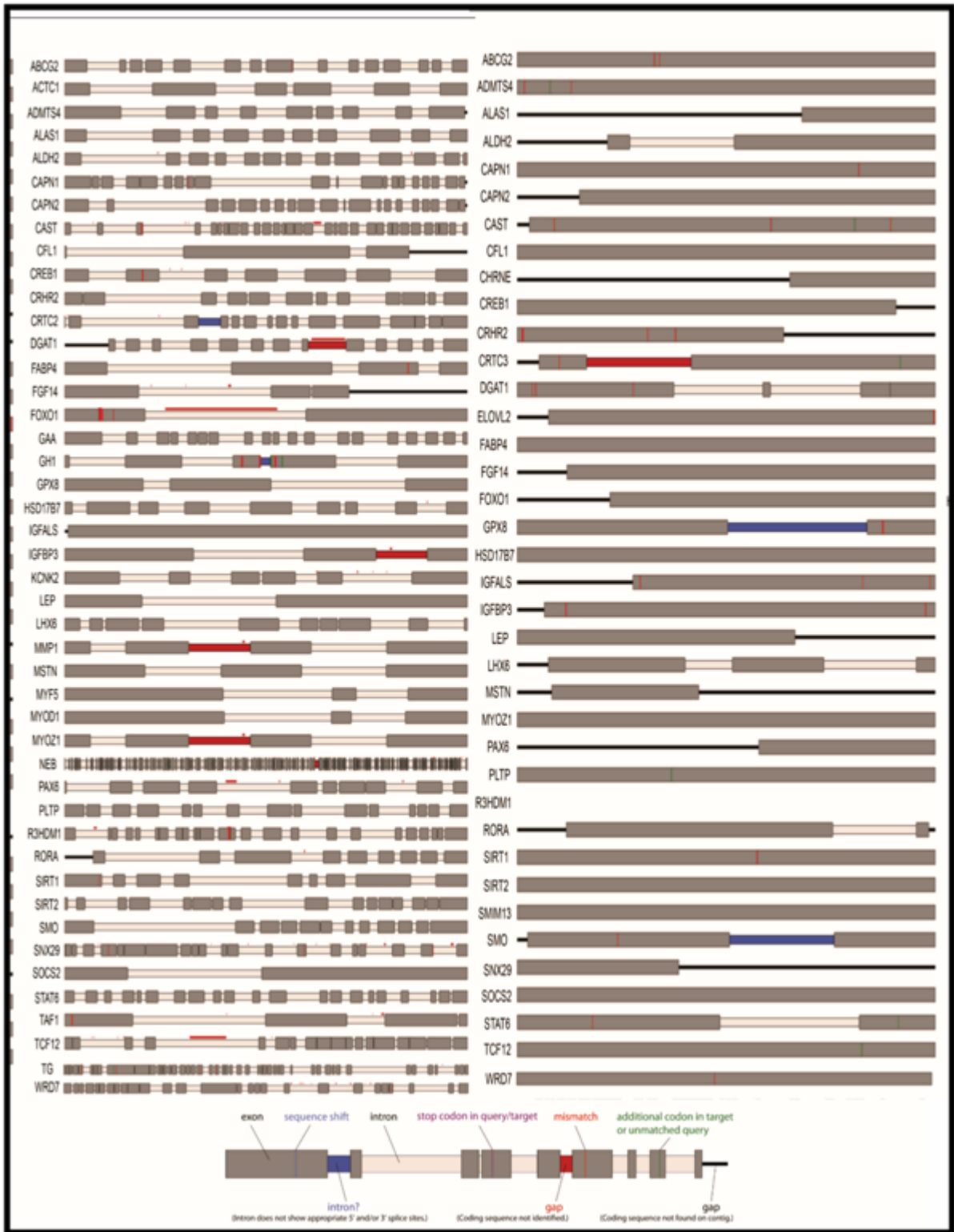
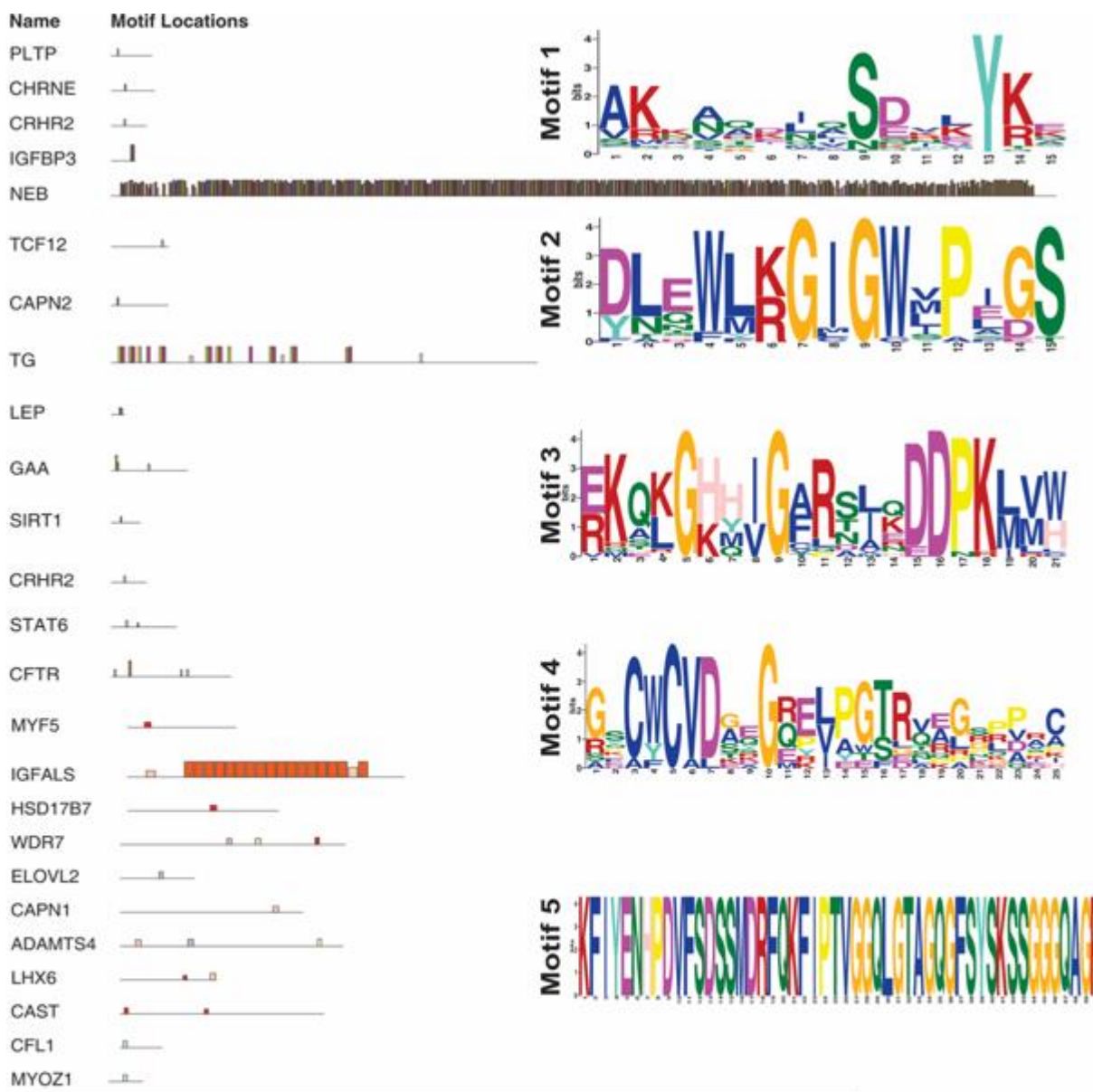


Figure (2): (A) and (B) gene structure analysis of growth and development genes in cattle and buffalo respectively.

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Motif	Symbol	Motif Consensus	Motif Frequency
1.		AKKAQDIQSDVLYKE	217
2.		EKQKGHHIGARSJKDDPKLW	21
3.		KHKFTSVPDTPEIIL	98
4.		KTGYDLPVDAJPIVA	43
5.		DLEWLGIGWLPIGS	21
6.		GSCWCVDZGRELPGTRVEGSPPAC	11
7.		PRAFGLAGLRELNLSHNRLA	18
8.		PQCSADGSYSFVQC	10
9.		KFIYENHPDVFSDSSMDRFOKFIPTVGGQLGTAGQGFYSKSSGGGQAGR	2
10.		MPYGGYEKASKRMTFPQMPKFDLGPLLSEPLVLYNQNLNRPSPNRTPIPW	2

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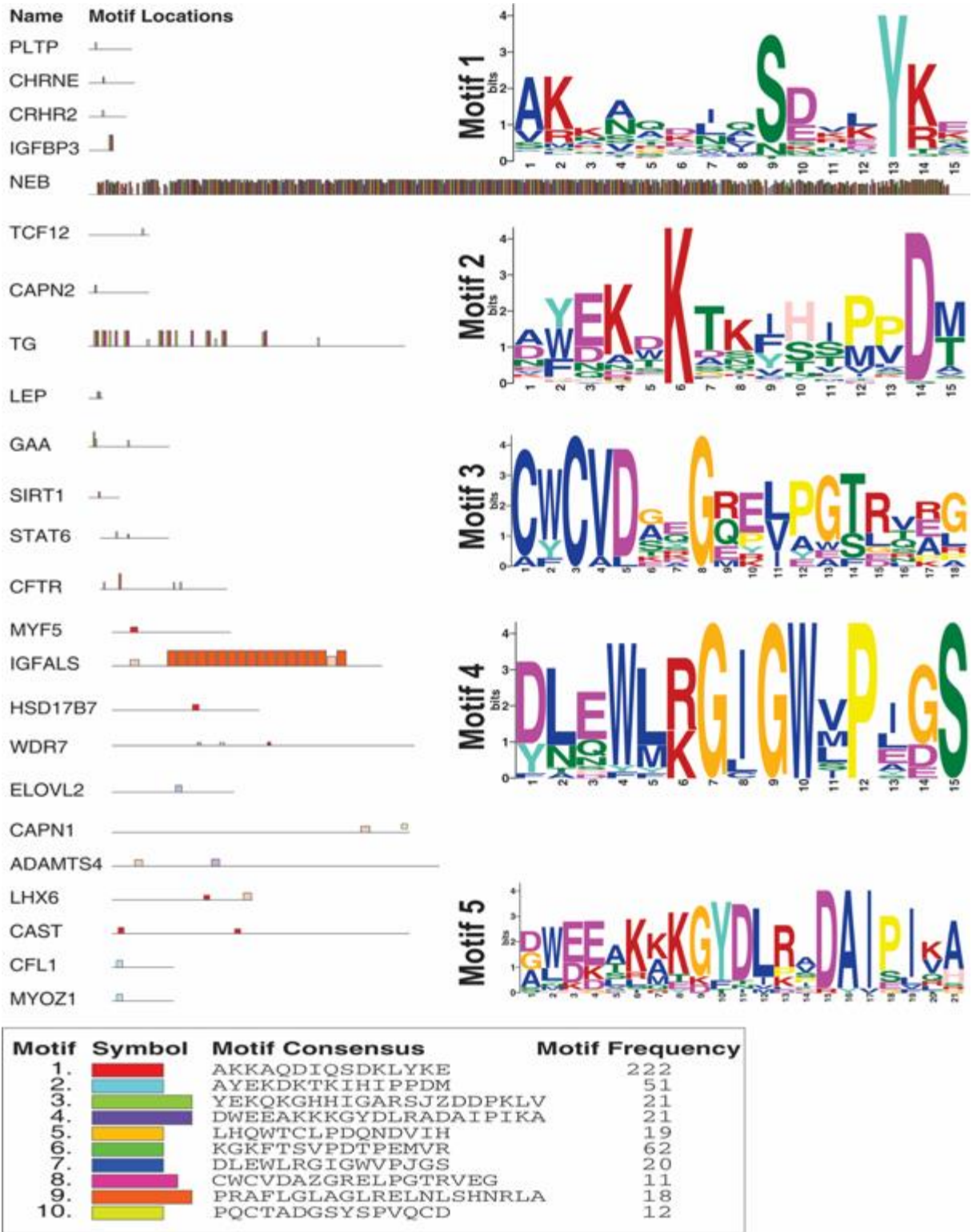


Figure (3): (A) and (B) were motif analysis of growth and development genes in cattle and buffalo respectively.

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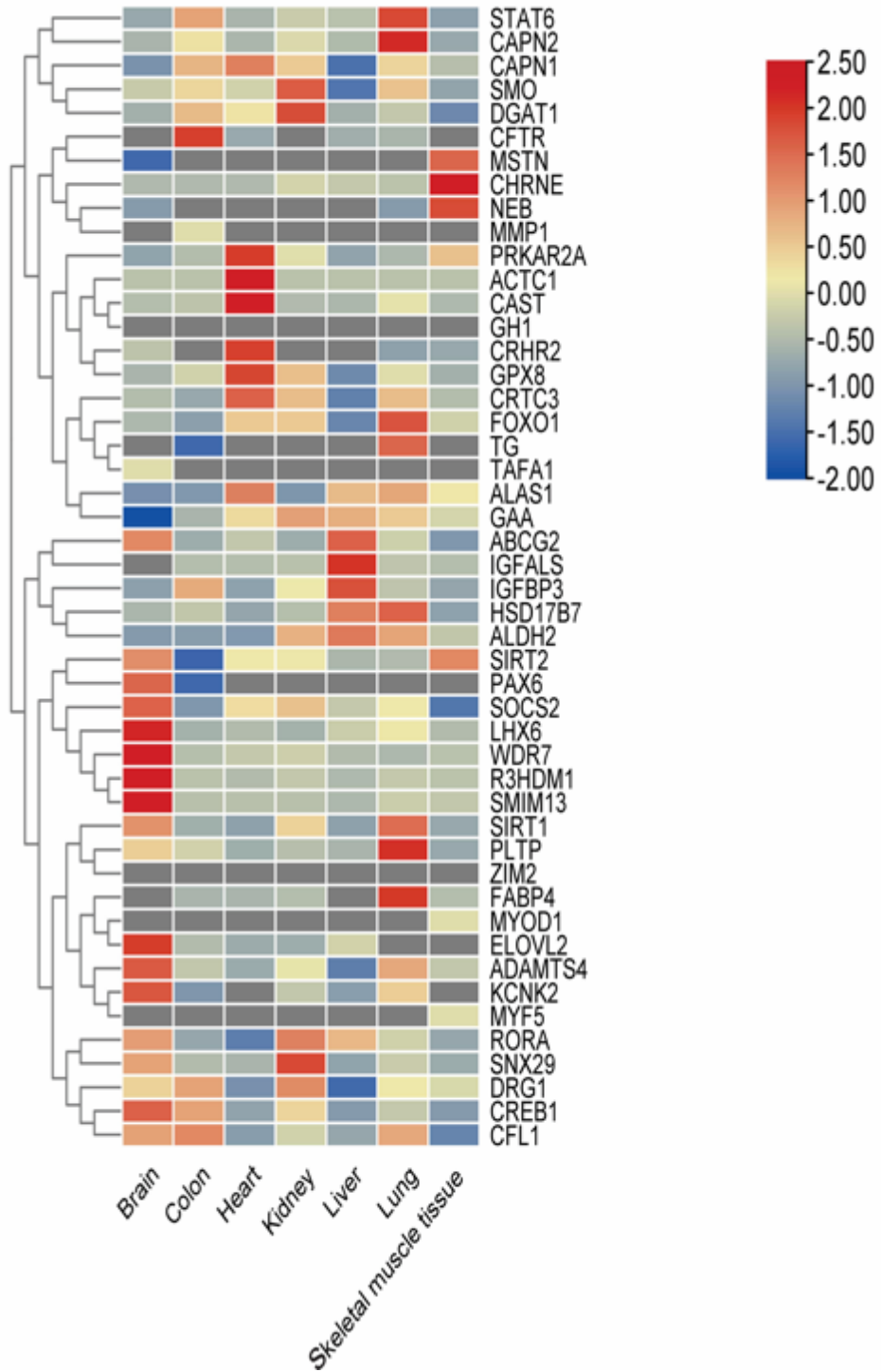


Figure (4): Heat map of growth and development related genes in different tissues of cattle

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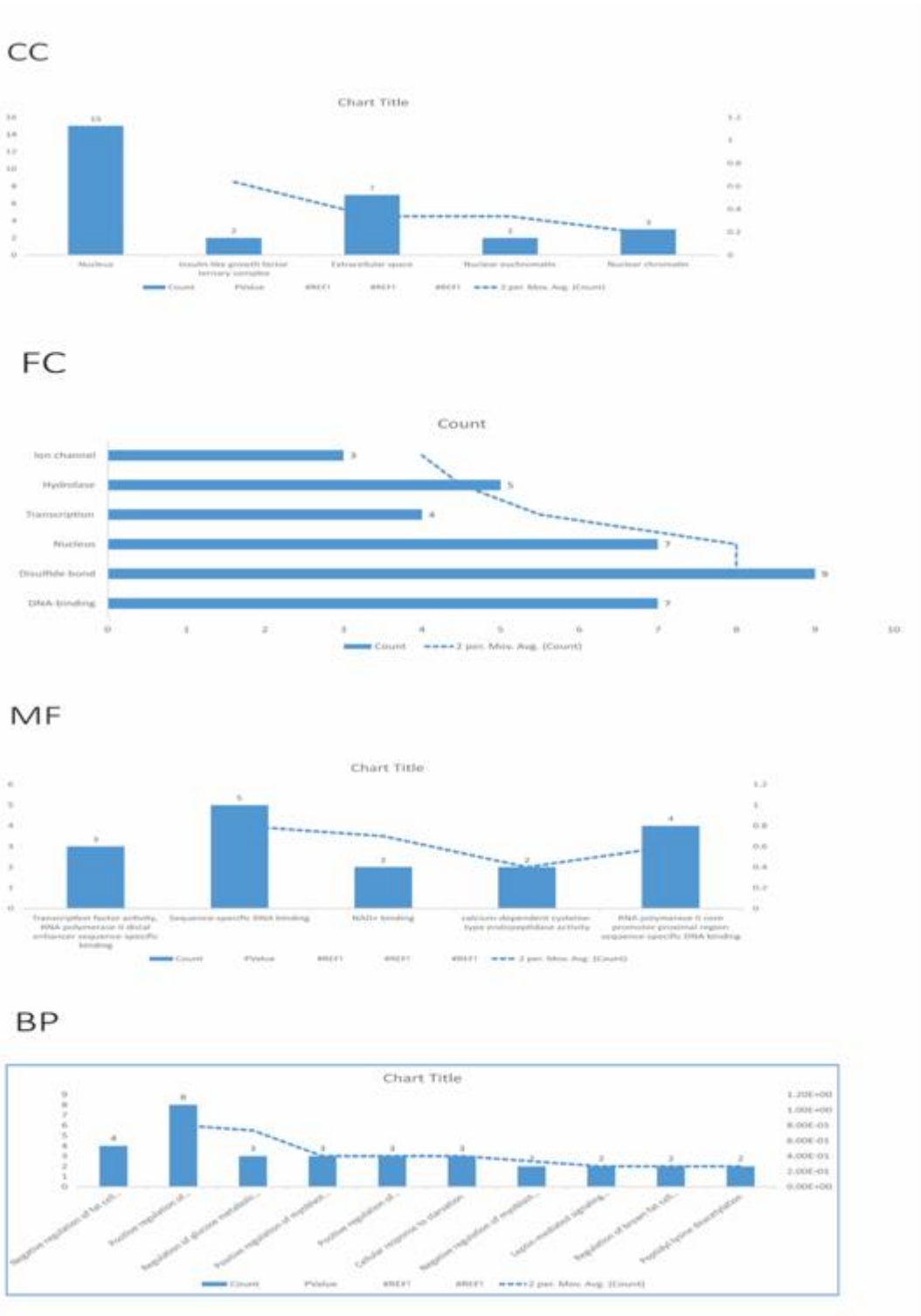


Figure (5): (A), (B), (C), and (D) graphs of Cellular component, Functional category, Molecular function and Biological process respectively that show gene annotation result.

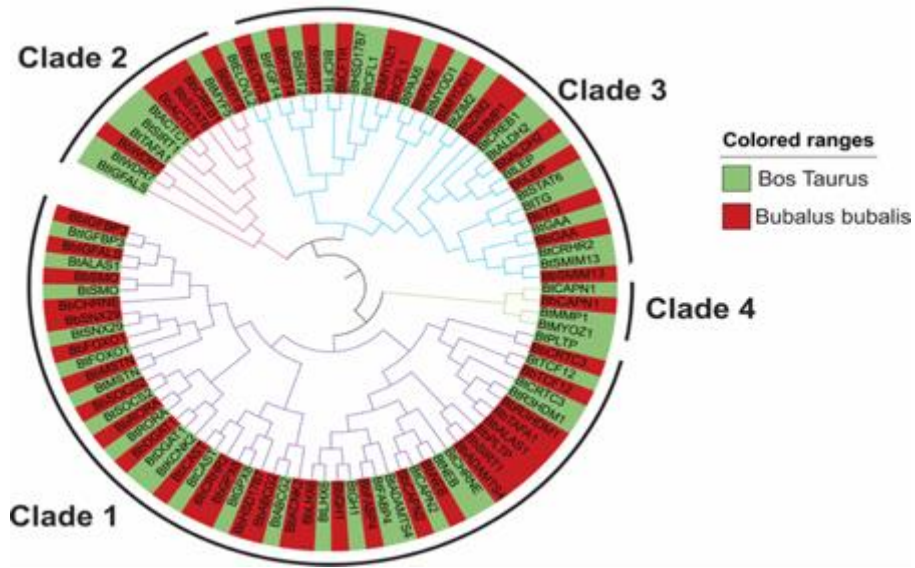


Figure (8): Phylogenetic analysis of buffalo (Bb) and cattle (Bt). The amino acid sequence was aligned by CLUSTALW and newick file format was prepared with the help of MEGA V.5.0 and then the phylogenetic tree was made using the neighbor-joining method using iTOL.



