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Probiotics and Biotechnology Advances in Reducing and Preventing Colorectal Cancer; Minireview

Hana R. Bajes[1]*, Emad A S Al-Dujaili[1]

[1] Faculty of Pharmacy, Middle East University, Amman, Jordan.

ABSTRACT

Background: Probiotics have been consumed to add health benefits to the human body, however, with aid of biotechnology, probiotics have been used specifically to prevent or reduce cancer. Colorectal cancer can be caused by different factors; primarily the imbalance of normal flora in the intestines. Intake can by fermented food, supplements, or as a carrier to an anti-cancerous agent.

Aim and objectives: The intent of this review is to provide relevant information on the effect of probiotics on colorectal cancer and the different mechanism of actions. Some probiotics have been demonstrated; some downregulated inflammation, inhibited the expression of certain markers, or interacted with chemical pathways that lead to apoptosis.

Methodlogy: Relevant data were extracted and evaluated, and this was made possible by searching different search engines primarily PubMed and Science Direct using relevant keywords. Collection of literature lasted for about four months.

Results: Some societies have been observed for their low prevalence of colorectal cancer which was associated with their rich probiotics diet. Currently, Food industry is racing toward the innovation of new products that can be enriched with viable probiotics and constant research is aimed toward finding effective methods to target colorectal tumor and reduce or inhibit its proliferation.

Keywords: Probiotics, Colorectal Cancer, Drug Delivery, Carcinogenesis.

1. INTRODUCTION

The notion that bacteria can benefit human health is difficult to understand, and due to the lack of understanding surrounding its potential therapeutic uses, it was not universally accepted. However, the existence of good bacteria in the living system can protect the body from harmful bacteria and can prevent certain cancers, a fact that has come a long way to be proven. Modern biotechnology has paved the way for the identification of the stains of some probiotic bacteria and genetically modified ones(1).

A significant expansion in microbial and industrial biotechnology in probiotics and the promising potential of therapeutics of probiotics has led to increased scientific research in this field, specifically cancer which remains on top of the list compared to the wide varieties of diseases probiotics are tested against. A thorough literature search was conducted to find out if there is an association between cancer prevention and advances in probioticsand to our knowledge, no similar published work existed. This review concentrated on colorectal cancer prevention. The aim of this literature review is to study the effect of probiotics in preventing and reducing the recurrence of colorectal cancer. In addition, are there advances in biotechnology that can provide new strategies to produce more effective genetically modified probiotics targeting this type of cancer.

1.2 Probiotics Definition

The word probiotics derived from Latin, means 'for life'. Fermented products, such as beer, bread, wine, kefir,

* dean-pharmacy@meu.edu.jo; edujaili555@gmail.com.

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and cheese have been widely used before discovering the microorganisms involved in their production[2]. The Food Agricultural Organization/World Health Organization (FAO/WHO) defined probiotics as "live microorganisms which when administered in adequate amounts confer a health benefit to the host." (Brown and Valerie, 2004). Probiotics are nonpathogenic microorganisms, primarily bacteria and yeast, that contribute to health of an organism.

1.3 Development of probiotics

Probiotic use extends back to ancient history of Turkish, Roman, and Mongolian civilizations. In modern history, the term became more common after 1980; the introduction of the concept itself is credited to Nobel laureate Élie Metchnikoff, who hypothesized that Bulgarian peasants who consumed yogurt lived longer[3]

Many scientific papers regard Metchnikoff as the father of the idea that probiotics are beneficial to human health. He suggested that lactic acid bacteria in dairy products could lower the pH in the colon by breaking down lactose and inhibiting the growth of proteolytic bacteria. His finding explained the reason villagers in a mountainous area of Bulgaria who consumed a large amount of fermented milk products lived longer than the general population. In the Far East, in 1930 Dr. Minoru Shirota obtained the first culture of *Lactobacillus casei* strain *Shirota* isolated from the human intestines and demonstrated that the strain discovered is resistant to gastric acid and bile acid; therefore, after oral administration, it can reach the lower intestine. Dr. Shirota developed 'Yakult', a dairy product. As a result, he postulated that the daily intake of this fermented product may encourage intestinal health and prolong the lifespan[2].

