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Review Article

Anticancer agents from Bacillus thuringiensis Delta-endotoxins

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Abstract

Cancer is one of the most fatal diseases that rarely any cancer patient survives from it. Cancer affect different ages and sex causing great humanity losses reaches up to 100,000 patient / year according to the recent statistical analysis. It also, affects different tissues causing irreversible cytopathological changes result in highly undifferentiated cells that hard to be controlled or eradicated. The chemotherapy, radiotherapy and surgical interference still used in elimination of the disease since decades however both radiotherapy and chemotherapy did not prove acceptable success in the cancer treatment until now, unfortunately the surgical interference could not be more helpful as it did not overcome the malignancy metastasis which gets back wilder after surgical interference due to metastasis. So, it was sound good to use the biological anti-malignancy agents in eradication of cancer cells. Biological anticancer agents provide a confident success in cancer therapy which includes many microbial metabolites derived from the members of Family *Bacillacae* such as *Bacillus thuringiensis*, *Bacillus polymixa* and other members explored recently in the Saudi environment. For example in a previous studies recorded by us some serovars of *Bacillus thuringiensis* enzymatically activated parasporal inclusion proteins proved a potent anti-malignancy effect on acute lymphocyte leukemia, lung carcinoma, larynx carcinoma and uterine cervix carcinoma *in vitro* and a great result was recorded *in vivo* on the Ehirlch Acites Carcinoma. These biological anti-malignancy agents had a selective direct cytotoxic effect on cancer cells in addition to improving the immune status (immunomodulation) which helps in destruction of the cancer cells and dysfunction of their metastasis properties. So, this project is aimed at extraction of potent biological anti-malignancy agents from new members of Family *Bacillacae* and broadly investigating their direct cytotoxic effects on cancer and normal mammalian cells, their ability to differentiate between normal and cancer cells, *in vivo*, vital functions disturbance, *in vivo* immunomodulation in tested lab animals, diminishing of the metastasis properties in the cancer bearing lab animals, cancer cell receptors, pest rout of administration and formulation of the explored biological anti-malignance agents in a stable and suitable forms.

Keywords: Anticancer agents, *Bacillus thuringiensis*, Biotherapy, Delta endotoxins.

1-Malignancy and public health importance

Cancer is now highly common among other disease in Kingdom of Saudi Arabia. Progress made in cancer therapy has not been sufficient to significantly lower annual deaths rate, so there is an urgent need for new strategies in cancer control. Prevention is most practical strategy to control cancer occurrence and spread. Cancer bio-prevention aims at halt or reverses the development and progression of precancerous cells through use of non-cytotoxic microbial metabolites. Subsequently, the identification, mechanistic investigation, validation and utilization of microbial metabolites have become an important issue in current public health-related research. It will be of importance to provide a variety of cancer bio-preventive and biotherapeutic agents with different molecular, cellular targets and acting by multiple mechanisms.

For the identification of novel cancer bio-preventive a broad spectrum of cell and enzyme based *in vitro* assays with markers relevant was set up for measuring inhibition of carcinogenesis during the initiation, promotion, and progression stages. These bioassay systems offer fast and sensitive identification and evaluation of lead compounds for the development of effective bio-preventive and anti-tumor agents and then elucidation of their mechanism of action.

Genus *Bacillacae* importance as Immunogin, Food preservative (antimicrobial) and anticancer.

a- Antimicrobial importance of genus *Bacillacae*:-

Lactic acid bacteria (LAB) and their probio-active cellular substances exert many beneficial effects in the gastrointestinal tract. LABS prevent adherence, establishment and replication of several enteric mucosal pathogens through several antimicrobial mechanisms (Nadu AS, ***et al.*, 1999).** LABS also release various enzymes into the intestinal lumen and exert potential synergistic effects on digestion and alleviate symptoms of intestinal meal absorption. Consumption of LAB fermented dairy products with LAB may elicit antitumor mutagenic activity, decrease is several enzymes implicated in the generation of carcinogens, mutagens, or tumor promoting agents, suppression of tumors, and the epidemiology correlating dietary regimes and cancer. Specific cellular components in LAB strains seem to induce strong adjuvant effects including modulation of cell mediated immune responses, activation of reticuloendothelial system, augmentation of cytokine pathways and regulation of interleukins, and tumor necrosis factors (Naidu AS*, et al.,* 1999). Enteric pathogens may cause gastrointestinal disease in humans & animals and antibiotics have often been used to prevent such disorders. However, the use of antibiotics is no longer recommended due to complications including the emergence of drug resistant strains (Karmartiar *et al*., 2004, *O'flaherty* et al., 2005 and *Takeuchi* et al., 2005) and the potential for chronic toxicity (Dundas *et al*., 1999); thus, alternative approaches to the prevention of gastrointestinal disorders have been suggested. Many reports show the usefulness of lactic acid bacteria (LAB) as probiotics for humans and animals (Brashears *et al*.**,** 2003; Hamilton-Miller 2003 and Sartor 2005) for the probiotic functions, several factors are usually considered. For example, the capability of LAB to adhere to cells of the host gastrointestinal epithelium and to serve as a barriers to protect it from infection by enteric pathogens, such as *Salamonella* spp. or *Escherichia coli* (Jin *et al*.**,** 1996; Chou and Wemer 1999, Coconnier *et al*., 2000); the organic acids produced by LAB which maintain a competitive advantage by inhibiting enteric pathogens in the gastrointestinal tract (Naidu *et al*., 1999).