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Revolutionizing Forensic Odontology: The Integration of 3D Scanning and AI for Enhanced Identification Processes

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Abstract

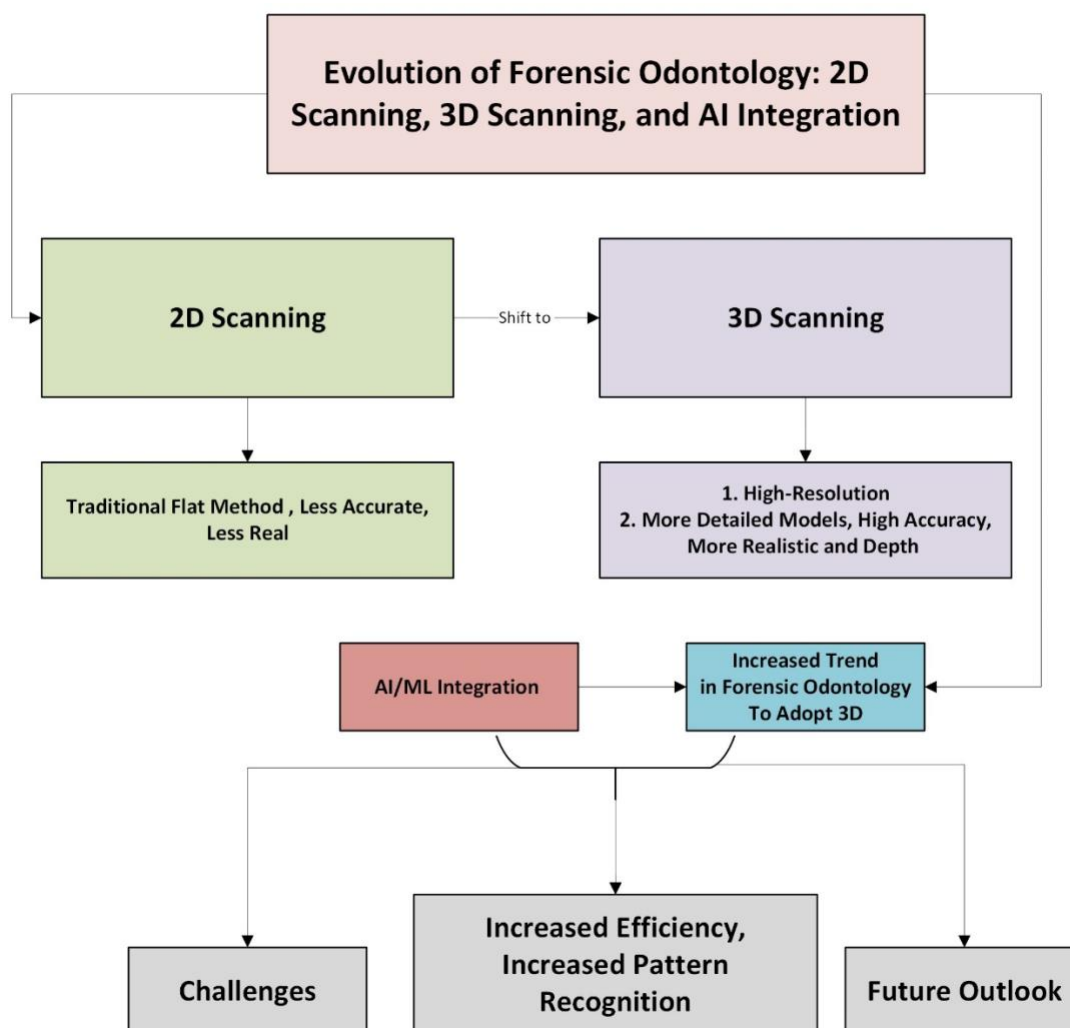
Nowadays, most forensic odontological analyses destined for legal purposes include improvements in 3D scanning technologies with the aim of enhancing the precision of forensic identifications. The current paper addresses the combination of 3D picture scan data and artificial intelligence: it reviews uses, limitations, and prospects of AI in its application to forensic odontology. Where earlier methods were limited, 3-D scanning techniques allow the creation of much more realistic models of dental structure, enabling closer comparisons with dental records and other information. These technologies, when combined with artificial intelligence, can even automate such processes as pattern recognition, further speeding up the reliability of dental identification in forensic cases. Not all is perfect with the technology. Further, defects in the models generated may well be caused by external reasons such as lighting, movement during scanning, and equipment limitations. Besides this, 3D photo's scanning using AI effectively requires highly knowledgeable people in advanced hardware and software technologies. As a matter of fact, the intricacy at which AI algorithms are designed demands an in-depth knowledge of their implementation to effectively apply them in forensic activities. Apart from this, constant system calibration and the care in handling scanning equipment are also needed to ensure accuracy and reliability. If these tools work effectively, AI coupled with 3D photo scanning can do much to increase the accuracy, efficiency, and rapidity of forensic odontology, particularly identification cases. The growing corpus of research findings and breakthroughs in technology, despite such challenges, portend a bright future for the application of AI and 3D scanning in the field of forensic odontology, opening the door for improved forensic techniques and methodologies of identification. This review discusses such breakthroughs, obstacles, and the potentiality for wide application of these technologies in the near future.

Keywords: Forensic odontology, 2D images, 3D images, AI, dental Investigation.

Graphical Abstract

MUHAMMAD S. KHAN

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Introduction

Over time, dental procedures for forensic human identification have consistently proven to be highly useful and reliable. If precise and comprehensive dental data obtained before death are accessible, which are necessary for a definitive identification, this can be accomplished. In field of forensic odontology, many specific dental data coding systems have been created for the purpose of utilising them in reports and computer-assisted identifications (Reesu *et al.*, 2020). Forensic odontology (FO), according to Keiser-Neilson, is the "branch of forensic medicine that, in the interest of justice, deals with the proper handling and

examination of dental evidence as well as the proper evaluation and presentation of the dental finding. A subdivision of forensic medicine is referred to as forensic odontology, is widely recognised as a reliable and cost-effective scientific method for identifying individuals in the aftermath of mass disasters (MDs), alongside cases involving crimes and accidents (Dong *et al.*, 2022). Forensic dentistry, also known as forensic odontology, is one of the three main identifiers acknowledged by Interpol for victim identification in mass casualty events or Mass disaster. Forensic dentistry is the field that examines the intersection between dentistry and the legal system. The utilisation of various digital radiographs



and photographs using scanning techniques is essential for the clearance process in the domain of forensic dentistry (Yazdani et al., 2022). Radiographs are commonly used in clinical practise, and both intra-oral and extra-oral X-ray examinations are essential for diagnosis and planning treatment. In addition to the dental charts and written notes, the patient record contains photographs. Comparing one set of records to another is a crucial aspect of forensic dental investigation. This method requires for use of the radiological images, which depict how the teeth and facial tissues appeared at a specific moment. This method of determining a person's stage of development for identification or other legal purposes, such as determining their age for criminal sentence or immigration, can be done using dental x-rays. Additionally, it can be utilized in judicial investigations to look for tooth and facial damage (Viner & Robson, 2017). Determining a person's age and gender using forensic dentistry mainly relies on the identification approach provided by conventional radiography. The field of forensic dentistry makes use of a wide variety of radiographic pictures, such as panoramic radiographs, cephalometric radiographs, lateral and oblique radiographs, and intraoral periapical radiographs. During the past few years, there has also been an increase in the usage of digital radiographs, which are utilized to differentiate between premortem images obtained from dental offices and centres and post-mortem radiographic photographs that are employed for independent recognition (Kukade et al., 2022).

Radiographs of the dentition are vital components of dental records and play a pivotal role in the process of ascertaining an individual's identity. Several research suggestions have been put forward in the past two decades for the development of semi-automatic (Chen & Jain, 2005; Jain & Chen, 2004) and automatic (Banday & Mir,

2018) dental identification procedures using two-dimensional (2D) radiographs. However, methods based on 2D radiography had several shortcomings. The process of tooth segmentation required a lot of time and produced inaccurate data due to the low image quality brought on by blurring dental radiographs. The retrieval and recognition of 2D radiography in an automated manner can provide challenges due to the substantial alterations in tooth shape and arch that may arise from different imaging perspectives (Arunkumar et al., n.d.; L. Wang et al., 2020).

To overcome the inherent constraints of 2D-based approaches, it is crucial to develop a functional and efficient automated 3D dental identification system that would improve the identification process. The utilisation of three-dimensional (3D) imaging in the field of dentistry has experienced a substantial surge in recent years. This is leading to the transformation of clinical practises and laboratory procedures into digital workflows (Pitta, 2019). An alternative to using traditional imprint materials, the development of intra-oral scanners allows for the direct digitalization of a patient's dental arches (Naidu & Freer, 2013; Ting-shu & Jian, 2015). The process of utilising a laser scanner allows for the conversion of dental casts into 3D models. This digital system provides numerous significant benefits, such as decreased impression time, decreased patient burden, improved storage and retrieval efficiency, enhanced accuracy, immediate access to 3D diagnostic information, and convenient portability of digital data (Chalmers et al., 2016; Wesemann et al., 2017). These models can subsequently be used for alignment and matching, as well as for an automated study of comparable dental structures (Martin et al., 2015). However, 3D photo scan data in forensic odontology also poses some challenges including Data Quality and Resolution, Variability in



Anatomical Structures, Segmentation and Reconstruction Issues and Integration with Other Data Types.

Literature review

The emerging role of 3D printing in forensic odontology, a technology that transforms digital models into physical objects. It identifies key applications, including bite mark analysis, dental age estimation, gender identification, facial reconstruction through 3D computed tomography, and physical modeling. While the paper provides useful insights into the benefits of 3D printing, it stresses the importance of further research to evaluate its precision, consistency, and to develop standardized protocols for its application in forensic odontology [29].

By merging 3D scan data with photogrammetry software, this method facilitates the precise alignment of AM (ante-mortem) and PM (post-mortem) images, enhancing forensic identification accuracy. The study analyzes a range of 3D imaging tools, highlighting their advantages and drawbacks. A noteworthy development, the Combined Holding and Aiming Device (CHAD), was created with 3D printing to address alignment issues in forensic dental imaging. This device, along with the Modified External Aiming Device (MEAD), was assessed in comparison to other devices, specifically for error rates in radiographic exposure of PM intraoral periapical images. Both CHAD and MEAD achieved low positioning errors without exposing participants to ionizing radiation. Nonetheless, the study acknowledges that more extensive validation is needed due to its small sample size, suggesting that innovations like CHAD could significantly improve the accuracy of AM-PM image alignment and victim identification. [17].

Forensic facial reconstruction (FFR) plays a critical role in identifying unknown remains by reconstructing facial

features from skull structures, aiding in potential identification. Technological advances, particularly in open-source software, have made FFR more affordable and accessible. This study outlines a protocol using tools like PPT GUI for 3D scanning, MeshLab for point cloud processing, and Blender for creating facial models and textures, all of which depend solely on digital cameras. The procedure supports both forensic and research contexts, making it versatile [18]. The integration of medical imaging with rapid prototyping offers an innovative approach to developing 3D models of anatomical structures for forensic purposes. Techniques such as computed tomography (CT), CT angiography, MRI, and photogrammetry allow researchers to create detailed 3D polygon meshes. These meshes can then be transformed into color-enhanced models that highlight specific pathologies, including bone fractures, vascular ruptures, heart infarctions, and injuries like bite marks. Such anatomically accurate and fully colored models enhance forensic analysis by providing clear, tangible representations of evidence, which is invaluable for investigations, educational applications, and legal proceedings [19]. Utilizing computer-aided design (CAD) and 3D printing technology in medical reconstruction offers significant advantages for patients with craniofacial abnormalities. CAD facilitates precise planning and customization of surgical templates and implants, aligning them with the unique skeletal structure of each patient. Coupled with CT imaging, this technology allows for the creation of accurate physical models, such as implant prototypes or skull replicas, through methods like CAM/CNC and rapid tooling. This integrated approach improves surgical preparation, enhances visualization, and provides patient-specific solutions that minimize operative errors and reduce



procedure time, ultimately streamlining craniofacial reconstruction [20].

Digital radiography and photographs of pulverised tooth fragments were both included in the activities that assessed one's capacity to estimate another person's age. In addition, computerised measurement instruments and tables categorised by age groups were used. PM results were matched to the AM data using the Interpol standard, and thereafter an analysis was conducted. This comparison and reconciliation were all part of the process of identifying the body. Some of the contributions that can be made because of this study are as follows:

1. The supply of digital educational resources in "forensic odontology", including "dental identification" following numerous deaths and dental age estimate across various age cohorts.
2. Demonstrating the use of electronic patient records, which include "intraoral scans" of the teeth, "digital radiographs", pictures, and written records of dental treatment.
3. Implementing a hybrid instructional method that can be carried out in its entirety online.
4. Making available an efficient resource that can encourage and engage students in the activity of expanding their interest and knowledge of the topic at hand
5. Utilising the newly available opportunities presented by digitalization and intraoral scanning in the field of forensic odontology [21]. 3D printing technology in dentistry has transformed the creation of dental appliances such as models, restorations, and surgical guides. The process begins by capturing data from intraoral optical scanners and cone beam computed tomography (CBCT). This data is then converted into a standard tessellation language (STL) format, which

is further refined in 3D modeling software. The use of this technology improves the precision of dental treatments, reduces costs, and speeds up the overall process. By enabling more accurate, efficient, and accessible procedures, 3D printing has become a game-changer in modern dental practices. [22]. The ability to visualize osteological evidence in court is crucial, particularly with the use of advanced 3D imaging techniques like MRI, CT scans, and surface scanning. These methods provide a more precise and detailed representation of evidence compared to traditional 2D images, facilitating a deeper analysis that can be pivotal in determining the cause of death. Moreover, 3D imaging can reduce the emotional burden by eliminating the need for graphic autopsy photographs and presenting the evidence from multiple angles. Despite these advantages, the use of 3D digitization also brings challenges, such as the need for accurate reconstructions of crime scenes and a lack of standardized practices in forensic settings [24]. The role of 3D printing in forensic medicine and pathology through an extensive review of existing literature. It highlights the various ways in which 3D printing is currently applied, such as for reconstructing injuries, comparing injuries with weapons, and enhancing evidence presentation in legal contexts. The technology is also recognized for improving anatomical modeling, facilitating better communication among forensic experts, and serving as a tool for education. However, the adoption of 3D printing in forensic medicine faces challenges, including high costs, the need for specialized equipment, and time-consuming processes [25]. The use of 3D printing in forensic odontology, specifically in creating accurate replicas of human teeth for forensic purposes. The research involved five different 3D printing methods: FDM, SLA, DLP, PolyJet, and SLS, which were tested using models of



extracted teeth. The results demonstrated that the printed replicas matched the original teeth within a margin of 0.5 millimeters, with Digital Light Processing (DLP) being the most precise method for forensic applications [26]. The combination of smartphone cameras and monoscopic photogrammetry for 3D bitemark analysis holds significant promise in forensic investigations. This approach could offer a low-cost, accessible alternative to traditional methods. Forensic odontology utilizes the unique features of an individual's dental impression to match bite marks to potential perpetrators. However, various factors such as the force of the bite, tooth morphology, and the quality of the images can influence the precision of this analysis. The integration of smartphone technology and photogrammetry presents a promising solution to these challenges, though further research is needed to validate its effectiveness and accuracy in forensic contexts [27]. The use of high-quality smartphone selfies as ante-mortem (AM) data in forensic dental identification, particularly when traditional dental records are missing. The study compares selfies to 3D post-mortem (PM) scans using two techniques: 2D visual comparison and 3D superimposition. The results show that 3D superimposition significantly improves the accuracy of matches, achieving a 94.2% success rate in correctly rejecting mismatches, compared to a lower 77% accuracy using 2D methods. This suggests that selfies, when combined with advanced 3D techniques, could serve as a reliable alternative for AM data in forensic identification [36]. Additionally, AI is the backbone of analysing 3D data, especially in dental record administration and forensic data analysis. In this regard, IDIS uses intelligent pattern recognition techniques to computerize the dental record matching process and considerably enhance identification accuracy in forensic scenarios. IDIS consolidates methods and

algorithms of identification that make possible the analysis of huge dental records, which are indispensable in forensic odontology. It enhances the traditional dental record using odontogram, which are visual representations of dental features to thereby enable automated comparisons. Besides that, AI-powered dental image analysis utilizes 3D scans in anomaly detection and effective management of patient records, hence indicating the importance of automatic feature extraction in the interpretation of data. The identification process is accelerated by the integration of AI technology in forensic investigations due to the increased levels of accuracy, therefore becoming an indispensable tool in contemporary dentistry and forensic sciences today (Chomdej et al., 2006). AI-based techniques are transforming forensic investigations related to the detection and matching of tooth patterns. Machine Learning is employed intensively to analyse big dental datasets, increasing the accuracy and speed of identification and matching dental records with unidentified remains. Their major focus is on the identification of salient features within the dental structures, highly essential for forensic odontologists, mainly in tooth arrangement and morphology. The automated dental identification system uses artificial intelligence in the matching process and considerably speeds up forensic investigations with greater speed and accuracy (Abdel-Mottaleb et al., 2003). This is further enhanced by the inclusion of pattern matching algorithms that permit the comparison of dental patterns from different sources—a fundamental identification of identity and evidence required for lawsuit purposes. In total, all these AI-powered technologies constitute a serious breakthrough in forensic analysis, enabling methodologies to identify cases so much more accurately and faster in complexity (Abdel-Mottaleb et al., 2003).



Table 01: Comparison of Traditional vs. 3D Photo Scan Methods in Forensic Odontology

Criteria	Traditional Methods	3D Photo Scan Methods
Accuracy	Moderate (dependent on plaster casts, etc.)	High precision (down to millimeters)
Data Storage	Physical models and 2D records	Digital, easy to store and share
Reproducibility	Limited	Highly reduceable
Cost	Lower	Higher initial investment
Time efficiency	Slower, manual comparisons	Faster, automated with AI integration
Non-invasiveness	Invasive (plaster models, X-rays)	Non-invasive, digital scan
Portability	Non-Portable	Digital format, easily transferable

Table 01 Depicts the comparison of traditional vs. 3D photo scan methods in forensic Odontology

The report indicates several technological challenges that relate to the application of 3D-scanning technologies, one of which is the multi-camera device "Botscan," for the documentation of injury in forensic investigations. Among the most relevant challenges, the price of the complicated Photobox system-which features 70 cameras and several light panels-is out of reach of most forensic departments. Further, the stationary nature of the device means it is limited to subjects who can physically reach the scanning area; thus, eliminating seriously injured individuals. The usefulness of the device relies on appropriate illumination and subject posture, which is vulnerable to

impairment should the former conditions be bad. It is also in posture and clothing that the scan can be interfered with since the latter masks the injuries, and essential postures are not feasible practically for a lot of people. Lastly, although 3D models have visual representations, they cannot replace tests done physically which would distinguish between kinds of damage; hence, 3D documentation is a priceless tool but by no means a flawless alternative for traditional forensic procedures. These limitations underpin the need for further research and development in raising the integration of current 3D technology within forensic practice(Sieberth et al., 2020).

Table 02: AI Tools Used in Forensic Odontology

AI Tool/Algorithm	Application Area	Advantages	Challenges
Machine Learning Models	Dental pattern matching	Faster and accurate	Requires large datasets
Deep Learning Algorithms	Bite mark analysis	High precision	Computationally expensive
Neural Networks	Age estimation from dental data	Can process complex data patterns	Prone to overfitting in small datasets
Image Recognition Systems	3D photo scan comparison	Automated analysis, large-scale capability	Dependent on high-quality input data

Three-dimensional convolutional neural networks (3D CNNs) represent a powerful application of artificial

intelligence (AI) in image processing and recognition, leveraging deep learning to handle both generative and descriptive

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tasks. Unlike traditional models, CNNs have the ability to autonomously identify key features from data without human intervention. The unique strength of 3D CNNs lies in their capacity to process three-dimensional data, such as 3D volumes or a series of 2D images, like slices from a cone-beam computed tomography (CBCT) scan. The primary aim is to foster collaboration between forensic medical experts and AI engineers, enabling professionals with basic knowledge of AI to implement it in forensic research. This paper presents a new workflow for applying 3D CNNs to analyze full-head CBCT scans, exploring its potential in five forensic research areas: (1) sex determination, (2) biological age estimation, (3) 3D cephalometric landmark annotation, (4) growth vector prediction, and (5) facial soft-tissue estimation from skull data. Ultimately, the integration of 3D CNNs could revolutionize forensic medicine, significantly improving analysis

workflows through advanced neural network technology (Thurzo et al., 2021). The use of two convolutional neural networks (CNNs), VGG16 and ResNet101, for estimating dental age (DA) within an eastern Chinese demographic. We utilized a dataset comprising 9,586 orthopantomograms (OPGs), which included 4,054 boys and 5,532 girls aged between 6 and 20 years. The performance of both CNN models was assessed using various metrics, including accuracy, recall, precision, and F1 score. The findings revealed that VGG16 surpassed ResNet101 in overall performance, achieving a remarkable accuracy of 93.63% for the 6-8 age group. This suggests that VGG16 has significant potential for application in both clinical settings and forensic investigations related to DA estimation. This version retains the essential information while using different phrasing to ensure originality (J. Wang et al., 2023).