1.4 Strains and sources of probiotics

Probiotic strains associated with human health are of the following genera: Lactobacillus, Bifidobacterium, Saccharomyces, Enterococcus, Streptococcus, Pediococcus, Leuconostoc, Bacillus, Escherichia coli. There are more than 400 species identified[3]. In addition to their natural presence in the human intestines, they have been modified into supplements such as powders, drinks, tablets, and chewable tablets. They play a role in fighting against other harmful bacteria, aiding in digestion, and detoxifying the bodily systems. They are added to soy products, milk, cheese, yogurt, juices and many other food products[4, 5]

1.5 Colorectal cancer

Colorectal cancer epitomizes the most common malignancy of the gastrointestinal [GI] tract. It is the third most common cancer and is one of the most common health problems in the world[6]. Most colorectal cancers begin a polyp, or a growth on the inner lining of the colon or rectum. However, not all polyps become cancer, as the chance of a polyp developing into a cancer depends on the type of polyp. There are 2 main types of polyps:

1. Adenomatous polyps (adenomas): These polyps occasionally mature into cancer. For this reason, adenomas are called a *pre-cancerous condition*.
2. Hyperplastic polyps and inflammatory polyps: These polyps are more common, but are generally not pre-cancerous[7]

Colorectal cancer has different stages and can metastasize if the final stage has reached; as explained in figure (1).

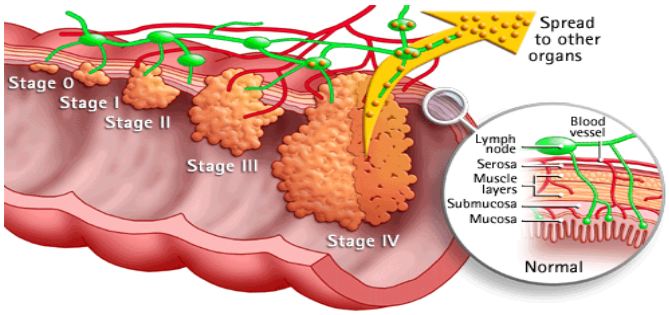

Figure (1): Colorectal cancer polyps and stages[8]

CRC is more prevalent in industrialized countries than in developing ones, and is four times more likely to occur. Dietary habits and lifestyle, rather than racial factors, may explain this neoplasm, as it has been demonstrated by studies on migrants. The diet is most likely cause of pathogenesis of CRC. Studies have discovered a link between a high consumption of red meat and animal fat and an increased risk for CRC development, whereas a diet rich in vegetables and fruits appears to protect against CRC[9]. Thus, imbalance in the normal gut flora caused by diet or some drugs can lead to CRC[6].

This imbalance is called gut dysbiosis; it is the reduction of normal flora and the overgrowth of pathogenic ones which is associated with CRC[10]. Dysbiosis of gut bacteria generally occurs in cancer tissues which are exposed to microbes in the colon and rectum. Recent studies established the strong relationship between the imbalance of normal flora and cancer progression in the gut. For example, many opportunistic bacteria species, such as *Helicobacter hepaticus*, *Streptococcus bovis*, enterotoxigenic *Eschericha coli* (ETEC), enterotoxigenic *Bacteroides fragilis* (ETBF), and *Fusobacterium nucleatum*, are all confirmed to be responsible for CRC[11].

Andrew, et al performed a study comparing human colon tumor tissue with normal adjacent tissue. It was found that the tumor microenvironment contained relatively higher levels of the genus *Fusobacterium* and depletion of the phyla *Bacteroidetes* and *Firmicutes*, which implied an imbalance in the colon flora[12].

It is inevitable to mention that symptoms include episodes of diarrhea or constipation that extend for days, rectal bleeding, jaundice, blood in the stool, abdominal pain, loss of appetite, and fatigue[13].

2. Association of Colorectal cancer and Probiotics

2.1 Studies and Mechanism of action

In the Journal of Cancer Epidemiology, an article investigated the reason why the rate of colorectal cancer in developing countries, such as West Africa is low compared to the US for example. It was found that the reduced incidence of colorectal cancer in West Africans was due to cancer-protective factors such as the starchy, high-fiber, spicy, peppery foodstuff that is low in animal protein, which many West African nations maintain as part of their diets[14].