b- Anti Cancer and Immuno-modulating importance:

Lactobacilli species, which is used in dairy based foods and dietary supplements, is nonpathogenic and safe for human consumption (Salminen,S *et al*., 1998 and Naidu, A. *et al.,* 1999). It is also a common compared of the human commercial microflora. Their long record of human exposure and consumption has led to their generally regarded as safe classification. Viable and nonviable *lactobacillus* species have anti-tumor abilities (Seow S.W., *et al*., 2002). Patients with carcinoma of the uterine cervix who received heat killed *Lactobacillus casei* YIT9018 intradermally and radiation therapy had enhanced

tumor regression compared with those given only radiation therapy (Aseno M., *et al*., 1986). In animal models such as Meth A fibrosarcoma bearing mice intrapleural administration of lactobacillus prolonged the survival of tumor bearing animals and suppressed tumor development (Aso, Y., *et al*., 1992). Similarly for azoxymethane induced colon cancer in rats consumption of Lactobacillus species prolonged the survival of tumor bearing animals and reduced the number of colon cancers formed (Aso,Y., *et al.,* 1995). In humans with superficial bladder cancer oral consumption of *Lactobacillus* was found to increase recurrence free periods (Masuno T., *et al.*, 1991), the same thing was noted in mice that oral consumption of *L. rhamnosus* GG (Aseno *et al.,* 1985*,* Lim, B *et al.,* 2002).

Lactobacillus species is believed to primarily act by enhancing the host immune system, although there have been some reports of cytotoxic effects on cancer cells (Manjunath, N. *et al.,* 1989 and Fichera, G.A. and Giese, G.,1995) *Lactobacillus casei*, Shirota strain, has been recognized as a typical probiotic strain.

Pre- clinical studies, in several animal experimental models have shown that LC9018, a heat killed preparation of the Shirota strain, exerts potent anti-tumor and anti-metastatic activities after intra pleural, intralesional, intra venous and oral administration. The anti-tumor activity of the Shirota strain has also been investigated in several clinical trials. The oral administration of Biolactis Powder, a powder formulation of *L. casei*, Shirota strain, reportedly suppressed recurrence after transurethral bladder tumor resection (Aso,Yand Akazan, H.,1992 and *Aso,Y et al*.,1995).

Intrapleural injection of LC9018 combined with doxorubicin significantly prolonged the survival of patients with malignant pleural effusions (Masuno, T. *et al.,* 1991). Moreover, intra-dermal administration of LC9018 with radiation therapy also had a survival prolonging effect in patients with stage IIIB cervical cancer (Okawa, T. *et al.,* 1993).The mechanism of anti-tumor activity has been recognized as the augmentation of the innate cell mediated immune system, including macrophages and natural killer cells by *L. casei*, Shirota strain (Kato,I *et al* 1983 and Matsuzaki,T *et al*., 1988). Intra-vesical BCG caused the infiltration of macroplages and T cells, probably type Th_1, in bladder submucosal tissue (Bohle, A. *et al*., 1990).

It has been reported that tumor necrosis factor- α (TNF-α) directly induces tumor cell apoptosis *in vitro* and enhances the tumoricidal activity of macrophages (Wang,C.Y *et al*., 1996 and Hori, K *et al*., 1987). LC9018 enhanced production of TNF-α when co-cultured with macrophages derived from peripheral blood *in vitro* (Hara,h *et al* 1989). Also, it has been reported that intra-pleural injection of LC9018 induces marked production of cytokines, such as IL-1B, interferon-Gamma, IL-12 and TNF -α, in the pleural cavities of tumor bearing mice (Takahashi, T. *et al*., 2001). Furthermore, treating mice with anti-tumor necrosis factor-α mAb completely abolished the anti-tumor activity of LC9018. In addition intra-pleural injection of recombinant TNF-α partially restored the survival prolonging effect of LC9018 in Meth A-bearing mice pretreated with anti-tumor necrosis factor-α mAb (Yasutake, N. *et al*., 1999).Therefore, it is likely that LC9018 induces the production of TNF-α by macrophages in bladder tissues. Together these results suggest that TNF-α has a pivotal role in the anti-tumor activity of LC9018 against MBT-2 bladder tumors.

Therefore, the mechanisms by which LC9018 enhances cell mediated anti-tumor immune responses are thought to involve the stimulation of macrophages infiltrating the bladder mucosa by LC9018 (Le,J *et al*., 1983).In clinical trials there were no serious symptoms after intra-pleural or intra dermal injection of LC9018 except for a few mild cases of fever, transient hepatic dysfunction and skin lesion(Masuno, T.*et al*., 1991 and Okawa, T. *et al.*, 1993). Intravesical instillation of LC9018 may represent potent immunotherapy for prophylaxis against bladder tumor recurrence without severe side effects.

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