Table 03: Prospective Future Applications of 3D Photo Scanning and AI in Forensic Odontology

Application Area	3D Photo Scan Role	AI Integration	Potential Impact
Bite mark analysis	Precise modeling of bite marks	Automated pattern matching	Faster and more reliable identification
Age estimation	Detailed 3D dental structure scans	Age prediction through machine learning	Non-invasive and accurate
Dental identification in mass disasters	Creation of comprehensive 3D dental records	Automated search and matching	Speed up identification process

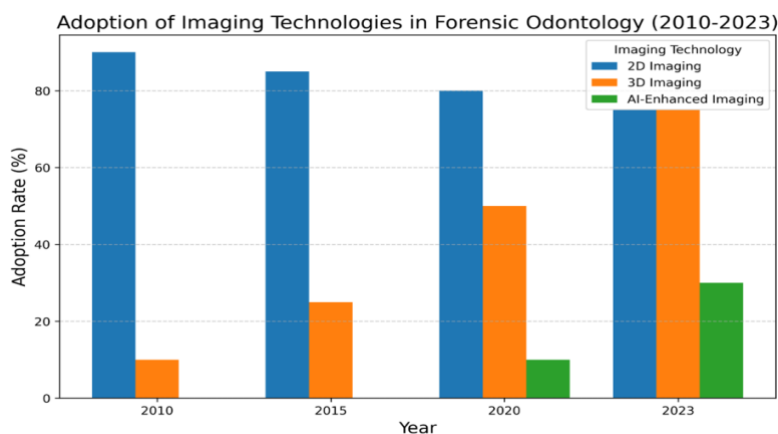
The application of 3D scanning technologies in forensic odontology is no doubt a quantum leap as far as gathering and processing evidence goes. As it is represented in the market projection graph Figure, from the year 2021 to 2030, significant growth is expected in the field of 3D scanning. These are driven by breakthroughs in technology, a reduction in

cost, and the increased accuracy of 3D scans compared with the previous 2D scanning methods, thus enhancing the identification process of human remains. Most importantly, the integration of 3D scanning with artificial intelligence opens new horizons in forensic analysis. AI can help analyze complex 3D data sets and detect patterns that may be tricky for the

human analyst to spot. Such a synergy of technologies is foreseen as further sealing the role of 3D scanning in forensic odontology with a view to further enhancing forensic practices and justice verdicts (Matsuda et al., 2020). A comparison of 2D and 3D scanning technologies in forensic odontology from 2010 to 2023 reflects a big difference in the adoption rate. Represented on this graph is the rate of adoption; though 2D imaging had dominated this area for quite some period of time, the spread of 3D scanning can be seen, showing upticks both in accuracy and detail. It partially relates to the fact that 3D technology is more capable of fully and precisely modelling dental structures, which makes the identification process easier and increases the quality of forensic evidence. The application of artificial intelligence with 3D scanning is also a widening practice, and this is probably likely to accelerate its implementation even more. Besides, AI technologies have the potential to analyse advanced sets of data better, which helps raise the reliability of forensic investigations even higher. Yet another factor that is most probably going to continue, since forensic specialists understand more and more the reason for

3D against 2D approaches, is going to make the need for further training and investing in these innovative ways of imaging even more urgent (Ishwarkumar-Govender & Nalla, 2024). The graph of adoption versus time, as taken from the graph in Figure X, would serve to underpin that the trend of forensic odontology adoption has taken a dramatic turn for imaging technologies from 2010 through 2023. This drift toward the latest types of imaging methods—especially AI-enhanced 3D scanning—reveals an emerging awareness of their higher potential value in serving the purposes of forensic investigation. AI, when used with imaging technology, increases the accuracy of dental evidence examination and assists in finding patterns that are very difficult to be found using traditional methods. Graph: The emerging acceptance of AI-enhanced imaging is consistent with advances in technology and an increasing awareness of its benefits within the forensic community. This development is within the broader push toward digital solutions in forensic odontology and further underlines the fact that training and research remain crucial in perfecting these new breeds of tools (Li et al., 2024).

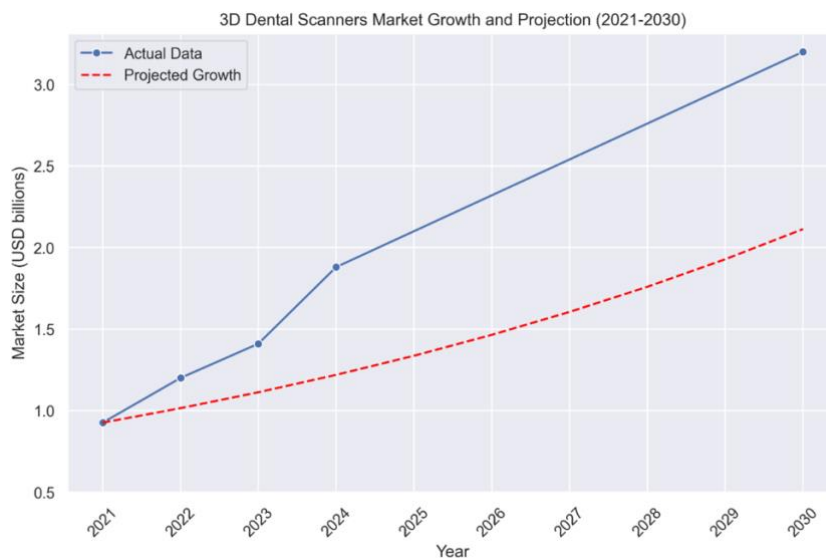
Adoption of imaging technologies, including AI-enhanced methods



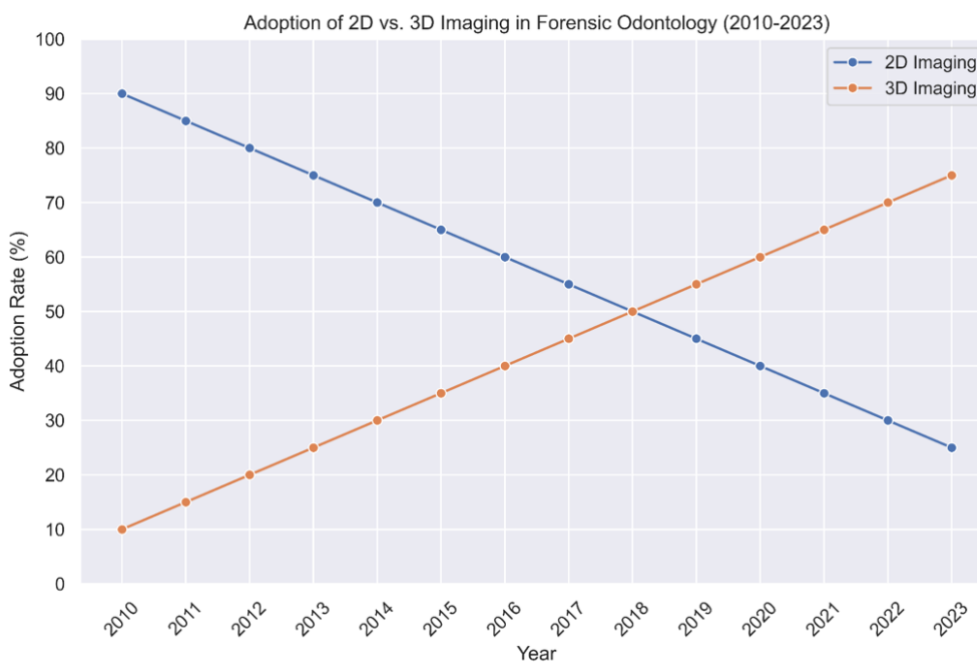
3D Dental scanner market growth and projection (2021-2023)



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Adoption of 2D vs 3D scanning in forensics odontology from 2010-2023



Conclusion

In this regard, the integration of 3D photo scan data and AI in forensic odontology enables the creation of extremely detailed models through the use of modern methods of photogrammetry and scanning for the capture of dental structure images that aid in identification. However, such techniques are likely to be burdened by errors related to lighting conditions,

motion artifacts, and the precision of the scanners. The use of AI in this field has great potential, but it requires considerable expertise in software as well as in the interpretation of data. In the same way as other AI technologies, correct training and cautious application are extremely important to achieve accurate results. Where correct application of AI with 3D imagery is made, forensic investigations



become much quicker, more effective, and more reliable, and help considerably in the identification of human remains and in court processes. The technology has great promise, which, over the coming decades and with incorporation into more conventional processes, might just change the way the field works: eradicating human mistake and vastly improving results.

Declarations

Ethical approval and consent to participate: Not Applicable.

Consent for publication: Not applicable

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Availability of data and materials: Not Applicable.

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Biodiversity Survey and Distribution Trends of the Bumblebees (*Hymenoptera: Apidae*) in District, Bajur Tehsil Arang, Khyber Pakhtunkhwa:

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ABSTRACT

This paper deals with the distribution of *Bombicidae* specimens across various localities of District Bajur, Tehsil Arang, Khyber Pakhtunkhwa. All in all, seven areas have been prospected for collection: ARANGI, MAZDAKK, NARANJ, GHAZI BABA, TAWHEED ABAD, SERAY TOP, and PIKET. The results reflect an apparent difference in the abundance of the specimens, out of which ARANGI turned out to be the most productive site, contributing 43.8% toward the overall specimens, followed by MAZDAKK, which also attained a contribution rate significantly high but lower at 21.7%. If NARANJ and GHAZI BABA add moderate percentages, the minor ones are TAWHEED ABAD, SERAY TOP, and PIKET-environments probably poorer or due to poor research effort. This variation emphasizes how highly productive ARANGI and MAZDAKK are, supporting the implication of research that is necessary for understanding the factors controlling the specimen distribution and for reinforcing efforts of collecting in those less represented localities. The collected specimens were brought to the laboratory where the specimen was pinned and labeled. All the specimens were relaxed in a relaxing jar for 24 hours, after which the legs and wings of the specimens were spread. Identification of the specimens was completed with the help of a microscope identified and preserved in the lab for further identification.

INTRODUCTION

The genus *Bombus*, from the tribe *Bombini*, is the home of the bumble bee. This is the only surviving group within the genus *Bombus*, which has some 250 identified species worldwide. Originally, bumble bees are cold-adapted species, which enabled them to live in some of the highest latitude and elevation ecosystems and to attain high diversity levels in both arctic and boreal regions. Species found

in the highest latitudes include many conspicuous and endemic species found under some of the most extreme conditions on the planet.

Evidence has been found that, in recent years, the bumblebee species have declined, especially within the developed regions such as Western Europe and North America. Most of the bumblebees have suffered in abundance because of agricultural wasteland using the loss of their natural habitat.



Bombini is one of the 4 groups of corbiculate bees *Apidae* which includes *Meliponini* or stingless bees, *Euglossini* or orchid bees and the *Apini*, or honey bees (Cardinal *et al.*, 2011). There are about 22 species together with 6 true species of bumblebees belonging to the subgenus *Psithyrus* in Britain, Benton, 2006. They are mainly found in high altitudes in the region of the Northern Hemisphere, also distributed in South America where little low land tropical species have been identified. They are 9-27 mm in size, with fuzzy hairs covering the body, typically yellow and black veined with an apparent wing. The female bumblebee possesses a broad hind leg with a cupped-shaped area for collection. The number of tergites-seven in males, and six in females the segments of the antennae-twelve in females, and thirteen in males differentiate sex in the bumble bees. They are social insects in nature having a single queen within the colony.

The colonies of the bumblebee often are often smaller than the honey bees, with almost up to fifty individuals in the nest.

Female bumble bees do sting frequently; while generally ignored by other living organisms .

Cuckoo bumble bees do not make nests; queens of these bumble bees attack the nests of other species of bumble bees, kill the resident queens, and then lay their eggs into the nest after that they are looked after by resident workers of the previous queen (Williams, 1998). More than 2/3rd of crop species are those which require insect pollination to reach their full yield and are pollinated by bumblebees. A few cases, bumble bees give higher

pollination services as compared to *Apis mellifera* for example, in blossoms *Vaccinium corymbosum* (blueberry) bumble bees were capable of pollinating more than three times per minute as compared to honeybees (Daly *et al.*, 2013 In), also; *Trifolium pratense* (clover), alfalfa (*Medicago sativa*), broad beans (*Vicia faba*) tomato (*Lycopersicon esculentum*) (Corbet *et al.*, 1991) and raspberry (*Rubus idaeus*), (Willmer *et al.*, 1994). Several of the family Fabaceae are highly specific food plants for bumblebees, Pywell *et al* 2005. Bumblebees are in decline both in their range and in population and at least nine species are of conservation concern and one, the short-haired bumblebee *Bombus subterraneus* has not been seen since 1989 and is presumed extinct. Anonymous. Among them, the genus *Bombus*, the only one extant genus in the tribe *Bombini* comprises more than 250 species; Williams *et al.* proposed a simplified subgeneric classification of the genus *Bombus* and reduced the number of subgenera from 38 to 15 using new strongly supported estimate of phylogeny for almost all bumblebee species. They have recognized 10 new subgeneric synonyms as well (Williams 2008).

Psithyrus was treated separately as a genus while are now believed into the family *Bombus*, (Williams, 2008). Fifteen subgenera have been identified in the genus *Bombus* that often to be seen as monophyletic e.g., *Bombus rpestris*, *Bombus lapidaries*, *Bombus dahlbomii*, *Bombus fervidus*, *Bombus ruderatus*, and *Bombus atratus*., (Williams, 2008).

There are declining due to intensive agricultural farming collateral pesticide damage and insensitive

development. The construction of thousands of new homes is taking place on agricultural sites and threatens to destroy large areas of flower-rich sites which bumblebees and other invertebrates depend on worldwide. Slaughtering by so-called organic pesticides has reduced their population. Geographically, different areas of Bajur Arang have not yet been studied for the bumblebee's taxonomy. This is a unique area that comprises microclimatic zones and many undistributed areas. The resources of bumblebee were rich here, due to alpine, subalpine, and mountainous areas. No special attention has yet been given to the *Bombus* species of District Bajur. A taxonomic study is going on, keeping in view the importance of the *Bombus* species.

MATERIALS AND METHODS

Study area Arang Bajur

The proposed Study entitled "Taxonomy and Distribution of Bumblebees (*Hymenoptera: Apidae*) of Different Areas of District Bajur " was conducted in the diverse ecological zone of district swat, i.e., ARANGI, MAZDAKK, NARANJ: GHAZI BABA, TAWHEED ABAD, SERAY TOP, PIKET.



Collection of Bumblebee

Bumblebees are the range from 9mm-27mm in size. So sweeping of hand net was used in their habitat. On flowers, sweeping was utilized as well.

Killing

Dry killing jar was used for killing of bumblebees. Cyanide was used as a killing agent because it is the most quick and effective chemical for killing of insects.

Pins, Pinning, and Labeling

Three-number size insect pins were used for pinning. Collected insect specimens were pinned at the right side of the thorax. Field label was inserted below the specimen in pins incorporating necessary information.

Relaxing and Spreading

Specimens were kept in the relaxing jar for 24-48 hrs. Antennae, mouthparts, wings and legs were spread properly.

Storage of specimens

The relaxed specimens were pinned in a wooden box and naphthalene balls were kept in the boxes to save the specimens from the attack of the museum pests. Silica gel small pouches were also kept for absorbing the moisture of boxes to save the specimens from fungus attack.

Identification

All bumblebee specimens collected were studied using a Nikon microscope with up to 400X magnification. Identifications were

done using the available literature and identification keys: Williams (1991); Williams *et al.*, (2008); Williams, P. 2009, Williams *et al.*, 2010. Specimens were identified up to the species level.

Description

The descriptions are made from the most obvious and observable characters. In this present work, all collected specimens were described using the terminologies of Williams, 1991.

Repository

Collected specimens were submitted to the Insect Museum, Department of Entomology, Abdul Wali Khan University Mardan.

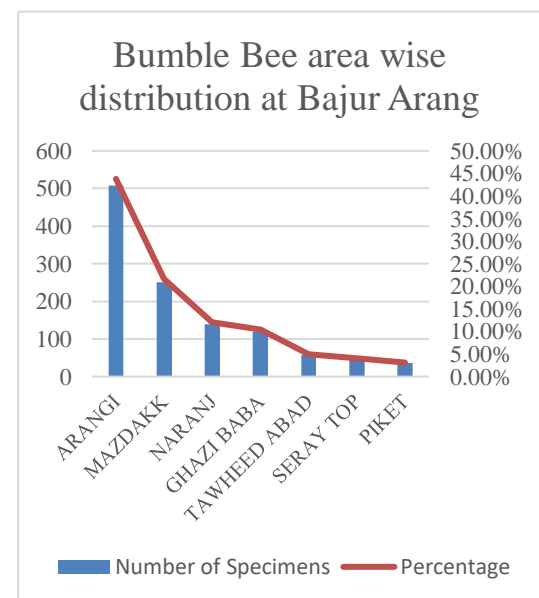
RESULTS

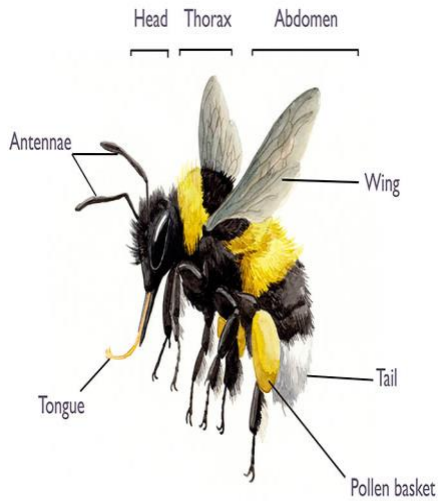
Collection of the specimens of family Bombicidae was carried out in the present study at different localities of District Bajur tehsil Arang, Khyber Pakhtunkhwa. ARANGI: 507, MAZDAKK: 251, NARANJ: 139, GHAZI BABA: 120, TAWHEED ABAD: 58, SERAY TOP: 47, PIKET: 36 The above information shows that the distribution of the specimens is not even within the site. Therefore, ARANGI, with 43.8%, has the most of all the available specimens, thus, being very productive. MAZDAKK has a contribution of 21.7%, which, although significant, is lesser, making it important but not as high as ARANGI. While NARANJ and GHAZI BABA show reasonable contributions, they appear to perform a somewhat leading but balanced role in the general distribution. The contribution is the least probably due to lesser favorable conditions or less collection in areas

where the specimen count was relatively lesser, such as TAWHEED ABAD, SERAY TOP, and PIKET. This distribution underlines the variability in the availability of specimens and indicates that further research should be directed to sites ARANGI and MAZDAKK, while other locations may benefit from an increased focus with a view to understanding and improving their specimen yields.

Table 1. The percentage of Bumblebees recorded from district Bajur Arang Utman Khail.

Location	Number of Specimens	Percentage
ARANGI	507	43.8%
MAZDAKK	251	21.7%
NARANJ	139	12.0%
GHAZI BABA	120	10.4%
TAWHEED ABAD	58	5.0%
SERAY TOP	47	4.1%
PIKET	36	3.1%





Bumblebees, genus *Bombus*, are among the most conspicuous bees besides European honey bees - chiefly because of their larger size. Over 250 species are known worldwide; many can be recognized by their black hair that is marked with various patterns of yellow, orange or white stripes. At least six species of bumblebees can be seen in the Santa Barbara area. However, one of those Crotch's bumblebee - *Bombus crotchii* is considered Endangered. Bumblebees are social insects and they form colonies having one queen.

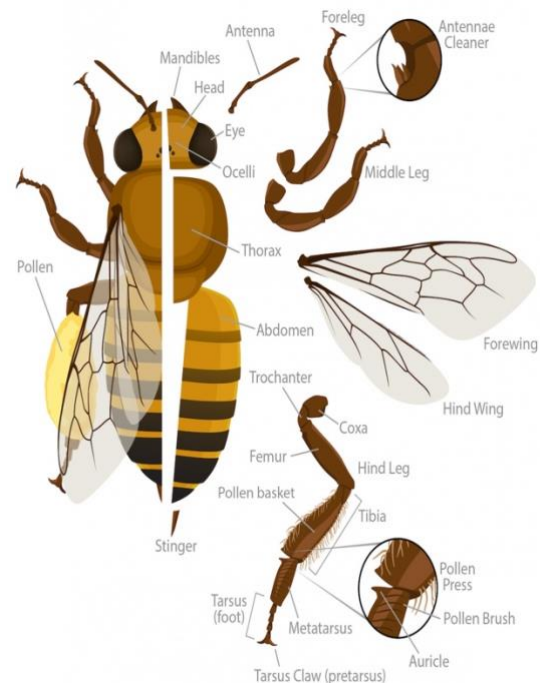
Shape of Body:

The body of Bumblebee is large and robust. Their bodies measure 7mm to 27mm in body length. Most are thinly hairy, usually with dense hairs but bear long plumose hairs. The ventral surface of the gaster, propodeum, anterior face of gasteral tergum I and head bear little or no hair. Distal parts of the limbs are usually black or light brown and never bear bright yellow, red or metallic colours. The general appearance is similar to bumble bees although there are several

morphological characters useful for identification of different subgenera as well as species under a stereomicroscope.

Antennae:

Bumblebees possess geniculate antennae. Females: 12 segments; 1 scape, 1 pedicel and 10 flagellomeres. Males: 13 segments; 1 scape, 1 pedicel, and 11 flagellomeres.



Head:

General Description: The head of the bumblebee is hypognathous. It bears 2 compound eyes and 3 ocelli. The face is densely hairy or smooth, depending upon the species. **Identification:** Shape and puncture distribution of clypeus and oculo-malar area is important.

Mouthparts:



Mouthparts represent various appendages like the tongue, palp, maxilla, and mandible. Number and shape of mandibular teeth is very crucial for the identification of species that including keels, sulcus obliques, basal teeth, intercalary teeth, apical teeth, and incisora.

Legs

The legs of the bumblebee include coxa, trochanter, femur, tibia, basitarsus and tarsus. Mesobasitarsus and hind tibia are very useful for identifying a number of species. Females have pollen-collecting structures corbicula and rastellum.

Wings:

Bumblebees have two pairs of wings transparent or hyaline, in some cases with darkened or metallic reflections. Colour patterns on the wings furnish diagnostic characters for several species.

Abdomen:

In females, there are 6 visible gastral terga and sterna [TI-VI, SI-VI], while in males, there are 7 visible, gastral terga and sterna [TI-VII, VI-VII]. Another important character in species identification is the ventrolateral keel on the gastral sternum [hypopygium] VI.

Taxonomic Characters:

Bumblebees can be identified on the basis of different morphological characters like color of the pubescence, sculpturing of labrum, number of mandibular teeth and 7th tergum and sternum in females, shape of

mesobasitarsus and corbicular area of metabasitarsus.

Distribution:

They generally occur at elevations ranging from 1650 to 5500 meters above sea level. Their distribution is recorded from Afghanistan, India, Nepal, and Pakistan (Williams, 2004; Williams et al., 2010). For this survey, they were gathered from Skardu, Kharmang Olding, and Shigar areas and are very frequent around the lower mountain coniferous forests.

Host-Plants:

It feeds on the following plants: *Artemisia absinthium* L., *A. spp.*, *Cirsium falconeri* (Hook.f.) Petrak, *Cirsium arvense* (L.) Scop., *Helianthus annuus* L., *Chenopodium botrys* L. (Chenopodiaceae); *Convolvulus arvensis* L. (Convolvulaceae); and *Prunella vulgaris* L. (Williams 1991; Rifat 2010).

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BIOLOGY AND LIFE CYCLE OF RICE MOTH *Corcyra cephalonica*, *Lepidoptera, Pyralidae*

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Abstract

The rice moth, *Corcyra cephalonica*, is a significant pest of stored food commodities, causing both quantitative and qualitative damage to grains through its larvae, which feed on cereals, pulses, oilseeds, spices, and dried fruits. The species exhibits complete metamorphosis with a life cycle including an egg incubation period of 5 days, a larval period of 23-25 days, a pupal period of 10 days, and an adult lifespan of approximately 1 week. The larvae damage grains by feeding within silken webs, often converting stored grain into a webbed mass, rendering it unfit for human consumption (Bhandari *et al.*, 2009). Efforts to rear *C. cephalonica* on efficient food media resulted in the production of robust moths and eggs, which are crucial for rearing egg parasitoids (Pathak *et al.*, 2010). Recent studies have focused on alternative pest control methods, given the growing concerns over chemical pesticide use. Fenoxycarb, a juvenile hormone analog, has shown promising results in controlling *C. cephalonica*. Six different concentrations of fenoxycarb (0.025%, 0.05%, 0.1%, 0.25%, 0.5%, and 1.0%) were tested on last instar larvae, with concentration-dependent mortality observed. Higher concentrations (0.5% and 1.0%) resulted in larval mortality before reaching the adult stage, while lower concentrations (0.025% and 0.05%) led to developmental delays, morphological abnormalities, and reduced fecundity in females. Moreover, exposure of normal eggs to fenoxycarb prevented hatching in 37.2%-57.2% of eggs, indicating its gonadotropic action (Begum and Qamar, 2016). In an effort to optimize rearing conditions for *C. cephalonica*, nine dietary formulations were tested, incorporating various combinations of rice, wheat, sorghum, and groundnut. The diet comprising sorghum and groundnut (T6) yielded the best results, with the shortest larval (30.33 days) and pupal (7 days) periods, the lowest total developmental period (47.33 days), and the highest rates of adult emergence (82%) and fecundity (312.33). This diet also resulted in the longest female longevity (9.67 days) and highest male longevity (8.33 days), contributing significantly to



40 mass rearing efforts for the large-scale production of *C. cephalonica* (Arun Kumar *et al.*,
41 2018).

42 This research offers valuable insights into the biology, pest control, and rearing
43 optimization of *C. cephalonica*, highlighting the potential of fenoxycarb as an effective
44 management tool and providing suitable diets for large-scale production.

45 **Keywords:** Life cycle, Rice moth, *Corcyra cephalonica*, *Lepidoptera*, *Pyralidae*.

46 Introduction

47 The rice moth (*Corcyra*
48 *cephalonica*) is a moth of the family
49 Pyralidae and kingdom Anamalia. This
50 small moth can become a significant pest.
51 *Corcyra cephalonica* the rice moth can be
52 considered the Indian meal moth of the
53 tropics. It is found in Hawaii and
54 occasionally in some southern U.S. ports.
55 The larvae are general feeders and prefer
56 warm climates and occur commonly in the
57 equatorial regions of Asia, Africa, and
58 Caribbean. It is much less common on the
59 mainland than the Almond moth,
60 (*Ephestia cautella*), which it is often
61 misidentified (Sedlacek *et al.*, 1996). Its
62 caterpillars feed on dry plant stuffs such as
63 seeds, including cereals (e.g. Rice). Other
64 recorded foods are flour and dried fruits
65 (Hill *et al.*, 2002).

66 Rice moth, *Corcyra cephalonica*, is
67 economically an important stored grain
68 pest in Asia, Africa, North America and
69 Europe. Its larval stages cause serious
70 damage to rice, gram, sorghum, maize,
71 groundnut, cotton seeds, peanuts, linseeds,
72 raisins, nutmeg, currants, chocolates, army
73 biscuits and milled products. While
74 feeding the larvae leave silken threads
75 which produce dense webs containing
76 their faecal matter and cast skin which

77 contaminate the grains (Ayyar *et al.*,
78 1934).

79 Moth is usually seen in large
80 numbers on walls, poles, or containers
81 where grains are stored. The larvae are
82 exceptionally good at producing “paper
83 thick” webbing for its cocoons. The
84 caterpillars produce a large amount of
85 frass (in which they hide) compared to
86 other stored food moths. This material can
87 attract other stored food pests such as
88 Flour Beetles (*Tribolium* spp). (Tripathi *et*
89 *al.*, 2018).

90 *Corcyra cephalonica* is
91 industrialized for many of the natural
92 enemies mass-bred in the laboratory for
93 use in field against crop pests, which are
94 dependent on either egg or larval stages of
95 *C. cephalonica* because it is easier and
96 cheaper to produce natural enemies on
97 different stages of *C. cephalonica* than on
98 their original hosts (Kumar and Murthy,
99 2000).

100 The rice meal moth, *Corcyra*
101 *cephalonica* Stainton is one of the serious
102 insect pests of stored milled rice and other
103 milled cereal products in India. But
104 another economic importance of this insect
105 is that the eggs of these insects are used as
106 diet to mass multiply the bio-agent like
107 *Trichogramma* spp. The biology and
108 bionomics of this pest under controlled



109 laboratory conditions was studied. An
 110 experiment was conducted during July
 111 2015 to October 2015 in the Biological
 112 Control laboratory, Department of
 113 Entomology, IGKV, Raipur at 27 OC + 20
 114 OC (and 75+5% RH to study the different
 115 diet performance on the biology and
 116 bionomics of rice moth, *C. cephalonica*.
 117 Five cereals viz., rice, wheat, pearl millet
 118 (jowar), sorghum (bajra) and maize were
 119 tested solely along with their
 120 combinations. The female moth had longer
 121 body length and weight as compared to
 122 male moth. Both male and female reared
 123 on mixed diet with a combination of
 124 (rice+jowar+maize) had maximum body
 125 weight and body length. There was a high
 126 positive co-relation between fecundity and
 127 female body weight. The mixed diet of
 128 rice jowar maize was highly superior, in
 129 comparison to others for mass production
 130 of *C. cephalonica*. The shortest life cycle
 131 was found in the combinations of bajra
 132 jowar maize up to 35 and 40 days
 133 respectively and longest life cycle was
 134 found in rice extending of 60 to 70
 135 days. (Bhardwaj *et al.*, 2017).

136 Freshly laid egg was glistening,
 137 pearly white in colour with irregularly
 138 sculptured surface having small divided

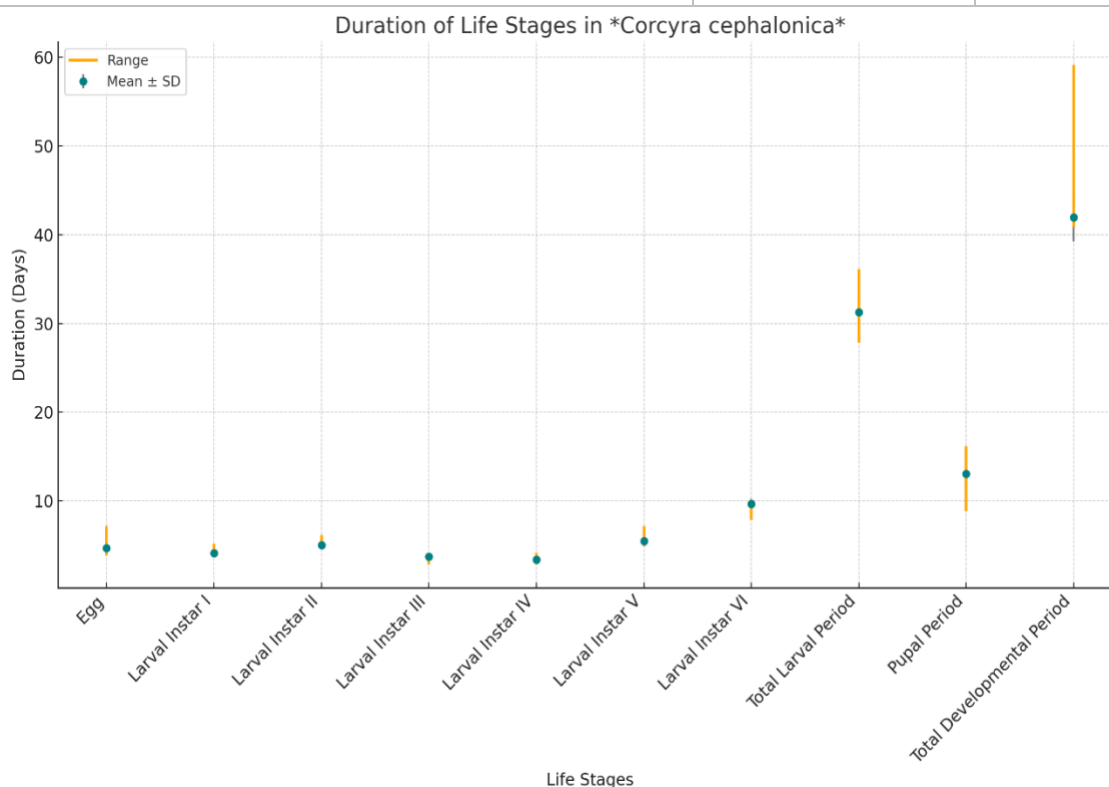
139 uneven areas on the surface. Egg was pear
 140 shaped and gently rounded at one end and
 141 pointed at the pedicel end with brownish
 142 tinge. Egg duration ranged from 4-7 days
 143 with average of 4.66 days. The larval
 144 development was inside the grain cluster.
 145 Larva was dirty white with brownish head.
 146 The larval period ranged from 4 to 5, 5 to
 147 6, 3 to 4, 3 to 4, 5 to 7 and 8 to 10 days
 148 with a mean of 4.13, 5.04, 3.73, 3.40, 5.46
 149 and 9.69 days, respectively for six larval
 150 instars (Table 1). The above results are in
 151 conformity with studies made by Ayyar
 152 (1934) who recorded 57 days on sorghum
 153 and Seshagiri Rao (1954) reported 47 to
 154 57 days on broken maize. Predominance
 155 of females was observed among the
 156 population raised in the laboratory culture
 157 with female: male ratio of 1.51:1 and
 158 female: male ratio of 1.79:1 in the
 159 collections from godown was observed
 160 (Table 2). Dominance of females over
 161 males was also recorded by Ayyar (1934)
 162 and Teotia and Singh (1975). Mating
 163 period ranged from 60 to 130 minutes with
 164 mean of 90.55 minutes. The per-
 165 oviposition period ranged from 1 to 2 days
 166 which is slightly different from Ayyar
 167 (1934) who reported 2 to 3 days on paddy.
 168 (Jagadish *et al.*, 2010).

169 Duration of Life Stages, Biological Parameters, and Sex Ratio of *Corcyra* 170 *cephalonica*

Parameter	Range	Mean ± SD
Egg	4 - 7 days	4.66 ± 0.50
Larval Instars		
- Instar I	4 - 5 days	4.13 ± 0.16
- Instar II	5 - 6 days	5.04 ± 0.31
- Instar III	3 - 4 days	3.73 ± 0.25
- Instar IV	3 - 4 days	3.40 ± 0.23
- Instar V	5 - 7 days	5.46 ± 0.35
- Instar VI	8 - 10 days	9.69 ± 0.52



Total Larval Period	28 - 36 days	31.26 ± 1.16
Pupal Period	9 - 16 days	13.06 ± 0.86
Total Developmental Period (Egg + Larva + Pupa)	41 - 59 days	41.95 ± 2.68
Mating Period	60 - 130 minutes	90.55 ± 11.83
Pre-Ovipositional Period	1 - 2 days	1.35 ± 0.32
Ovipositional Period	6 - 8 days	7.70 ± 0.44
Post-Ovipositional Period	1 - 3 days	2.20 ± 0.51
Adult Longevity	9 - 12 days	9.58 ± 0.79
Sex Ratio (Female: Male)		
- Mated Males	4 - 6	5.53 ± 0.43
- Laboratory Culture		1.51: 1 ± 0.31
- Godown Culture		1.79: 1 ± 0.30



The moths are nocturnal and each female lays 90-200 eggs having 5 days incubation period, 23-25 larval period, 10 days of pupal period and adult life span of 1 week. *Corcyra cephalonica*, the so far known

only living member of the genus *Corcyra*. The larvae of *Corcyra* feeds on almost all sorts of stored food commodities like cereals, cereal products, oilseeds, pulses, spices, dried fruits, nuts, and biscuits. Rice

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moth is an external feeder of all kinds of grains. The life cycle shows complete metamorphosis. The damage is mainly caused by the larvae which feed on grains under silken webs and render them useless for human consumption (Bhandari *et al.*, 2009). Rearing *Corcyra* on efficient food media resulted in production of robust moths and robust eggs. The size of the egg considered as one of the criteria for assessing the health of the insect. For rearing of egg parasitoids utilization of robust host eggs is important (Pathak *et al.*, 2010).

The larvae cause damage to broken grains by forming silken webs and feeding inside them. When infestation is high the entire stock of grains may be converted into a webbed mass. The pest causes both quantitative and qualitative losses. Storing grain in store houses, to keep them free from being damaged by insect pests is a problem confronted by every householder, whether a cultivator or user. The success achieved so far in making the stored grains free from insect pests has been based largely on pesticidal usage. Increasing awareness of the hazards caused due to the use of chemical pesticides and several reported cases of food poisoning has created renewed interest in the use of plant products as grain protectants (Jhala *et al.*, 2018).

Six different concentrations viz. 0.025%, 0.05%, 0.1%, 0.25%, 0.5% and 1.0% of fenoxycarb were topically applied at 2 μ l dose to the last instar larvae of rice moth, *Corcyra cephalonica*. There was a concentration-based and time-dependent response with respect to various life cycle parameters as quantified in the present work. The larvae treated with 0.5% and 1.0% fenoxycarb did not reach the adult stage as the mortality occurred owing to direct knockdown, incomplete moulting and unsuccessful metamorphosis. At concentration 0.05% and 0.025% fenoxycarb resulted in retardation of

metamorphosis and developmental rate of the surviving *C. cephalonica* larva/pupae which, during developmental path, showed morphological abnormalities. The females that emerged from treated stock exhibited malformed reproductive system along with reduced fecundity and hatchability. Furthermore, when the normal eggs were contact exposed to fenoxycarb (0.025% to 1.0%) the hatching was prevented in 37.2%-57.2% eggs; thus, indicating the gonadotropic action of the current juvenoid. Therefore, fenoxycarb appears to be a promising agent for the control of *C. cephalonica* with the pronounced effects on the development and reproduction. (Begum and Qamar, 2016)

Nine experimental dietary formulations (T1-T9) were prepared which composed of rice, wheat, sorghum, rice groundnut, wheat groundnut, sorghum groundnut, rice sesamum, wheat sesamum and sorghum sesamum as base diet to rear and maintain the rice moth, *Corcyra cephalonica* under laboratory conditions. All the diets were fortified with baker's yeast 5 g, wettable Sulphur @ 5 g, and Streptomycin sulphate 50 mg. The parameters studied in the present work were eggs hatching percentage, incubation period, larval period, pupation percentage, pupation period, total developmental period, percent adult moth emergence, percent male and female moth emergence, male and female longevity and fecundity. The Diet T6 (sorghum 1000 g groundnut 50 g) was found to outperform other dietary formulations as it resulted in lowest larval period (30.33 days), lowest pupation period (7 days), lowest total development period (47.33 days), highest adult emergence (82%), highest adult female emergence (52.11 days), highest male longevity (8.33 days), highest female longevity (9.67 days) and highest fecundity (312.33). The obtained results provide suitable diets for mass rearing, thus contributing significantly for the large



scale production of *C. cephalonica*. (Arun Kumar *et al.*, 2018).

Control and Management

Assessing the effectiveness and parasitism by *Trichogramma evanescens* to prevent *Corcyra cephalonica* from infesting rice in paper and jute bags. Eight small jute or paper bags filled with 5 kg of organic rice grains were prepared and the openings sealed. Sentinel egg cards were prepared with thirty fresh eggs of *C. cephalonica* glued onto small pieces of paper cardboard. Eight sentinel egg cards were introduced into a plastic box measuring 60 × 40 × 21 cm, i.e. four cards on top surface of the bag and the box bottom, respectively. Approximately 500 adults of *T. evanescens* were released 10–30 cm away from the egg cards. The control boxes contained no parasitoids; there were five replicates for all treatments and controls. Two experimental conditions were tested, i) placing a single *T. evanescens*-release unit with sentinel egg cards placed every 3–4 days without any further replacement of the release unit for three weeks, ii) both new host eggs and *T. evanescens* release units were replaced every 3–4 days. Mean emergence of *C. cephalonica* was significantly ($p > 0.001$) suppressed by the release of *T. evanescens*. There was statistically no significant difference on the number of emerged moths on paper bag compared to jute bag. All sentinel egg patches were visited by *T. evanescens*. There was no correlation between the distance (10–30 cm) at which the sentinel egg cards were placed away from the *T. evanescens* release point and the number of parasitized *C. cephalonica* eggs. There was no decrease in parasitism over time. The results demonstrate that *T. evanescens* has the potential for host-location ability and parasitism of *C. cephalonica* both on paper and jute bags. This parasitoid could be a promising candidate for the biological control of moth pests in bagged stored products. The

life cycle of *Corcyra cephalonica* was studied under ambient laboratory conditions (temperature range 27.5–30°C and 60–73% RH) on groundnut, bambara groundnut and cowpea. The mean developmental period ranged from 33.2±0.2 to 45.3±1.8 days on whole, broken and powdered forms of the food media. Egg hatchability was found to be 83%, while adult longevity ranged from 1.5±0.5 to 11.9±1.3 days for males and 1.5±0.5 to 16.5±1.2 days for females. Sex ratio (♂: ♀) of emerged adults ranged from 1:1 to 1:2.1. Mean fecundities ranged from 128±5 to 157±8 on the food media. In experiments to assess the insecticidal potential of three plant materials against *C. cephalonica*, *Eichhornia crassipes* powder showed a higher efficacy than both *Citrus sinensis* peel powder and the leaf powder of *Chromolaena odorata* at dosages of 0.5–2.0 g per 40 g of legume seed. At the higher dosage of 2.5 g, *C. sinensis* was more effective and reduced the population of *C. cephalonica* by half when compared to the population in control jars over a period of 1.5 months. Adarkwah *et al.*, (2015).

Both male and female moths produce pheromones that attract each other. The moths are excellent fliers, and a typical grid pattern can be established to monitor for their presence and population trends. These moths will not be attracted to the pheromones of other stored food moths such as Indianmeal moths and Almond moths. Separate traps and lure combinations should be used to monitor each species efficiently if both species are present. Adams *et al.*, (2017).

Besides being a pest, it is the factitious host for 75 natural enemies of which 60 of parasitoids and 15 of predators including a few that are host-specific in nature. It is also served as a host for nematodes and mites. Its wide acceptability is unique and turned out to be a boon for mass production of bio-control



agents. In South Asia at different commercial insectaries the rice moth, *C. cephalonica* (Stainton) (Lepidoptera: *Pyrallidae*), is mass reared as a host for egg parasitoids of the genus *Trichogramma*, the larval parasitoid, *Braconhebetor* (Say) (Hymenoptera: *Braconidae*), and as prey for the predator, *Chrysoperlacarnea* (Stephens) (Neuroptera: *Chrysopidae*). In India, it is being utilized for mass production of number of natural enemies in various bio-control research, developmental and extension units. Chaudhuri *et al.*, (2017).

Literature Review

Allotey and Azalekor., (2000) Studied the life cycle of *Corcyra cephalonica* under ambient laboratory conditions (temperature range 27.5–30°C and 60–73% RH.) on groundnut, bambara groundnut and cowpea. The mean developmental period ranged from 33.2±0.2 to 45.3±1.8 days on whole, broken and powdered forms of the food media. Egg hatchability was found to be 83%, while adult longevity ranged from 1.5±0.5 to 11.9±1.3 days for males and 1.5±0.5 to 16.5±1.2 days for females. Sex ratio of emerged adults ranged from 1:1 to 1:2.1. Mean fecundities ranged from 128±5 to 157±8 on the food media. In experiments to assess the insecticidal potential of three plant materials against *C. cephalonica*, Eichhornia crassipes powder showed a higher efficacy than both Citrus sinensis peel powder and the leaf powder of *Chromolaena odorata* at dosages of 0.5–2.0 g per 40 g of legume seed. At the higher dosage of 2.5 g, *C. sinensis* was more effective and reduced the population of *C. cephalonica* by half when compared to the population in control jars over a period of 1.5 months.

Coelho *et al.*, (2007) tested Annona coriacea lectin (ACLEC) for insecticidal activity against larvae of two pyralid moths, *Anagasta kuehniella* and

Corcyra cephalonica. ACLEC produced ~ 50% mortality and mass loss in *A. kuehniella* larvae when incorporated into an artificial diet at levels of 1.5% and 1.0% (w/w), respectively. In contrast, the inclusion of up to 2% ACLEC in the diet did not significantly decrease the survival or weight of *C. cephalonica* larvae. The nutritional indices for *A. kuehniella* and *C. cephalonica* suggested that ACLEC had a multi-mechanistic mode of action and was an antifeedant for both insects. The toxicity in *A. kuehniella* apparently resulted from a change in the gut membrane environment and consequent disruption of digestive enzyme recycling mechanisms. Affinity chromatography showed that ACLEC bound to midgut proteins of *A. kuehniella* and *C. cephalonica*. However, the 14 kDa subunit of ACLEC was not digested by midgut proteases of *A. kuehniella* but was degraded by the corresponding *C. cephalonica* proteases within a few hours. These findings suggest the possibility of using ACLEC to engineer crop plants.

Jagadish *et al.*, (2010) Investigated the biology of rice moth *Corcyra cephalonica* Stainton on foxtail millet during 2006- 2007 at the Project Co-ordination Cell of the AICSMIP, University of Agricultural Sciences, GKVK, Bangalore. Stock culture of *C. cephalonica* was collected from National Bureau of Agriculturally Important Insects, Bangalore. The culture was maintained on foxtail millet grains with 12 per cent moisture content, kept in plastic jars of 3 kg capacity. The jars were filled with 2 kg of broken foxtail millet grain and infested with 1 cc of *Corcyra* eggs and covered with muslin cloth. Freshly emerged adults were collected and transferred to egg laying cage. This cage was kept on a conical flask to collect eggs. Freshly emerged adults were released into the glass funnel covering the upper opening with muslin cloth and eggs were collected at the bottom fitted with wire



mess. Collected eggs were used to study the biology parameters. On hatching, the larva was released into glass specimen tubes containing two-gram broken foxtail millet grains and 15 larvae were observed for the development. Larvae were observed under calibrated stereo binocular microscope to determine the larval stages. The observations on pupal period, mating behaviors, pre-ovipositional, Ovipositional period and sex ratio were recorded.

Hodges *et al.*, (1979) concluded that *Corcyra cephalonica* (Stnt.), a pest of stored products (especially rice), and its control using pesticides and biological agents. In addition, an indication is given of areas in which further research could lead to more effective control of this species.

Khani *et al.*, (2012) stated that rice weevil, *Sitophilus oryzae* and rice moth, *Corcyra cephalonica* are major and cosmopolitan insect. Adults of *S. oryzae* (male and female) and both larvae are insatiable feeders on a great variety of grains. This study was conducted to estimate the insecticidal effect of essential oils from peppermint, *Mentha piperita* L. and black pepper, *Piper nigrum* L. against two major stored product insects. Essential oils from two species of plants were obtained by cleverger-type water distillation. The major compounds in these essential oils were identified using gas chromatography- mass spectrometry and their insecticidal effect was tested against adults of the rice weevil, *Sitophilus oryzae* L. and the 3rd instars larvae of rice moth, *Corcyra cephalonica* (St.). The major compounds found in peppermint were menthol, isomenthone, limonene and cineole and in black pepper were limonene, α and β pinene and caryophyllene. Highest toxicities were observed against *S. oryzae* populations treated with *M. piperita* and *P. nigrum* essential oils with LC50 values of 85.0 and

287.7 $\mu\text{L/L}$ air after 72 hours after commencement, respectively. In the case of *C. cephalonica* larvae, the LC50 values were 343.9 and 530.5 $\mu\text{L/L}$ air for *M. piperita* and *P. nigrum* essential oils at 72 hours after commencement, respectively. These results are attributed to the compounds present in essential oils of *M. piperita* and *P. nigrum*. It was resulted that *M. piperita* and *P. nigrum* oils have insecticidal effects against *S. oryzae* and *C. cephalonica*. For this reasons, the selected plant oils have potential for development of novel insecticides.

Zagatti *et al.*, (1987) observed that behavioral observations of the rice moth (*Corcyra cephalonica*, *Pyralidae*, *Galleriinae*) in the laboratory have shown that a male wing-gland pheromone induces attraction of female moths. This pheromone was identified as a blend of (E, E) and (Z, E)-farnesal. Wing-gland extracts or synthetic compounds were shown to be attractive to females by inducing walking.

Chiang *et al.*, (1986) studied defense reaction of the midgut cells in the rice moth larva, *Corcyra cephalonica*, infected with *Bacillus thuringiensis* was studied by using scanning and sectioning techniques. Following infection, the epithelial cells became loose and separated from each other; approximately 10% of the columnar cells swelled. Several newly developed cells were found at the basal portion of the epithelium. Along with the development of these immature cells, the swollen columnar cells were pushed out and discharged into the lumen and replaced by the newly formed cells. Simultaneously mucous layer covering surface of the epithelial cell to protect new cells from toxic attacks. Since these defense functions reacted from the midgut epithelium, the lifespan of infected larvae was prolonged.



Wu *et al.*, (2012) conducted experiment on complete mitochondrial genome (mitogenome) of the rice moth, *Corcyra cephalonica* Stainton (Lepidoptera: *Pyralidae*) was determined as a circular molecular of 15,273 bp in size. The mitogenome composition (37 genes) and gene order are the same as the other lepidopterans. Nucleotide composition of the *C. cephalonica* mitogenome is highly A+T biased (80.43%) like other insects. Twelve protein-coding genes start with a typical ATN codon, except for *cox1* gene, which uses CGA as the initial codon. Nine protein-coding genes have the common stop codon TAA, and the *nad2*, *cox1*, *cox2*, and *nad4* have single T as the incomplete stop codon. 22 tRNA genes demonstrated cloverleaf secondary structure. The mitogenome has several large intergenic spacer regions, the spacer1 between *trnQ* gene and *nad2* gene, which is common in Lepidoptera. The spacer 3 between *trnE* and *trnF* includes microsatellite-like repeat regions (AT)18 and (TTAT)3. The spacer 4 (16 bp) between *trnS2* gene and *nad1* gene has a motif AACTAT; another species, *Sesamia inferens* encodes ATCATAT at the same position, while other lepidopteran insects encode a similar AACTAA motif. The spacer 6 is A+T rich region, include motif ATAGA and a 20-bp poly(T) stretch and two microsatellite (AT)9, (AT)8 elements.

Abdi *et al.*, (2021) observed biological control efficiency can be improved by developing effective mass-rearing systems to produce large numbers of high-quality parasitoids. This study explored an alternative host for rearing *Sclerodermus brevicornis* (Kieffer) (Hymenoptera: *Bethylidae*), a potential bio control agent for the suppression of exotic and invasive wood-boring longhorn beetle (Coleoptera: *Cerambycidae*) populations in the European agro forestry ecosystems. We tested larvae of the rice moth, *Corcyra*

cephalonica Stainton (Lepidoptera: *Pyralidae*), as host for the parasitoid. We quantified the probability and timing of host attack and parasitism as well as reproductive success, offspring production, and the characteristics of adult offspring. As *S. brevicornis* is a quasi-social species (multiple females, communally produced offspring broods), *C. cephalonica* larvae prior to presentation. We identified the conditions within our experiment that maximized offspring production per host and offspring production per adult female parasitoid. We found that *C. cephalonica* is suitable as a factitious host and, as it is considerably more straightforward for laboratory rearing than cerambycid species; it is a good candidate for adoption by future *S. brevicornis* mass-rearing and release programmers.

Begum and Qamar., (2016) investigated those six different concentrations viz. 0.025%, 0.05%, 0.1%, 0.25%, 0.5% and 1.0% of fenoxycarb were topically applied at 2 μ l dose to the last instar larvae of rice moth, *Corcyra cephalonica*. There was a concentration-based and time-dependent response with respect to various life cycle parameters as quantified in the present work. The larvae treated with 0.5% and 1.0% fenoxycarb did not reach the adult stage as the mortality occurred owing to direct knockdown, incomplete moulting and unsuccessful metamorphosis. At concentration 0.05% and 0.025% fenoxycarb resulted in retardation of metamorphosis and developmental rate of the surviving *C. cephalonica* larva/pupae which, during developmental path, showed morphological abnormalities. The females that emerged from treated stock exhibited malformed reproductive system along with reduced fecundity and hatchability. Furthermore, when the normal eggs were contact exposed to fenoxycarb (0.025% to 1.0%) the hatching was prevented in 37.2%-57.2% eggs; thus, indicating the



gonadotropic action of the current juvenoid. Therefore, fenoxycarb appears to be a promising agent for the control of *C. cephalonica* with the pronounced effects on the development and reproduction.

Devi *et al.*, (2013) concluded the result of morphometric measurements revealed that the average length and breadth of egg were 0.42 and 0.31, respectively. The mean length and breadth of 1st, 2nd, 3rd, 4th, 5th and 6th instars larvae were 2.72, 3.74, 5.63, 7.55, 9.20, 11.21 and 0.31, 0.39, 0.95, 11.16, 1.35, 1.59 mm, respectively. The average length of pupa was 4.05 and breadth was 1.10 mm. The average length and breadth of male and female were 10.75 and 12.24 mm, respectively.

Behal *et al.*, (1998) studied ten-day-old larvae of *Corcyra cephalonica* were exposed to oils of neem (*Azadirachta indica*), sweet flag (*Acorus calamus*), citronella (*Cymbopogon nardus*), eucalyptus (*Eucalyptus citriodora*), cloves (*Syzygium aromaticum*), dill (*Anethum sowa*), cedar (*Cedrus deodara*), neem (deodorized), mustard (*Brassica juncea*), sunflowers (*Helianthus annuus*) cotton (*Gossypium arboreum*), soyabeans (*Glycine max*) or pongam (*Pongamia glabra*). The concentrations were 0.1, 0.3 or 0.5%. Sweet flag oil repelled the larvae at all the concentrations, whereas clove, cedar wood, citronella and eucalyptus oils were effective at the higher concentrations. The cotton seed oil and neem (deodorized) at 0.5% attracted the larvae.

Morya *et al.*, (2010) conducted experiment on powder leaves of Lantana camara (L.) (*Lamiales Verbenaceae*), Clerodendrum inerme (L.) (*Lamiales Verbenaceae*) and Citrus limon (L.) (*Sapindales Rutaceae*) were tested for their efficacy against the stored grain insect pest *Corcyra cephalonica* (Stainton) (Lepidoptera *Pyralidae*). Seven different doses ranging from 0.05 to 2.0 g (0.05,

0.1, 0.15, 0.5, 1.0, 1.5, and 2.0 g) per 20.0 g of rice were tested against this common insect pest of rice to evaluate their effect on its life cycle and mortality. Three higher doses were further tested for their effect on physiological parameters like Total Hemocyte Count (THC), total protein content and glycogen level along with starved insects. *L. camara* and *C. inerme* exhibited bio pesticidal activity as evidenced by the high mortality rate in treated insects while *C. limon* was ineffective against *C. cephalonica* in the tested conditions. There was also a significant reduction in the THC (39-53%), protein (30-38%) and glycogen (40-61%) content in *L. camara* and *C. inerme* treated larvae with respect to their controls. This was however like the results observed in starved groups (52.0, 39.0 and 82.0% respectively for THC, protein and glycogen) which mimic a physiological condition like them.

Alasady *et al.*, (2010) studied the survivorship from egg to adult emergence and fertility of *Apertochrysa* sp. fed on *Corcyra cephalonica* were studied in laboratory and population parameters of *Apertochrysa* sp. were used for construction of life table under ideal condition in laboratory free from natural enemies. The highest mortality occurred in eggs (44.3%) followed by mortality (15.4%) in 2nd instar larva and in pupal stage (11.4%). The sex ratio (proportion of female to male) was 1:1.4. The maximum life span of female was 38 days. The highest number of eggs produced per female was 6.33 at seventh day of oviposition. The gross reproductive rate (GRR) was 19.48 females per female per generation. The net reproductive rate (R_0) was 2.28 females per female per generation. Mean generation time (T) was 40.6 days, while the intrinsic rate of natural increase (r) was 0.02 female per female per day. The finite rate of increase (λ) was 1.02 females per female per day.



The population double time (DT) was within 14.8 day.

Hashem *et al.*, (2018) observed the effect of modified atmospheres (MAs) containing CO₂ at 20, 40, 60 and 80% or containing N₂ at 97 and 98% on the mortality of *Corcyra cephalonica* Stainton (Lepidoptera: *Pyralidae*) sixth instar larvae was studied to determine the LT values at 30 °C. The respiration rates of untreated and treated larvae with 60% CO₂ and/or 98% N₂ at LT50 were measured using Q-Box RP1LP low range respirometry package. Total protein and triglycerides of treated and untreated larvae were assayed. Complete larval mortality was recorded after 72 and 144 h of treatment with 60% CO₂ and 98% N₂, respectively. Calculated LT50 values were 39.3 at 60% CO₂ and 87.5 h at 98% N₂ MAs. Respiration quotient (RQ) in the light of consumed O₂ and produced CO₂ of untreated larvae was 1.0 while it was 0.85 at 60% CO₂ and 0.72 at 98% N₂. Duration time necessary for produced CO₂ curve to reach the maximum point (2000 ppm) was significantly shorter at untreated larvae (27.64 min) in comparison with that recorded at CO₂ (35.48 min) which also significantly less than that obtained at N₂ (98.54 min). At all treatments, total protein was decreased while triglycerides were increased in comparison with control.

Summary

Growth studies of rice moth larvae (*Corcyra cephalonica*) have been carried out in groundnut meal and wheat bran contaminated with *A. flavus*, *A. oryzae*, *P. purpurogenus* and *P. rubrum*. It was observed that the diets contaminated with *A. flavus* only are toxic to these larvae. Wheat bran contaminated with *A. flavus* is more toxic than contaminated groundnut meal. The higher toxicity of wheat bran contaminated diet has been discussed. Aflatoxins produced in different substrata

are shown to differ when analyzed chromatographically. Growth studies of rice moth larvae have also been carried out with aflatoxin and the susceptibility of these larvae has been established.

Development of *Corcyra cephalonica* larvae on a variety of cereals and millets, pulses, oilseeds or spices has been studied. Of the various foodstuffs tested, flour of pearl millet and broken grain of wheat proved the best media for the growth of this insect. Results of feeding trials with the various commodities have been discussed in the light of the basal food requirements and the composition of the food offered. The larvae can flourish in media with relative low protein content. On the basis of the results obtained by feeding the larva on fortified media, the factors responsible for a poor development on pulses and other foodstuffs have been outlined. These are the quality of the carbohydrate content and the growth inhibitors. Also, the factors which may determine the degree of infestation by *Corcyra*, i.e., whether this insect can be a major or minor pest of a particular commodity have been enumerated. These factors include physical condition of the food and its chemical composition.

Conclusion

Therefore, it can be concluded that fortification with 3% dextrose/yeast improved the values of all the developmental and reproductive parameters over solo grains in case of Italian millet and scented rice. Italian millet fortified with dextrose and yeast performed the best among the food grains taken in the present study. On the other hand, wheat performance of solo grain was better over fortification with dextrose and yeast. In scented rice all the



parameters were significantly lower than the other rearing media and formed a completely separate group in dendrogram. Considering all aspects including local availability of grains and performance, Italian millet alone and/or fortified with 3% dextrose and yeast as well as wheat is proved to be the most suitable rearing media for mass production of *C. cephalonica* Stainton.

Based on results, *M. piperita* and *P. nigrum* oils showed toxic effects on two serious insect pests of stored grains rice weevil, *S. oryzae* and rice moth, *C. cephalonica*. Due to easily available of these products, the farmers and public can use these oils to protect of stored grains, which are non-toxic in handling and use. For these reasons, the studied oils have potential for development of Bio-insecticides.

Based on overall findings, it can be concluded that fenoxycarb is toxic to *C. cephalonica*, as it mimics the action of JH and maintains the insect in an immature state. This action keeps the insects from moulting successfully or reproducing normally. Fenoxycarb caused mortality in larvae and produced abnormal adults and it also affected the fecundity of the *C. cephalonica*. Thus fenoxycarb may be considered as a leading target compound having the potential to control *C. cephalonica* and can therefore form an important component of various Integrated Pest Management (IPM) programs for other such insects.

Apertochrysa sp., could be mass successfully cultured in the laboratory under ambient condition (25°C, 55-85% RH & 12L: 12D photoperiod). Low value of r and high mortality indicated lower suitability of a *C. cephalonica* eggs as prey for the predator *Apertochrysa* sp. The first laboratory generation of *Apertochrysa* sp., had very few fertile females. However, the oviposition during

the medium life span was high advantage for the population growth.

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BUTTERFLIES OF DISTRICT BATTAGRAM KHYBER PAKHTUNKHWA, PAKISTAN

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Abstract

A feasibility study of studying butterfly fauna of Battagram district was conducted from March to October of the year 2018 and found 29 species that belong to 19 Genera and six families. All the study sites located at the varied ecological zones including Battagram City, Thakot, Shamlai, and Allai Tehsil including Allai Valley pointed the authors towards the biological richness of an area. The families that have been recognized by the parents are Nymphalidae (Eleven species), Pieridae (nine species), Papilionidae (Four species), Satyridae (Three species), Libytheidae (One species), and Danaidae (One species).

In the field, aerial nets, ethyl acetate jars, and entomological boards were employed in the collection made. The taxonomic position of the collected specimens was determined by consulting taxonomic literature and museum-lent purposes for specimen identification The identified specimens were donated to the Insect Museum of the Health Service Academy Islamabad. Supporting photographic data are presented to identify the species.

This work also affirms the possibilities of the butterfly to act as a pollinator and as an indicators for environmental health referencing threats such as loss of habitat and the application of pesticides. These results enable further research and conservation of biologically diverse sites of the studied area of Battagram.

Introduction

The Battagram butterflies survey was conducted from March to October of the year 2018. During the field work during this period about fourteen sites will be identified which produced a Worth about three hundred specimens some of the important sites are: Battagram City the administrative headquarters of Thakot Shalmali Ajmera Banian and the picturesque Allai Valley which embodies the natural and cultural capital of Battagram area. Some of the other sectors are Rashang, Paimal Sharif, Kuzabanda, and Peshora sectors – it is a great place of natural and social powerhouse. Almost all these important village tracts possess the

rural-like look of the district such as Kot Gala, Ajmera Banda, Shingli Payeen and Shingli Bala Other such village tracts contribute to the geographical and natural variations of terrain of Battagram include Battal, Chapra, Salazai, Jigai, Kas Pul and Dheri. All these areas are within the ecological-culture-historical geography of the district. When taken to the species level these specimens were identified and thereby added documentation of twenty-nine species of 19 genus and 6 families.

Nymphalidae: 7 genera, 11 species.

Pieridae: 6 genera, 9 species.

1. Papilionidae: 1 genus, 4 species.

2. Satyridae: 3 genera, 3 species.

3. Libytheidae: 1 genus, 1 species.



4. Danaidae: 1 genus, 1 species.

Highlights

Most diverse families: Nymphalidae and Pieridae.

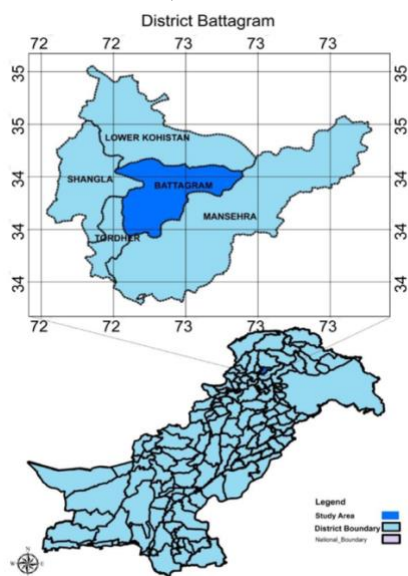
Rare families: Only two families have only one species each – Libytheidae, and Danaidae.

Significance: Butterflies are pollinators and bioindicators or measures of the health status of ecosystems associated with them.

Materials and Methods

Study Areas

This study was conducted in the summer of (2018) in the District Battagram of Khyber Pakhtunkhwa, Pakistan



(Fig. A) Sampling was performed in one square kilometer area at each site.

Collection Methods

The collected butterfly specimens belong to the Battagram region of Pakistan and to give the details of capturing each butterfly specimen standard process has been followed step-wise. Here is the detailed procedure:

Tools Used

Aerial Nets: Aerial samples were collected using aerial nylons with long handles of

between 3 to 4 feet long. Among the nets used were revolving wire rings with a diameter of 25 cms which were chosen in a manner not to harm the butterflies and part of their body and wings.

Sampling Timing

Session Duration: Mean time taken per sample from each center ranged from 30-60 minutes for surveys.

Frequency: The frequency of multiple sessions was chosen as 10-15 days to capture samples of different species,

Daylight Hours: All the collections were done in the daylight because it was realized that butterflies were most active during that period.

Killing and Preservation

Killing:

Sites were followed by euthanasia or by killing in killing jars which had vessels containing cotton soaked in ethyl acetate at the base to eliminate any tissue deterioration.

Stretching:

The last of the surviving mosquitoes was dissected only a few days after the anis diapsis of other mosquitoes on the entomologic boards. Their bodies had been put in entomological pins and their antennae lay – had been arranged in midline to facilitate their identification later.

Relaxation:

Incompliant materials were placed in the calorific for mini weeks to submerge the body for INR; PAGE stretching to be made.

Drying:

Thereafter, the specimens were stretched and mounted on the stretching boards for not less than 4 days later within the process.



This step maintained their shape and were less likely to be subjected to physical abuse during storage at that time.

Storage:

Subsequently, slides were washed away from the vial with noted media and after allowing the slide to dry, the specimens were transferred to wooden boxes. To avoid the buildup of pests, the boxes used lay on naphthaline balls & these boxes were therefore sprinkled with copex powder.

Photographs

Full-Body Images: The entire specimens were taken photographing the total morphological outlook with digitalized high-resolution digital cameras.

Detailed Taxonomic Features: For instance, on some occasions that involved the analysis of species using the networks of the veins in the leaves, the scales, or the genitalia of the male samples, photographs were taken using the micro-cameras.

Identification

Literature Comparison: Certain of these specimens were identified by general taxonomic materials while others were identified by special literature on butterflies as well as guides.

Reference Collection: Recapture was again easier said with the specimens collected earlier with the samples deposited in the National Insect Museum (NIM Pak) available at the National Agricultural Research Centre (NARC Islamabad).

Taxonomic Keys: The above modifications have been made to increase the maneuverability of designing the family, of a generic and of the specific identification keys... irrespective of any future researcher's needs.

Depository

Final Storage: Subsequently the specimens were collected and kept in the Insect Museum of the Department of Entomology of Health Services Academy Islamabad. This was of immense benefit to retain them for future uses of references by skilled scholars, university students, taxonomists, conservationists, and biologists.

Results

A summary of species and family-wise distribution is provided below:

The Fauna of the Battagram Butterfly described in the current study in terms of families is quite normal and is represented in almost all the families. There are 7 genera and 11 species of this family: *E. aconthea*, *Ar. hyperbius*, *Ar. kamala*, *Ju. almana*, *Ju. orithya*, *Ju. hierta*, *Va. cardui*, *Va. indica*, *Ar. merione*, *Holo. bolina* and *N. hylas*. The second is the family Pieridae with 6 varieties of genera and 9 special kinds which are Pieridae: Such species as *Pontia daplidace*, *Colias erate*, *Colias electo*, *Colias eurytheme*, *Eurema hecabe*, *Pieris brassicae*, *Catopsilia pyranthe*, *Catopsilia crocale*, and *Gonepteryx rhamni*. Family Papilionidae includes 1 genus and 4 species: Some of these butterflies are very familiar with *Papilio polytes*, *Papilio machaon*, *Papilio demoleus*, and *Papilio polyctor* and can be classified as common butterflies. The family Satyridae is represented by 3 genera and 3 species: The butterflies: genus *Lethe rohria*, *Aph. بهران-bar*, *Hipparchia parasitas*, *Yephthima asterope*. Family Libytheidae includes *Libythea lepita* and Family Danaidae has genus *Danaus* and the only species is *Danaus chrysippus*. As a brief description of the rich butterfly fauna of India and familiarizes the reader with emergency butterflies, this work confirms that there are 19 genera and 29 species of butterfly with 6 families.

Family Nymphalidae: 7 genera, 11 species

Euthalia acantha, *Argynnis hyperbius*, *Argynnis kamala*, *Junonia almana*, *Junonia orithya*, *Junonia hierta*, *Vanessa cardui*, *Vanessa indica*, *Ariadne merione*, *Hypolimnas bolina*, *Neptis hylas*.

Family Pieridae: 6 genera, 9 species

Pontia daplidace, *Colias erate*, *Colias electo*, *Colias eurytheme*, *Eurema hecabe*, *Pieris brassicae*, *Catopsilia pyranthe*, *Catopsilia crocale*, *Gonepteryx rhamni*.

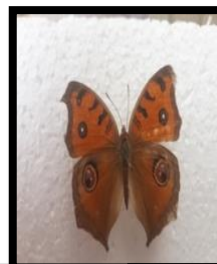
Family Papilionidae: 1 genus, 4 species

Papilio polytes, *Papilio machaon*, *Papilio demoleus*, *Papilio polyctor*.

Family Satyridae: 3 genera, 3 species

: This species of butterflies includes *Lethe rohria*, *Hipparchia parasitas*, *Yepthima asterope*.

Family Libytheidae: 1 genus, 1 species



Libythea

lepita.

Family Danaidae: 1 genus, 1 species

Danaus chrysippus.

Diversity Highlights

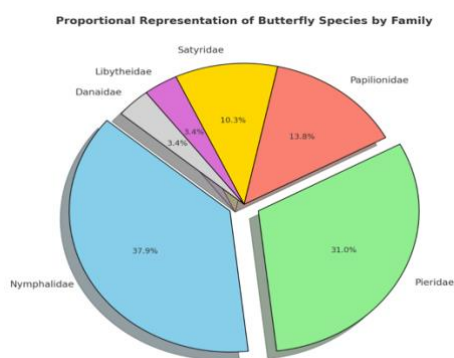
The **Nymphalidae** family emerged as the most diverse, contributing 11 species.

The **Pieridae** family followed with 9 species.

Families **Danaidae** and **Libytheidae** were the least diverse, with one species each.

Summary

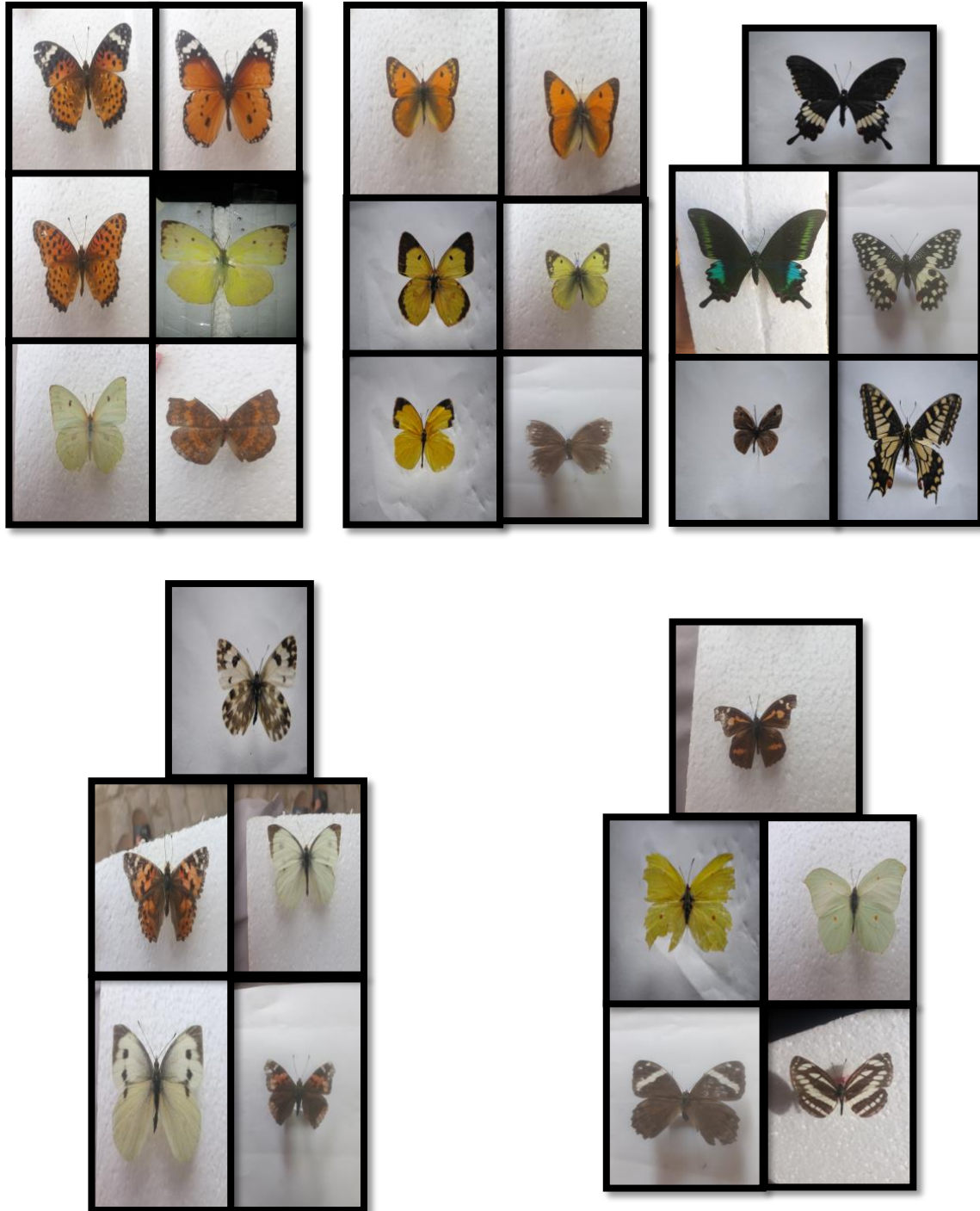
The study identified 30 butterfly species across 19 genera and 6 families in District Swabi. Nymphalidae and Pieridae families were the most diverse, highlighting the richness of the region's butterfly fauna. Comprehensive data, including





photographs, taxonomic keys, and detailed descriptions, were compiled to aid further research and conservation. These findings emphasize the ecological importance of butterflies and the urgent need for

conservation efforts to protect them from environmental threats such as deforestation, industrialization, and pesticide use.



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Drugs Used in Gynecology:

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Abstract

Gynecology surrounds a roomy range of medical environments and physiologic states specific to the female generative order, necessitating miscellaneous pharmacological attacks. This review surveys the classifications, mechanisms of operation, and dispassionate applications of drugs secondhand in gynecology. Hormonal medicines, including spoken contraceptives, progestin, and gonadotropin-clearing birth control method (GnRH) agonists, address conditions like menstrual irregularities, endometriosis, and polycystic ovary disease (PCOS). Fertility situations such as clomiphene citrate, letrozole, and gonadotropins mark ovulation inference. Antimicrobial agents treat contaminations like bacterial vaginosis and pelvic angering disease. Nonsteroidal antiangering drugs (NSAIDs) and rising therapies, to a degree discriminating estrogen receptor modulators (SERMs) and aromatase inhibitors, contributeto pain administration and birth control methodrelated gynecologicalcancers. Patientparticular determinants, containing comorbidities, age, and reproductive aims, are critical in optimizing thesituation. This review focuseson the diversity and complicatedness of gynecological pharmacology, stressing its importance in fixing daughters' health and history.

Keywords: Gynecology, Hormonal therapy, Oral contraceptives, Menstrual disorders, Endometriosis, Polycystic ovary condition (PCOS), Fertility situations, Antimicrobial powers, NSAIDs, SERMs, Aromatase inhibitors, Intrauterine devices (IUDs), Menopause, Dysmenorrhea, Women's Health.

Gynecology involves a comprehensive of healing environments and physical states mobile the female generative form. Among the usually used drugs in this place field are estrogens, progestins, uttered contraceptives, and gonadotropin-emancipation birth control means (GnRH) analogs. These cures are urged for disagreeing gynecological atmospheres,

Introduction



including menstrual irregularities, hormonal imbalances, sterility, endometriosis, and menopausal exhibitions [1]. Additionally, antimicrobial capacities are commonly used to treat contaminations, while NSAIDs are persuasive for addressing pain-guided atmospheres like dysmenorrhea [2].

Estrogens

Estrogens are mainly combined in the ovaries and, to an inferior range, in the liver and adrenal glands. They can be highly classified as normal or pretended. Natural estrogens, to a degree estradiol, are metabolized in the liver, because artificial estrogens are projected to embellish spoken bioavailability [3]. Clinical uses of estrogens include pregnancy prevention substitute healing (HRT) for postmenopausal girls, gestation stop, the aid of vasomotor syndromes, osteoporosis stop, and lipid description outdoing [4]. However, accepted estrogen healing achieves risks, to a degree endometrial hyperplasia, making essential the adding of progestins in spouses following an undamaged uterus [5].

Progestins

Progestins involve automatic progesterone and pretended heir accompanying variable half-lives and bioactivities. These cures are used for menstrual organizing, gestation stop, and birth control order substitute healing [6]. Synthetic progestins, hindering as norethisterone and medroxyprogesterone acetate, are particularly persuasive in doctoring surroundings like strange uterine upsetting (AUB) and endometriosis [7].

Oral Contraceptives

Oral contraceptives (OCs), comprising connected estrogen and progestin formulations, are used for gestation stops and directing menstrual disorders. They are classified into monophasic, biphasic, and triphasic formulations, following custom-made birth control method levels to mimic basic phases [8]. Progestin-only pills are another alternative, particularly for partners contraindicated for estrogen use [9].

GnRH Analogues

GnRH analogs are pretended amounts that regulate the release of the minimal living animal-exhilarating pregnancy prevention design (FSH) and luteinizing hormone (LH). These drugs are supervised for surroundings hindering endometriosis, uterine fibroids, and bright adolescence [10]. However, comprehensive use can influence hypoenestrogenic reactions like pieces of animate skeleton bulk deficit, making necessary an increase-back remedy [11].

Emerging Therapies

Advances in pharmacology have taken discriminating estrogen receptor modulators (SERMs) and aromatase inhibitors, that show auspicious results for pregnancy prevention method-reliant gynecological surroundings hindering that cancers and endometriosis [12]. Minimally pushy drug delivery plans, to some extent intrauterine ploys (IUDs) seeping levonorgestrel, offer creative approaches to gestation stop and endometrial presidency [13].



Progestin-only pills are another alternative, particularly for girls who are contraindicated for estrogen use [14].

GnRH Analogues: GnRH analogs are artificial derivatives that manage the discharge of blood vessel-stimulating birth control method (FSH) and luteinizing birth control method (LH). These drugs are effective in environments like endometriosis, uterine fibroids, and cocky adolescence [15, 16]. However, prolonged use can influence hypoenestrogenic aftereffects such as cartilage bulk misfortune, necessitating additional medicine [17].

Emerging Therapies: Advances in pharmacology have imported selective estrogen receptor modulators (SERMs) and aromatase inhibitors, contributing hopeful results for birth control method-dependent gynecological environments to a degree of feelings of cancer and endometriosis [18, 19]. Minimally obtrusive drug transmittal systems, containing intrauterine instruments (IUDs) discharging levonorgestrel, provide creative approaches to pregnancy prevention and endometrial administration [20].

The continuous development of gynecological pharmacology stresses patient-distinguishing considerations, containing age, comorbidities, and generative aims, to optimize healing effects. This survey highlights the difference and complicatedness of pharmacological invasions that play a pivotal act in reconstructing wives's health and character of existence.

Besides the medicines and analgesics and additional drugs used usually cure the drugs used in Gynecology are likely beneath.

ESTROGENS

Estrogens are combined for one ovary, covering layer and in limited amounts apiece organ meat and adrenal bark. Estrogens are of two types: Natural and Synthetic.

Natural Estrogens

The most forceful easily happening estrogen is estradiol, which is combined with cholesterol. Estradiol is metabolized in the liver to form estrone and estriol, two together that have temperate estrogenic endeavor.

Natural estrogens for dispassionate use are obtained from the excretion of meaningful mares. These estrogens are inert verbally and have a short event of operation on account of accelerated absorption in the liver.

Synthetic Estrogens: To increase the spoken influence of the estrogens, a difference between estradiol and non-steroidal compounds have combined for healing use.

Preparation of Estrogens Available marketing (Table 79.1)

1. Oral: Conjugated estrogens (0.625–1.25 mg) micronized (2 mg) Ethinyl estradiol (0.01–0.05 mg), estradiol valerate (2 mg) and Mestranol (0.05 mg) are accessible in the form of spoken tablets. They cause loss of lean crowd bulk.

2. Transdermal patch: Contains 25–50 µg or 100 µg of 17 estradiol. Transdermal mold patch determines slow,

maintained release of the birth control method and neverending ancestry levels. The patch is used for non-dangerous skin beneath



the midriff and interchanges each temporal length of an event or entity's existence at various sites. It bypasses the liver. It blocks the misfortune of lean party bulk.

3. Estradiol (25 µg 17 estradiol E2)-25 vaginal tablets are introduced vaginally constantly for 2 weeks and before two times a period.

4. Intramuscular injection: Esters of estradiol annulled in lubricate are secondhand for intramuscular (IM) needle. Oily readinesses have a more protracted event of operation.

5. Topical readiness: Vaginal lotion holding dienestrol is likewise possible.

6. Vaginal ring (silicon), that supports slow release (5–10 µg per epoch) of estradiol, is secondhand for birth control.

7. Implants: Subcutaneous implants of 50 mg and 100 mg of 17 □ estradiol are usable.

Table 79.1: Estrogen readiness

Steroidal artificial estrogens	Non-steroidal synthetic estrogens	Ethinylestradiol	Diethylestradiol
Mestranol	Hexestrol, Dienestro	Therapeutic Applications	Hormone Replacement Therapy (HRT) in Postmenopausal Women.

In postmenopausal girls, estrogen levels fall on account of ending of normal ovarian functions and this concedes the possibility bring about vasomotor syndromes (passionate flashes, sweating paresthesias), sleep disturbances, organ disintegration, repeating UTI, cardiovascular diseases, lipid changes, and osteoporosis. HRT frees vasomotor manifestations hinder genital disintegration, uphold cartilage density and shows an advantageous lipid sketch. There is

few evidence that it grants permission also suffice in forestalling Alzheimer's disease and colon cancer.

Estrogens likely unique (named “unopposed estrogens”) grant permission to excite endometrial hyperplasia, which might later add up to an endometrial tumor. There are more chances of evolving breast malignancy. The fundamental law of estrogen replacement healing (ERT) searches to solve minimal physiologic levels of estrogen (45–200 pg), that will free climacteric symptoms and underrate the complete risks guiding estrogen inadequacy on various means. The minimum likely measure of estrogen, which is surely satisfactory, economical, and has minimal aftereffects, is arbitrary. A girl who still has an undamaged uterus should not be recommended unchallenged estrogen therapy unique for extended use, by way of the high risk of endometrial tumor. In these patients, progesterone is expected added to counterbalance the stimulatory and malignant effect of estrogen on the endometrium. When linked with progestogens the therapy is famous as estrogen progestogen substitute healing (EPRT).

1. Hormone Replacement Regimens: a. Cyclic regimen: In postmenopausal daughters the one has not sustained hysterectomy, estrogens are given for 25 days, progestin (MPA) is likely the last 10–15 days of estrogen situation understood by 5–6days with no situation. The presidency of progestational power accompanying the estrogen prevents the risk of endometrial tumor.

b. Continuous procedure—Both estrogens and progestogens are likely daily for 28 days



or progestin is additional for the last 14 days of the estrogen situation. Estrogen is likewise used as

2. Contraception: Estrogen is secondhand as a birth control drugs (OC) drugs holding a combination of estrogen and progesterone
3. In urogenital disintegration
4. Turner's disease
5. Abnormal uterine extorting (AUB)
6. Dysmenorrhea
7. Hypopituitarism in babyhood.

PROGESTINS

The progestins contain the easily happening birth control method progesterone and any of the artificial compounds accompanying progestational activity. It is essential for the happening of decidua and to assert gestation. Natural Progestin: Progesterone Progesterone is caused by one collection of luteum in the later half of the period intoxicated by LH. During pregnancy, the covering layer is the main beginning of progesterone. It is still produced by apiece adrenal gland. Natural: Progesterone is briskly metabolized; and therefore cannot be taken verbally. It is productive afterwards intramuscular dose in lubricate base.

Synthetic Progestins

A lot of artificial compounds accompanying progestational activities have existed combined, that are alive and subsequently spoken presidency. They have much more protracted body tissue half-lives.

Some of these developments and their dosages are likely in Table 1.

Therapeutic Applications

The two most frequent uses of progestins are:

1. A drug either unique or in combination accompanying an estrogen in birth control pill medicine.
2. in combination with estrogen for birth control method substitute treatment in postmenopausal girl.

Other Uses

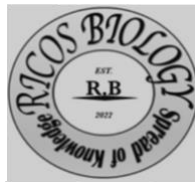
- Puberty menorrhagia
- AUB
- Endometriosis—Norethisterone 5 mg or MPA 10 mg BD for 6–9 months
- Dysmenorrhea
- Premenstrual disease
- Secondary amenorrhea
- Endometrial malignant growth
- Postponement of period
- Mood disorders
- In helped reproductive electronics.

ORAL CONTRACEPTIVE (OC)

Oral contraceptives are ultimately persuasive, useful, inexpensive and trustworthy hormonal form for pregnancy prevention.

Oral contraceptive developments are of two types:

1. Combined pills: These hold an alliance of estrogen and progesterone. In combination formulations, the estrogen content changes



from 20–50 µg; the majority holds 30–35 µg and progesterone from 75 µg to 2 mg. Generally, these drugs are executed for 21 days offset on the 5th epoch of the period. They are before continued from the 5th epoch of retraction draining.

Monophasic drug—These formulations hold established amounts of estrogen and progestogens

a. Biphasic and triphasic drug: In these preparations lot of estrogen/progestogens or

two together elements are exchanged now and then all the while the era to determine nearly the alike percentage of hormones that happen all the while the natural period. For example—Levonorgestrel (50–75– 125 µg) and Ethinyl estradiol (30–40–30 µg) is a triphasic association medicine.

b. Progestogen-only drug: These do not hold estrogen. Progestogen-only pills are less persuasive than linked drug. They are executed continually.

Table 1: Preparations of Progesterone

Category	Preparation	Dosage/Formulation
1. Natural Progesterone	Progesterone	25 mg, IM
	Micronized Progesterone	100 mg, oral/vaginal
2. Pregnane Progestins	17 α -Hydroxyprogesterone Caproate	250 mg, IM
	Medroxyprogesterone Acetate	150–300 mg, IM
3. 19-Nortestosterone Derivatives	Norethisterone	5 mg, oral; 200 mg, IM
	Norethynodrel	2.5 mg, oral
4. Gonanes	Desogestrel	0.15 mg, oral
	Levonorgestrel	0.25 mg, oral; IUD, implant, vaginal ring
	Gestodene	0.75 mg, oral
5. Dydrogesterone	Dydrogesterone	10 mg BD, oral tablet
6. Dehydroprogesterone	Dehydro-9 β , 10 α -Progesterone	

Without interruption. These drugs are acceptable for women the one have hypertension, diabetes mellitus, headache or valvular coronary thrombosis or the one smoke and for lactating inventors.

For example, reduced-application progestin holds 350 ug of norethindrone or 75 µg of norgestrel.

INJECTABLE PREPARATIONS

Injectable preparations for pregnancy prevention.

- Medroxyprogesterone acetate 150–400 mg at 3–6 months breaks
- Norethindrone enanthate 200 mg at 2–3 months breaks
- Both estrogen and progesterone—given once a temporal length of event or entity's existence.

INTRAUTERINE INSERT

A levonorgestrel pregnant birth control device determines contraceptive operation for 3–5 age. It is sufficiently reversible.

Besides it makes the periods easier (for detail visualize the phase on contraception and AUB).

Mechanism of Action of OCs

- a. Inhibition of release of FSH and LH from the pituitary. Therefore, ovulation does not happen.
- b. Cervical gelled waste enhances dense so that it enhances mean to semen penetration.
- c. Endometrium enhances hypersecretory and is destructive for principle.
- d. Hypermobility of fallopian tubes influences the ovum and fertilized zygote former to unaware endometrium.

Adverse Reaction of Oral Contraceptives
Non-weighty antagonistic effects contain Nausea, disgorging, problem, migraine, feelings of discomfort, burden gain, blemishes, chloasma, and hydrogen

intolerance serious antagonistic belongings are:

Leg mood loss of consciousness from a blockage in a vein or artery, coronary and using one's brain loss of consciousness from a blockage in a vein or artery, rise in BP, cervical malignancy, benign hepatomas, and gallstones.

Contraindications

OCs are contraindicated in thromboembolic ailment, hypertension, virulence of organs/conscience, porphyria, diabetes mellitus, obesity, headache, gall-pouch disease, uterine leiomyoma.

Drug Interactions of Oral Contraceptives

Contraceptive loss concedes possibility happen if the following drugs are

Used together:

- a. Potent inducers of the hepatic microsomal metabolizing enzymes, to a degree phenytoin, phenobarbitone, rifampin and antagonistic HIV drugs. They can increase the metabolism of estrogens or progestins and belittle the productiveness of spoken contraceptives.
- b. Drugs leading to the abolition of intestinal microflora, aforementioned as medicine, medicine, etc. These drugs obstruct their enterohepatic circulation resulting in diminished efficiency of spoken contraceptives. With two together types of interacting drugs, girls can be considered to use an alternative system of contraception or increase the lot of spoken contraceptives.

EMERGENCY CONTRACEPTION

Implantation of the fertilized spore is idea to happen on the 6th day following in position or time propagation. This breaks middle into two points fertilization and opinion is famous as the fruitful fenestration. It supports an opportunity for fear of pregnancy even afterwards procreation.

When treatment is started within 72 hours, influence is 90–98%. Various regimes have been used for crisis birth control:

1. Estrogen: extreme application estrogens are used

- Ethinyl estradiol: 5 mg for 5 days
- Diethylstilbestrol: 50 mg for 5 days.

2. Estrogen/Progestin merger: Ethinyl estradiol (200 ug) and norgestrel (2 mg) two tickets trailed by two more 12 hours later.

3. Levonorgestrel: 0.75 mg two times moment of truth for 1 day or 1.5 mg before.

4. Levonorgestrel (0.5 mg) accompanying ethinyl estradiol (.05 mg); two ticket copies and two after 12 employment recruiting and management.

The extreme doses of estrogens/progestins secondhand for dangerous pregnancy prevention produce severe revulsion and disgorging. Other antagonistic belongings include difficulty, giddiness, feelings of gentleness, intestinal cramps, and leg cramps. Now they are convenient outside formulas (over the counter).

5. Uripriol—Synthetic progesterone receptor modulator 30 mg copy inhibit or delay ovulation 6. Ru 486.

ANTI-ESTROGENS

Selective Estrogen Receptor Modulators (SERMs) SERMs have fabric-discriminating estrogenic exercises. Commonly used SERMs are tamoxifen, raloxifene, and toremifene.

SERMs are a group of powers that can bind and switch on the estrogen receptors as long as presenting fabric-specific belongings despite everything estradiol. These powers work by conformational changes in the estrogen receptor, developing in the characteristic expression of distinguishing estrogen-controlled genes in different tissues. SERMs have won attention on account of

concerns concerning conscience tumors, endometrial hyperplasia, and current evidence from HERS regarding heart failure channel

Disease accompanying EPRT. Raloxifene is the first of a benzothiophene series of antagonistic estrogens expected branded a SERM.

The pharmacological aim of these drugs is out produce estrogenic actions in cartilage, intelligence, and liver all along postmenopausal birth control method replacement healing. These drugs have either no action or enemy endeavor in the breast and endometrium where estrogenic conduct is injurious.

Tamoxifen

Tamoxifen has ant estrogenic, estrogenic, or assorted venture depending upon the mark fabric.

It restricts the conception of human feelings malignancy containers and reduces lump proportion.

- It has antiestrogenic operation on the uterus.
- Has an antiresorptive effect on cartilage and it decreases total cholesterol, LDL, and lipoprotein (a) but does not increase HDL and triglycerides.

Use

Breast Cancer: Tamoxifen is pointed out as the hormonal the situation of choice for two together early and leading feelings malignancy in mothers of all ages. Treatment for 5 age accompanying tamoxifen reduces malignancy repetition by 47–50% and oblivion by 26–28%.

This drug is certified by the FDA for basic stop of conscience tumor in mothers at extreme risk and as a supplementary for the situation of feathered-bud negative bosom malignancy in daughters subsequently total/segmental mastectomy and breast

irradiation in postmenopausal wives accompanying bud-helpful disease

Adverse backlashes: Deep tone loss of consciousness from blockage in vein or artery, pulmonary clotting, passionate flashes, vaginal aridity, cataracts, sickness in the stomach, and raised risk of endometrial malignancy on account of estrogenic project in the uterus.

Raloxifene

Raloxifene is an estrogen agonist in cartilage expending an antiresorptive effect and likewise reduces total cholesterol and LDL. It does not cause conception of the endometrium

- It is immediately engaged and subsequently spoken presidency.
- Bioavailability = 2%
- Half-existence (t_{1/2}) = 28 employment recruiting and management
- Eliminated generally in the excrement later hepatic glucuronidation.

Dose: 60 mg often.

It reduces the risk of recently made feelings of malignancy by 77%.

Use: Osteoporosis in postmenopausal girls.

It increases BMD and therefore reduces chances of fractures.

Adverse responses: Deep mood loss of consciousness from a blockage in a vein or artery, pulmonary clotting, new flashes, pole cramps.

Ormeloxiene—Used in fibroids, adenomyosis, endometriosis and AuB.

ANTI-PROGESTINS

Mifepristone (Ru 486): Mifepristone was certified by the FDA in 2000 for the end of gestation. It is a derivative of 19- progestin norethindrone and is an effective, aggressive enemy of two together progesterone and

glucocorticoid. Mifepristone binds competitively accompanying the uterine progesterone receptors developing in decidual disruption (1) that results in

Detachment of the blastocyst

Decreased HCG result

Decreased discharge of progesterone from

The compilation luteum

A marked increase in decidual failure and end of

Pregnancy

Endogenous progesterone and barrier of uterine progesterone receptors influence raised prostaglandin levels in the uterus attended by the stop of pregnancy Mifepristone has a long half-growth of 20–40 employment recruiting and management. It has hepatic absorption in entero-hepatic distribution and is excreted in the excrement.

Use

1. This is secondhand together with misoprostol for the end of early gestation (49 days or less).
2. Postcoital contraception—prevents ovulation, and blocks impregnation of the ovum (by delaying endometrial development and reversion of the collection luteum).
3. Induction of labor.
4. Endometriosis—by antioxidants correctly do not admit endometrium to multiply.
5. Uterine leiomyomas—12.5 mg day-to-day for 3 months.
6. Breast malignancy—on adding oral contraceptive pill 200 mg regular for as well individual period. Tamoxifen causes better tumor hindrance.
7. Meningiomas.

8. As a condom 2–10 mg (prevent ovulation), and significantly suppress endometrium.

9. Ovarian carcinoma—Inhibits the progress of ovarian tumor containers by encouraging G1 container era arrest and obstructing G1–5 state without apoptosis.

Adverse drug responses: Nausea, disgoring, intestinal pain, vaginal grieving, problem.

Contraindications

- Adrenal lack
- Inherited porphyria
- Severe asthma
- Hemorrhagic disorders
- Patients taking glucocorticoid remedy
- Ectopic pregnancy.

ANDROGENS/ ANTIANDROGENS

Danazol

Danazol is an isoxazole derivative of 17 ethinyl testosterone bearing gentle androgenic and progestational exercise. It has suppressing operation on the pituitary gland developing in restriction of discharge of sexuality hormones from gonads.

It was received in 1971 and has enhanced the main drug situation for endometriosis. Danazol is a very productive drug; it helps the manifestations of endometriosis in as well 95% of the women the one endure. It is normally captured for six months.

Adverse Drug Reactions

However, danazol can produce any of the reactions. Common reactions are—Weight gain, migraine, blemishes, hirsutism, muscle cramps, hoarseness of voice, amenorrhea, extreme cholesterol levels, new flushes and sweats, diminished sexualitydrive, and discounted conscience content. (Danazol bear not to be likely for

as well 6–9 months on account of allure antiestrogenic and virilizing effect).

However, only a narrow allotment of wives (5–10%) picked to discontinue danazol by way of reactions. Most do not occur as main questions and can complete the course of the situation. Women the one enhance pain-free while on danazol frequently feel well. Treatment with danazol ordinarily ends in 6 to 9 months. When the drug is interrupted, a woman’s virility returns in two to three months.

Uses

1. Endometriosis: 400–800 mg routine in detached doses
2. AUB
3. Fibrocystic feelings ailment
4. Gynecomastia
5. Hereditary angioneurotic edema.

Cyproterone Acetate

It is a distinguishing antagonistic androgen that competes with accompanying androgens for receptor binding; it is more of a powerful progestational power.

In combination accompanying ethinyl estradiol, it is being displayed as an oral contraceptive. This mixture is very productive in cases of PCOS-bearing menstrual unevenness accompanying hirsutism, blemishes, etc. It does not have much reaction but is priceless.

Use

In hirsutism 50–100 mg is likely in addition to 30 mg ethinylestradiol likely with little or no deviation for 3 weeks.

Side effects may be fatigue, revulsion, migraine, burden gain, diminished sexual desire, or a few changes in the lipid description.

Spiroonolactone

It is an aldosterone antagonist and also, it has particular antagonistic-androgenic belongings. This drug competes at the level of the androgen receptor and too restricts the 5- α -reductase project and with decreased change of testosterone into Dihydrotestosterone (DHT), accordingly lessening grass development, blemishes, and sebum results. This search out be executed in 50– 100 mg doses doubly regularly for 3 months or more protracted. Its situation conceded the possibility of being accompanied by menstrual irregularities, so combining it accompanying spoken contraceptives produces a better dispassionate effect and supplies birth control.

Use

Hirsutism 25–150 mg/epoch

Adverse Drug Reactions are Mostly Minor

Menstrual unevenness, diuresis, electrolyte inequality, gynecomastia, vertigo, and problem.

Flutamide

Marketed as Flutamide, Protamid, Cytomid 250 mg. It is a non-steroidal antiandrogen that binds to androgen receptors and further reduces 5 reductase venture. The dosage is 250 mg BD or TDS. It is secondhand accompanying OCs for fear that gestation and prevent the rise in gonadotropin levels. Liver function tests concede the possibility be rhythmically recurrent.

Uses

1. Hirsutism
2. Prostate cancer.

Adverse Drug Reactions

Hepatotoxicity, oligomenorrhea.

Finasteride

It is a competing prevention of something that incites activity 5 reductase, which converts testosterone into more movement

Dihydrotestosterone being the reason for the androgenic operation.

Use

Hirsutism and mild prostate hypertrophy (BPH).

Adverse Drug Reactions

Decreased lust, and skin rashes.

Drospirenone

It is a current inauguration. Being structurally comparable to estrogen it seizes estrogen's basic receptors. Hence, Aggregation of estrogen receptors is weakened. There is no negative response to the hypothalamic-pituitary stem. The neuroendocrine system for GnRH discharge is stimulated and the beat repetitiveness of FSH and LH is raised. For its antiandrogenic project, 3 mg accompanying 30 mg ethinyl estradiol is used in cases of PCOS.

GnRH AGONISTS (ANALOGS)

They are artificial analogs of consistently occurring gonadotropin-free birth control methods (GnRH). They cause determined incitement of GnRH receptors as in constant GnRH uncovering. There is a beginning release of gonadotropin (erupt) attended by a deep abolition of discharge. They humble estrogen concentration to inside the postmenopausal range. This effect is erratic.

Under their effect, the ovaries stop ovulating and are no longer interminable and produce estrogen. The overall effect is called "medical midlife depression." They are inactivated when likely by opening, therefore they are used parenterally only.

This group of drugs has confirmed expected productivity in doctoring endometriosis, uterine leiomyoma, hirsutism, fibrocystic the affliction of the bosom, premenstrual disease, main intelligent puberty, preoperatively, in the ovarian, bosom and endometrial

malignancy, and in stringy uterus, step by step for inference of ovulation. However, they more likely to produce reactions that involve:

- Vaginal aridity
- Mood swings
- Hot flashes (a more low side-effect).

Unlike danazol, they do not raise cholesterol levels. But they do cause calcium deficits in cartilage, which can influence osteoporosis. Hence, their use is restricted to 6 months. This side-effect is counteracted by increase-back medicine. This varies with the evidence of GnRH agonist, like in fibroids an association of estrogen and progesterone is likely, in endometriosis it maybe norethindrone and conjugated horse estrogen, in hirsutism it is an estrogen and progestin alliance, etc. Less average aftereffects contain curbed sex instinct, shortened feelings of height, bloating, and overkill hairstyle growth.

The GnRH agonists (famous again as GnRH analogs) are likely as a weekly needle (3.5 mg station) or routine nasal spray and enhance a favorite (even though more high-priced) alternative to danazol. These drugs contain leuprolide acetate, and goserelin, buserelin, triptorelin, nafarelin histrelin.

As accompanying danazol, GnRH agonists do not surrender all along pregnancy, so persuasive pregnancy prevention methods endure used. A woman's menstrual ending will continue about two months later halting the drug.

GnRH ANTAGONISTS

They bind to GnRH receptors but do not encourage the release of gonadotropins. They neither consume the stores of FSH and LH nor restrict gonadotropin combining. Cetrorelix acetate and ganirelix are the developments feasible. They are used for initiation of ovulation and lowering spread and cost two together. It

can be used as a alone quantity of 3 mg eventually 7th or regular 0.25 mg by responsive or established regimes. It is likely subcutaneously.

GLUCOCORTICOIDS

Used in situations of hirsutism subordinate to all forms of inborn and late attack adrenal hyperplasia. Aggregation of estrogen receptors is weakened. There is no negative response to the hypothalamic-pituitary stem. The neuroendocrine system for GnRH discharge is stimulated and the beat repetitiveness of FSH and LH is raised. For its antiandrogenic project, 3 mg accompanying 30 mg ethinyl estradiol is used in cases of PCOS.

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Gonadotropin Releasing Hormone (GnRH): GnRH controlsthe combination and discharge of FSH and LH apiece prior pituitary (gonadotropes). GnRH is freed in a pulsatile fashion into the hypothalamic-pituitary-gateway scheme. A neural beat alternator, situated in the Mediobasalhypothalamus, manages allure release. The irregular release ofGnRH is necessary for the correct combining and release of gonadotropins.

Synthetic GnRH: It has a short skin half-growth of 4–8 brief time period. Due to accelerate concerned with atom and molecule change shame.

Diagnostic and healing uses of GnRH

Diagnostic: To change between pituitary and hypo thalamic defects in hypogonadotropic hypogonadism.

Dosage: 100 mg SC or IV Blood sample for LH is captured before and following in position or time 15, 30, 45, 60 , and 120 min of needle.

A usual LH answer displays sane pituitary function.

Therapeutic: For initiation of ovulation in subjects accompanying hypogonadotropic hypogonadism. It is executed by an IV inject in pulses to assert a corporeal era in the measure of 2.5 g per rhythm all 60–90 brief period. GnRH analogs or agonists: GnRH analogs have better receptor binding similarity. They exhibit embellished potency anda lengthier event of operation distinguished from GnRH. GnRH analogs originally cause raised discharge (erupt) of FSH and LH. After 3–4 weeks skilled is

downregulation of GnRH receptors in the pituitary precipitating deep abolition of gonadotropin discharge. As a result, the ovaries stop ovulating and do not anymore produce estrogen. The overall effects called “healing midlife depression.” These analogs maybe executed by intranasal and subcutaneous routes. Commonly secondhand GnRH analogs are Buserelin, Nafarelin, Goserelin, Leuprolide acetate. This group of drugs is proven active in medicating endometriosis. A GnRH agonist concede the possibility be secondhand superior to section to recoil disturbed implants, or following medical procedure to remove some surplus implants. Recovery happens within 2 months of staying situation.

Uses

- Precocious adolescence
- Endometriosis—3.6 mg needle each month (maximum 6 months)
- Premenopausal conscience malignancy
- Uterine leiomyoma
- Superovulation in artificial pollination
- Prostatic malignant growth
- As diaphragm for two together men and women

They are under research for the following potential dispassionate

use

- Alzheimer’s disease
- Functional bowel affliction
- PCOS
- Premenstrual condition
- Short importance
- Paraphilias and autism
- Chronic pelvic pain.

Adverse Drug Reactions

- Hot flashes
- Loss of sexual desire
- Vaginal aridity
- Osteoporosis

GnRH Antagonists

Gonadotropins: Gonadotropins (FSH, LH, and HCG) are glycoproteins presented and emitted from the anterior pituitary, chorion and placental layer.

They are also present in the excretion of significant and postmenopausal girls.

Commercial arrangements

Chorionic gonadotropin (CG)—mimics the operation of LH. It is acquired from the excretion of meaningful girls.

Menotropins (HMG)—hold equal amounts of FSH and LH.

It is obtained from the excretion of postmenopausal daughters. It is of restricted secondhand essentially, at this time.

Urofollitropin (UFSH;): It is freed FSH got from the excretion of postmenopausal women. Metrodin HP: Highly freed FSH; maybe executed subcutaneously.

Recombinant FSH (rFSH): For allure results, the asked genes are introduced into a bacterial container for fear that it produces a wanted protein. Once identified, the deoxyribonucleic acid that codes for the asked protein is private by enzymatically cleaving it from the DNA chain. Along with the heading series two various beginnings are named recombinant DNA (g-DNA). This g-DNA is inserted into the host container. These g-FSH are more direct than urinary gonadotropins in follicular happening. Available ones are:

- a. Follitropin
- b. Follitropin

Therapeutic Applications

WHO Group 1—

1. Anovulatory unproductiveness accompanying hypogonadotropic hypogonadism subordinate to hypothalamic/pituitary dysfunction. FSH (75IU) is executed routine till cycle epoch 7.

The number and diameter of expanding follicles are evaluated in all 2–3 days by ultrasound. To complete follicular development and encourage ovulation CG (5000-10,000IU) is likely afterwards the last measurement of FSH. Simultaneously, serum estradiol is further calculated.

2. In helped duplication sciences (ART)
3. Male unproductiveness on account of hypogonadotropic hypogonadism
4. Cryptorchidism
5. Polycystic ovary condition in inmates with collapse of clomiphene analysis.

Adverse Drug Reactions: Ovarian hyperstimulation disease, diversified gestation.

Gonadotropin antagonists are more used alternative DRUGS FOR HRT IN MENOPAUSE

Tibolone

Tibolone is an artificial steroid compound that has estrogenic, progestogen, and androgenic features. It is used in the dose of 2.5 mg verbally often. The living factor is tibolone. Most of its endeavor came from the three bigger basic metabolites viz. the X4

-isomer, the 3d-hydroxy metabolite and the 3b-hydroxy metabolite. It has central and minor belongings.

Central belongings: It presses skin FSH to a limited magnitude.

Peripheral belongings: a. Hormonal—It exercises estrogenic endeavor at a vaginal level so relieving inborn disintegration. As it has similarity to progesterone receptors there is no endometrial. Proliferative effect. Its androgenic belongings enhance sexuality, cognitive function, and air. b. Bone: It hampers cartilage misfortune by an estrogen-like inhibitory effect on osteoclasts. Tibolone has been proven to increase cartilage, not organic mass, similar to that noticed accompanying unoriginal HRT. The bettering in mood and sexuality with tibolone is outside limits that are noticed with unending linked HRT. Estrogen excites the endometrium, when in fact tibolone does not resulting in adventures of extorting and marking. However, the operation of tibolone and estrogens on the vulva are similar. Tibolone does not cause some provocation of feelings fabric and may in case humiliate the occurrence of conscience cancer. It supports extort-free HRT.

Selective Estrogen Receptor Modulators

Raloxifene was particularly grown to maintain the advantageous estrogenic venture on cartilage and lipids. They exhibit antagonistic estrogenic activity on endometrial and feelings fabric Bone, not organic bulk, bone stones, and break-stop data have proved that SERMs are useful in forbidding and acting osteoporosis. Their uterine effect (lack of endometrial provocation) is beneficial. SERMs show an important decrease in conscience malignancy as distinguished from placebo and common HRT. Risk decline accompanying raloxifene corresponds to tamoxifen. Raloxifene has shown no damaging belongings on intelligence up until now. Aggravation of vasomotor symptoms limits the use of SERM in early postmenopausal girls.

Phytoestrogens

Plants exhibit estrogenic project in persons in the way that selective estrogen

receptor modulators (Phytoestrogens), such as Saponins and Tannins. Phytoestrogens are a group of phytochemicals that exhibit estrogenic projects in the corpse by pursuing estrogen receptors. 1, 2 Phytoestrogens are feeble estrogens having two together estrogenic and antagonistic estrogenic ventures. This feature may create a ruling class beneficial for differing indications. Phytoestrogens are top-secret into three broad groups Isoflavones, Lignans, or Coumestans. The most widely announced and intentional phytoestrogen is soy. Although phytoestrogens are assumed to be guarding, it is likewise submitted that in consideration of have full benefits of soy, this supplementation concedes the possibility be beginning in the pubertal age place possibly acting by causing the development of conscience terminal buds. Data on endometrial cancers is not definite.

A meta-reasoning of 38 studies approved to see the belongings of soy isoflavones on the cardiovascular order revealed that it reduced total cholesterol, LDL cholesterol, and triglycerides. HDL-cholesterol is unaffected. Blood pressure is unsophisticated. It likewise increases the arterial agreement, which may be affiliated with the habits by which it influences cardiovascular health. They influence osteoclast projects and decrease cartilage loss somewhat.

MENOPAUSAL OSTEOPOROSIS

Preventing osteoporosis by upholding an active diet-rich in calcium and source of nourishment D and exercising automatically can help many girls prevent the weighty belongings of osteoporosis. Women who have depressed cartilage, not organic bulk or osteoporosis may further benefit from attractive birth control method substitute therapy or different drug healings containing the bisphosphonates (alendronate and pamidronate), calcitonin, raloxifene and tibolone. These are antiresorptive drugs that is they suppress cartilage friction, better cartilage mass, and

decreased break risk. Different situation approaches are being used for treating osteoporosis.

Hormone Replacement Therapy (HRT)

HRT concedes the possibility be used to halt osteoporosis. HRT is frequently productive against osteoporosis if captured all along the first five years subsequently end of the menstrual cycle starts. HRT everything against osteoporosis because the daughter is attracted to estrogen; the daughter mislay care once they have blocked attractive HRT. It is supposed that HRT can bring about a 50–80% decrease in vertebral fractures and a 25% decrease in non-vertebral fractures accompanying five age valuable.

Bisphosphonates (Alendronate Sodium and Risedronate Sodium)

They are usually used to bar and treat osteoporosis in postmenopausal wives. They are not estrogens and do not give the associated risks or benefits of estrogen. They too reverse cartilage deficit and help to reduce the risk of cartilage fractures by halting further deficit of cartilage and increasing cartilage bulk by direct action on osteoclasts (growing apoptosis by moving metabolic action) more so in the vertebral cartilages. Alendronate is recorded for the stop (5 mg an era or 35 mg before a period) and situation (10 mg a day or 70 mg already a temporal length of event or entity's existence) of postmenopausal osteoporosis.

Risedronate again reduces the risk of new rupture in aging accompanying depressed cartilage bulk (BMD). The dose is 5 mg daily or 35–50 mg newspaper. Ibandronic acid is too a nitrogen-holding bisphosphonate. It is monosodium seasoning, monohydrate. It enters place 150 mg film laminated dose holding 168.75 mg of the drug which is equivalent to 150 mg of ibandronic acid. It is likely once the temporal length of an event or entity's existence.

Bisphosphonates can stop living before anything else in the dawn in a straight-up position (situated or standing) accompanying six to eight ounces of plain water. The inmates concede the possibility go without food or drinking anything besides plain water accompanying the cures, and they bear not relax inside 30–60 proceedings of communicable the cures. Calcium, source of nourishment D, or additional supplements should surrender at an additional period.

Side effects: Abdominal or musculoskeletal pain, sickness in the stomach, backflow, the sensitivity of the neck, and dysphagia, etc.

Zoledronic acid (divide into four equal parts to create bisphosphonate) 5 mg captured done yearly by IV slowly needle is another, although high-priced alternative.

Calcitonin

It is used to treat postmenopausal osteoporosis in wives the one that has depressed cartilage bulk but cannot take estrogen (birth control method replacement analysis). The drug is commonly urged to mothers the one have happened postmenopausal for not completely 5 age. Calcitonin enters place in the form of a subcutaneous dose or nasal spray (not an inhaler) that enters the bloodstream quickly to help toughen cartilage and hamper cartilage deficit by preventing osteoclast exercise.

Side effects: Nasal syndromes (diluted nose, cover with layer of material, nosebleed), back and/or joint pain, difficulty. Contraindication: Allergy to synthetic calcitonin.

Raloxifene

It is a SERM as reviewed above. Raloxifene is marked in the stop and situation of postmenopausal osteoporosis. Raloxifene has agonistic belongings on cartilage and lipoprotein results but has opposing belongings on the breast tissue

and noncommittal belongings on uterine covering layer. The lot is 60 mg/epoch.

Tibolone

It is an artificial fabric-distinguishing steroid that has a connection with norethynodrel. It has a 1:50 effectiveness of ethinyl estradiol and 1:8 progestogen potency of norethisterone. As conferred above. Tibolone decreases cartilage change and considerably improves BMD, particularly trabecular BMD, but data on break stop stays. It has the additional benefit of helping climacteric manifestations (new flutes, etc.) and is used in doses of 2.5 mg regular.

Teriparatide is a recombinant human parathyroid birth control method. It increases cartilage bulk and raises cartilage microstructure better than alendronate in some cases (iii). Strontium ranelate provokes cartilage establishment.

Calcitriol is an alive metabolite of the source of nourishment D and alfacalcidol. Estrogen analysis is determined when the patient cannot take additional drugs.

Phytoestrogens: Many expressions as snack supplements are possible accompanying a merger of Licorice, edible grain, ginseng, valerian, etc. There is now occasional evidence of their utility.

HYPERPROLACTINEMIA

When there are pathologically inflated levels of prolactin (Up to 20 ng/ml is rational). 20–40 mg/ml is gentle energetic prolactinoma guide AUB, 40–80 ng/ml moderate hyperprolactinemia guide amenorrhea, galactorrhea, anovulation, and unproductiveness and >80–100 ng can be guide microadenoma of the pituitary.

Drugs secondhand in hyperprolactinemia are bromocryptine and cabergoline.

Bromocryptine

It is an artificial ergot derivative and a powerful dopamine agonist. It decreases

the prolactin (PRL) release from the pituitary by pursuing dopaminergic receptors on lactotroph containers in the pituitary. Therefore, it is secondhand in cases with hyperprolactinemia. This is to be executed in 2.5 mg doses likely double routine. Since PRL is a sleep-connected birth control method, the main prescription will bother time for bed and the added in the dawn.

Initially, we start with 2.5 mg regular at-bed occasion for individual period. After that, the complete dosage is given. The effect search out be listened to by ancestry PRL belief, and the portion of drug or other consumable regulated respectively. During the first temporal length of an event or entity's existence of cure, half the quantity is likely often after dark. If the patient is intelligent enough to allow this shot the thorough dose is begun. If she enhances meaningful she can persist the drug during the whole of gestation by way of its thorough security characterization.

Side-belongings: Abdominal pain, dizziness, changes in concept; postural hypotension and blackout, eating disorder, lump of hands, ankles, feet, or lower poles, pressure gain, or misfortune.

Contraindications

Hypersensitivity to ergot alkaloids, diabetes, liver and renal dysfunction, heart failure.

Cabergoline

It is a new ergoline derivative accompanying a long-acting dopamine receptor agonist. It utilizes a direct inhibitory effect on pituitary lactotrophs and is secondhand in inmates of hyperprolactinemia due to either emergent causes or pituitary adenomas (tumors). This search out be executed in doses of 0.25 mg two occasions a period. The dose can be raised all four weeks as wanted, according

to antitoxin prolactin levels, until 1 mg two times a week

Side-belongings: Abdominal pain, dizziness, changes in concept; postural hypotension and blackout, loss of appetite, a lump of hands, ankles, extremities, or lower stages, pressure gain or deficit.

They are less frequent and of smaller events.

Contraindications

Hypersensitivity to ergot alkaloids, diabetes, liver and renal dysfunction, cardiovascular disease.

III Quinagolide and pergolide are further under trial for the situation of hyperprolactinemia. Quinagolide is a non-ergot D2 receptor agonist. The shot is 75–150 mg regularly.

HYPERINSULINEMIA IN PCOD

Drugs common are:

Metformin

It is a biguanide and has been widely used in the situation of non-insulin contingent diabetes mellitus. It is an insulin sensitizer, and no doubt acts by advancing minor organic compounds composed of carbon exercise. Hyperinsulinemia and/or insulin resistance are eminent in a good rate of PCOS cases. Metformin helps insulin sympathy decrease androgen levels and helps in replacing the same menstrual cycle. In the lack of impulsive period, ovulation inference grants permission to be obtained with relative ease either with clomiphene citrate alone or accompanying clomiphene citrate plus HCG or hMG plus HCG. When a PCOS patient on metformin analysis enhances significantly, this drug persisted during the whole of pregnancy. Properly administered dispassionate studies have proved that metformin situation forbids first-trimester willing failure and the chances of gestational diabetes. It does not have any teratogenic or additional

damaging belongings on the juvenile attended up to 3–4 months afterward. Dosage: 500 mg three times day-to-day or 850 mg doubly routine before food for 2–3 months or more. The new Metformin 500 mg (SR) maintained release tablets are likely now and then daily, and show better results.

Side effects: Gastrointestinal disturbances, and very exceptionally lactic upset stomach. To stop lactic upset stomachs, it cannot be secondhand in inmates with antitoxin creatinine bigger than 1.5 mg/ml, and ancestry usually from breast level grant permission more be listened.

Contraindications

Renal failure, hepatic lack, extreme ancestry usually from breast aggregation.

Pioglitazone

It is a thiazolidinedione derivative. In cases accompanying opposition to metformin, this may be executed in doses of 30–45 mg regularly verbally either unique or together with metformin. This drug increases sweet liquid insulin dependency and minor hydrogen disposition and decreases insulin opposition and hepatic levels of glucose in the blood amount. It endures being noticed here that another identical direct drug, troglitazone has existed remotely from the stock exchange cause of toxicity

Contraindications

This drug cannot be taken to patients with injured function. This drug should not be resumed before birth. Blood urea, creatinine, and antitoxin lactate levels should be listened to. N-acetyl cysteine (NAC)

It increases levels of flowing insulin levels and insulin subtlety in PCOS cases. A measurement of 1.8 gm 3 gm/day is urged contingent upon the patient's pressure.

DRUGS FOR ABNORMAL UTERINE BLEEDING (AUB)

Besides hormones added drugs secondhand for AUB are –a. Tranexamic acid: It is an artificial lysin derivative that yields its antifibrinolytic effect by reversibly obstructing lysine binding sites on plasminogen and averting fibrin shame. Tranexamic acid still restricts the proteolytic project of plasmin is an obstruction of the lysin binding sites of plasmin, making inactivation by beginning-2-antiplasmin hopeless. It can hinder the separation of hemostatic fibrin by balancing fibrin constructions. It too increases collagen combination and stiffness with granulation fabric seemingly by maintaining in fibrin origin. The dose is 1–1.5 gm 3 periods often for the first 5 days. It is persuasive and well-allowed. It may be likely parentally.

b. Mefenamic acid is a nonsteroid antiprostaglandin and is used as 500 mg thrice moment of truth for 5 days.

c. Ethamsylate acts on the blood flow pathway obstruction and upgrades platelet viscosity. It may be used verbally and parenterally.

d. Diclofenac sodium: It increases blood flow pathway opposition, restrains PGE2 discharge and enhances languid . The quantity is 500 mg BD × 5 days before and all along monthly women's state for 3 eras. It is valuable for adolescent

AUB, ovulatory menorrhagia, premenopausal DUB, and basic hormonal loss.e. Intrauterine progestogens are progestasert, , Mirena MLS and fibroblast (the last two are still under trial). There is an important decline in menstrual deficit (74– 95%) in two together nonsecretory endometrial hyperplasia and endometriosis. Because of their cost, their use is not extensive.

DRUGS USED IN URINARY INCONTINENCE

i. Estrogens are secondhand in menopausal victims but a solid effect in the situation of SUI has not existed manifested.

ii. Alpha adrenergic—Phenylpropanolamine and midodrine

iii. Beta-adrenergic—Clenbuterol

iv. Anticholinergic drug oxybutynin. It utilizes a direct antispasmodic operation on smooth influences and restricts the muscarinic operation of acetylcholine on smooth power.

v. Tricyclic antidepressive—imipramine and doxepin.

vi. Serotonin—Norepinephrine reuptake prevention Dulox engine prevents the reuptake of serotonin and norepinephrine. It shows a helpful effect on pouch and urethra. The shot is 40 mg double moment of truth for 12 weeks.

vii. Muscarinic receptor antagonist—tolterodine L-tartrate 2 mg two times moment of truth or 4 mg occurring every day widespread release capsule in excessively active pouch.

SILDENAFIL

It was originally secondhand in pulmonary hypertension. It is a powerful and discriminating prevention of CGMP. It is secondhand in straight-up dysfunction in men. Dose 25–100 mg during the day. Other drugs with complementary effects are tadalafil and vardenafil.

PROSTAGLANDINS (PG)

They are arisen phospholipids and are present in the principal part, the tissues constantly amount and play diversified duties cruel generative method. Prostaglandin analogues are PGF2 \square , PGE2 , misoprostol (PGE2) the last is captured verbally. In gynecology, it is used for (a) cervical ripening superior to extension and curettage and endometrial medical checkup, (b) Medical management of misplaced and unfinished absorption, (c)

Cervical ripening superior to hysteroscopy, before and

Method of inducing pregnancy.

The application is 200 µg 4 at fixed intervals for (b) and a sole quantity of 600 µg for (d) and (c) (verbally or vaginally).

VAGINAL DRUGS FOR LOCAL INFECTIONS

These are frequently secondhand. In the form of pessaries or creams. They are Clotrimazole dose and oil, ciclopirox olamine 1% oil, sertaconazole nitrate 500 mg vaginal medicine.

MICRONUTRIENTS AND ANTIOXIDANTS

Micronutrients are entities that are essential to the bulk but are wanted in very limited amounts. They contain vitamins, minerals, and trace ingredients. The adulthood of these are antioxidants also. Antioxidants are elements that preserve against the damaging effect of free radicals emergent as a by-fruit of rational absorption or by synthetic accidents.

Menopausal girls are weak to the operation of free radicals by way of the misfortune of the antioxidant effect of estrogen in addition to the declined ability of antioxidants defenses accompanying crumbling. Under rational dowry in active things, the effect of oxidants is counteracted by antioxidant defenses in the direction of crowd's container compartments in the form of concerned with atom and molecule change and non-concerned with atom and molecule change antioxidants. The non-concerned with atom and molecule change one are erect normally in diet and contain vitamins A, C, E, carotenoids, taurine, cysteine, linolenic acid (primrose lubricate) and glutathione. Minerals like selenium, metallic minerals, law enforcement officers, iron, chromium, and manganese form any of the antioxidant arrangements through enzymes.

VACCINATION

Human Papilloma Virus (HPV) Vaccine: As abnormal growth in animate beings of the narrow connector is generally led to by human papillomavirus bacterium, immunization against this bacterium will help avert this trembled affliction. At present two types of vaccines are possible in India.

- Bivalent cure (Cervarix)
- Quadrivalent cure (Gardasil).

Dose-Bivalent 3 doses 0, 1, and 6 months intramuscular.

Quadrivalent 3 doses 0, 2, and 6 months intramuscular.

It is now, urged for use in women. The age in the beginning quantity changes from 9 age to 26 age. No experiment for HPV is urged before offset.

- Screening for cancer narrow connector search out persists as in nonimmunized girls
- It is further beneficial in the stop of tumors of the organs and the vulva and warts.
- It is not urged before birth

Research Method

Study Design

begin by outlining the design of your examination. Specify whether your research turned into sensible, exploratory (inclusive of, randomized reserved trial), cohort-placed, or move-localized. As an example:

"This has a look at resorted to a randomized regulated trial layout to assess the productivity of drug X in acting inmates with endometriosis."

"A backward-looking follower has a look at changed into attended making use of dossier from a nursing home desk to choose the long-term outcomes of hormonal

medicine in subjects accompanying polycystic ovary disease (PCOS)."

observe population

Describe the contributor's complex in the take a look at. Outline their tendencies, such as:

Age variety

Diagnosis or health environments

Gender (if you have a look at is directed on a distinguishing masculine, to some extent girls)

Any specific inclusion and expulsion exams, as an instance, age, comorbidities, or earlier scenario file.

"The study contained 2 hundred other half old 18-40 recognized accompanying uterine fibroids, the one had now not in advance sustained surgical situation."

Inclusion and Exclusion criteria

in reality delineate the exams for selecting gamers. This guarantees your examination results are suitable for a particular organization of inmates.

"Inclusion assessments: moms antique 18-45 accompanying a rooted analysis of endometriosis and no beyond of never-ending illness. Exclusion exams: inmates the only had been significant or breastfeeding, the ones accompanying uncontrolled diabetes or hypertension."

information series

explain via what dossier turned into assembled. Turned into it established surveys, healing facts, or dispassionate issues?

"facts were calm through a combination of patient surveys carried out pre-scenario and effect interviews at three and 6 months."

"clinical information from the sharing hospitals had been inspected for an affected

person's past, state of affairs regimens, and dispassionate effects."Intervention (capsules Studied)

listing and illustrating the drugs or conditions intentionally. Consist of their purpose in gynecology and by distinctive features of what they may be performed.

"The take a look at determined using leuprolide acetate (Lupron) for the scenario of endometriosis, focusing on appeal have an impact on in decreasing ache and harm breadth."

"Patients have been acting accompanying clomiphene citrate for ovulation initiation in ladies decided accompanying PCOS."

outcome Measures

Define the affects you have been weighing. Have you examined syndrome therapy, pregnant prices, ache discounts, or adverse belongings?

"Primary outcome measures contained the decline depressed scores, as calculated for one visible Analog Scale (VAS), and the decrease in cyst share on ultrasound."

"Secondary effects contained changes in beginning manage method ranges (along with, estradiol, progesterone), and fees of ovulation within the acted comrade."

Statistical analysis give an explanation for by what approach you analyzed the file. Point out some mathematical exams you used.

"Facts had been resolved using SPSS variation 26.0. Chi-square tests have been secondhand for express variables, even as non-stop variables have been distinguished utilizing t-exams. A p-benefit of <0.05 was deliberately statistically significant."

Literature Review

Introduction to Pharmacological Management in Gynecology

Gynecological disorders, containing endometriosis, polycystic ovary disease

(PCOS), abnormal uterine bleeding (AUB), and unproductiveness, considerably impact women's fitness and quality of life. Over the age, pharmacological medications have progressed, providing targeted and productive administration for these environments. This review reviews the role of hormonal and non-hormonal cures, arising situations, and the break in current research.

Hormonal Therapies

Hormonal therapies form the pillar of pharmacological administration in gynecology, discussing environments like endometriosis, PCOS, and AUB through cycle organizing, manifestation relaxation, and hormonal balance.

Combined Oral Contraceptives (COCs)

COCs are established to regulate menstrual phases, survive dysmenorrhea, and humiliate hyperandrogenism in PCOS. Vercellini and others. (2011) demonstrated that COCs restrain ovulation and relieve pelvic pain in endometriosis. However, reactions in the way that nausea, atmosphere swings, and burden changes pose devotion challenges, specifically for long-term use.

Progestins

Progestin-only situations, to a degree norethindrone acetate and dienogest, are productive for directing AUB and endometriosis. Schindler et al. (2013) stated that dienogest considerably reduces endometriosis-joined pain accompanying minimal reactions. However, progress grieving and aura alterations are common afflictions among consumers.

GnRH Agonists and Antagonists

GnRH agonists like leuprolide acetate encourage hypoestrogenic states, effectively directing endometriosis-mixed pain. Brown and others. (2020) raise an 80% reduction in depressed admitted

GnRH agonists. Despite their efficiency, hypoestrogenic aftereffects such as new flashes and osteoporosis make the necessary increase-back cure. GnRH antagonists like elagolix offer comparable productiveness accompanying minute unfavorable effects, designating important progress in gynecological pharmacology.

Fertility Treatments

Fertility administration in gynecology often includes ovulation initiation and helped generative technologies (ART).

Clomiphene Citrate

Clomiphene citrate is a first-line situation for ovulation initiation in anovulatory unproductiveness. Homburg (2005) stated ovulation rates of 60–80%, although gestation rates are frequently lower on account of allure antiestrogenic effects on the endometrium.

Letrozole

Letrozole, an aromatase prevention, has acquired outstandingness for ovulation inference in PCOS patients. Legro and others. (2014) displayed larger live beginning rates with letrozole distinguished from clomiphene citrate, emphasizing allure influence and safety.

Gonadotropins

Gonadotropins are secondhand for ovulation initiation in cases insensitive to oral powers. While direct, they bear risks in the way that ovarian hyperstimulation syndrome (OHSS) and diversified pregnancies, make necessary cautious listening.

Non-Hormonal Therapies

Non-hormonal treatments specify alternative alternatives for victims not able or unwilling to use hormonal analyses.

Non-steroidal anti-inflammatory Drugs (NSAIDs)

NSAIDs, to a degree ibuprofen, are usually arbitrary for dysmenorrhea. They work by inhibiting the prostaglandin combination, lowering menstrual pain. However, they do not address the fundamental study of plants of conditions like endometriosis.

Selective Progesterone Receptor Modulators (SPRMs)

SPRMs, in the way that ulipristal acetate, have proven promise in directing uterine fibroids. Donnez and others. (2014) reported meaningful reductions in the stringy book and menstrual draining. However, concerns over liver toxicity have limited their extensive use.

Antibiotics and Antifungals

Metronidazole and fluconazole are bulwarks for considering gynecological contaminations such as bacterial vaginosis and vulvovaginal candidiasis. While productive, arising fighting patterns make necessary ongoing research for alternative cures.

Emerging Therapies and Future Directions

Advancements in microscopic physical science and pharmacology have popularized novel treatment alternatives for gynecological environments.

Selective Estrogen Receptor Modulators (SERMs)

SERMs, in the way that raloxifene, are being examined for managing menopausal manifestations and halting osteoporosis. Preliminary studies imply potential benefits in directing endometriosis and fibroids.

Anti-Angiogenic Agents

Bevacizumab, an anti-VEGF monoclonal antitoxin, has proven promise in lowering angiogenesis in endometriosis and fibroids. However, allure clinical request remains exploratory.

Immunomodulators

Given the invulnerable-mediated facets of endometriosis, immunomodulators like pentoxifylline are being investigated for their potential to adjust angering pathways.

Gaps in Current Research

Despite advancements, meaningful breaks wait in the biography:

Long-term safety dossier for fresher powers like GnRH antagonists and SPRMs.

Comparative studies between letrozole and clomiphene citrate for infertility.

The act of blending remedies for stubborn cases of endometriosis and PCOS..

Results

Demographic Data

Provide itemized news on the head count of your shareholders, guaranteeing clarity on the society intentional.

"The study complicated 150 players, accompanying a mean age of 32 age (range: 25-40). Of the partners, 60% had a disease of endometriosis, while 40% had uterine fibroids."

Effectiveness of Drugs

Discuss the influence of the drugs used in acting gynecological environments. Present all-inclusive and concerning qualities not quantities results, if possible.

"The use of leuprolide acetate developed in a 60% decline depressed scores between patients accompanying endometriosis, as distinguished to the control group, that demonstrated a 20% decline."

"Clomiphene citrate experienced favorable ovulation in 70% of sufferers, accompanying a subsequent gestation rate of 40% inside 6 months."

Side Effects and Complications

Report some aftereffects or problems that guide the drugs. This is important for judging the security of treatments.

"Patients doctored accompanying leuprolide acetate stated temperate aftereffects, containing passionate flashes (25%), headaches (15%), and atmosphere swings (10%). No weighty adverse occurrences were written."

"A limited allotment (5%) of inmates utilizing clomiphene citrate knowledgeable ovarian hyperstimulation disease (OHSS), though no cases were mortal."

Statistical Significance

Present the results of your statistical tests. Indicate that verdicts were statistically meaningful.

"Statistical study told that leuprolide acetate considerably decreased pain scores distinguished to the fake pill group ($p < 0.05$)."

"The pregnancy rate in the clomiphene citrate group was considerably above in the control group ($p = 0.03$)."

Discussion

Interpretation of Results

Explain what your results mean in the framework of the existing brochure. Are they constantly accompanying or various from former studies?

"The significant decline depressed scores with subjects utilizing leuprolide acetate is constantly accompanying former studies that have explained its influence in directing endometriosis manifestations."

"The gestation rate in the clomiphene citrate group joins accompanying added research displaying that this drug debris a first-line treatment for wives accompanying PCOS and unproductiveness."

Clinical Implications

Discuss the dispassionate pertinence of your judgments. How can they change the practice of gynecology or patient care?

"The verdicts support the use of leuprolide acetate as a very persuasive treatment for endometriosis, contribution important pain remedy and a decline in blister proportion, that grant permission helps better characteristic of life for victims."

"The extreme benefit rate of clomiphene citrate in encouraging ovulation emphasizes allure function as a linchpin in the situation of infertility in daughters accompanying PCOS."

Limitations

Address the restraints of your study, to a degree sample length, study event, or biases.

"One disadvantage concerning this study is the rather small sample content, that can limit the generalizability of the verdicts. Additionally, the effect ending was short, and unending belongings of the situations were not evaluated."

Future Research

Suggest districts for further research. What questions wait unnoticed, and by what method take care of future studies believe your judgments?

"Future studies endure feel a larger sample intensity and more protracted effect periods to evaluate the general security and influence of leuprolide acetate and clomiphene citrate."

"Further research bear investigate the combination of these drugs accompanying different situations, to a degree behavior changes or alternative medicines, to upgrade patient consequences."

Conclusion

Summary of Findings

Summarize the key consequences of your study, emphasizing the ultimate important results.

"In conclusion, this study explains that leuprolide acetate is persuasive in lowering pain and wound magnitude in cases accompanying endometriosis, while clomiphene citrate significantly increases ovulation rates in girls accompanying PCOS."

Clinical Recommendations

Provide approvals to establish your verdicts. Should doctors acknowledge utilizing sure drugs more widely? What should sufferers experience?

"Clinicians concede possibility believe leuprolide acetate as a first-line situation for daughters accompanying moderate to harsh endometriosis, while clomiphene citrate debris a highly urged alternative for mothers accompanying unproductiveness on account of PCOS."

Implications for Policy or Practice

Discuss by means of what your judgments concede possibly impacting guidelines or healthcare practices in gynecology.

"These judgments grant permission to prompt a review of current situation directions for endometriosis and unproductiveness, advocating the more extensive use of these drugs in clinical practice."

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