To assess the benefit of probiotics in anticancer mechanism, a study was published in 2016, tested the combination of *Lactobacillus plantarum* with 5-fluorouracil (5-FU), a chemotherapy drug for CRC, the combination selectively inhibited the characteristics of 5-FU-resistant colorectal cancer cells (HT-29 and HCT-116). *L.P* inhibited the expression of the specific markers CD44, 133, 166, and ALDH1 of cancer stem cells. The combination therapy of *L.P* and 5-FU inhibited the survival of CRCs and led to cell death by inducing caspase-3 activity, induced inactivation of the Wnt/β-

catenin signaling of chemo-resistant CRC cells, and reduced the formation and size of colon spheres[15].

In another article published in 2012, it suggested that there are different mechanisms by which probiotics act against CRC, such as alteration of the intestinal microflora; inactivation of cancerogenic compounds; competition with putrefactive and pathogenic microbiota; improvement of the host's immune response; anti-proliferative effects via

regulation of apoptosis and cell differentiation; fermentation of undigested food; inhibition of tyrosine kinase signaling pathways[6].

A clinical trial was conducted to evaluate the effect of probiotic plus prebiotic preparation on colorectal cancer. Thirty-seven colon cancer patients and forty-three polypectomized patients. Intervention with a synbiotic composed of *Lactobacillus rhamnosus* GG, *Bifidobacterium lactis* Bb12 and oligofructose-enriched inulin for 12 weeks resulted in reduced proliferation and DNA damage in colonic mucosa and the capacity of fecal water samples to induce necrosis in colonic cells in polypectomized patients. Increased production of interferon (IFN)-γ by peripheral blood mononuclear cells (PBMC) was observed in the cancer patients. Thus, several colorectal biomarkers were shown to be improved by the synbiotic treatment[16].

Several animal studies have demonstrated that (LcS) Lactobacillus casei strain Shirota augments the functions of natural killer (NK) cells and T cells, macrophages, and exerts anti-cancer activity. Several mechanisms have been proposed; one that LcS inhibited interleukin (IL)-6-mediated inflammatory responses in the colonic mucosa in a mouse model and suppressed the development of cancer. The results suggest that LcS can downregulate inflammation and then prevent the subsequent cancer development[17].

One study was published in 2017, has produced promising results; the study investigated the effect of *Leuconostoc mesenteroides (L.m),* isolated from dairy, on molecular pathways involved in the induction of apoptosis in colon cancer, HT-29 cell line. It was found that *L. m* could induce apoptosis in the HT-29 cancer cells that confirmed by various techniques such as DAPI staining, flow cytometry, DNA ladder, and gene expression analyses. In order to further understand the mechanism by which *L. m* could hinder the cell proliferation and induce apoptosis, the role of NF-kB gene; a key component of progressive, was studied. *L. m* increased NF-kB inhibitory subunit (IKB) and decreased the expression of RelA. NF-kB pathway can cross-talk with other pathways such as PI3 K/AKT pathway. Another pathway is MAPK; that may either stimulate or inhibit apoptosis in various cell lines by regulating transcription factors that control microRNAs and their biosynthetic machinery. MAPK was elevated in the *L.m* treated cell line[18].

In 2017, a study tested the anticarcinogenic activities and apoptosis-regulatory effect of aqueous extract of fermented barley with *Lactobacillus plantarum* dy-1 (LFBE) by subcutaneous transplantation tumor model of human HT-29 cells in nude mice. As a result, LFBE regulated of the transplantation tumor of human HT-29 cells in BALB/c nude mice and inhibited cell proliferation and apoptosis induction. It may be helped to increase the gene expression levels of Bax and caspase-3 and decrease those of Bcl-2 and cyclinD1. Based on the data collected, the development of fermented barley extract with *Lactobacillus plantarum* dy-1 as the main component of anticarcinogenic function food formed the bases of this experiment[19].

Another study was published in 2017 investigated the protective role of *Lactobacillus casei* (ATCC 393) in an induced mouse model of colon carcinogenesis. The experiment focused on aberrant crypt foci as preneoplasic (ACF) markers because they are generally assumed to be putative preneoplastic lesions of the colon, and on polyamine metabolism as a possible cause of colon cancer. Mice with specific criteria were administered 1,2-dimethylhydrazine dihydrochloride (DMH) based on the experiment protocol *L. casei* (ATCC 393) was

administered orally $10^{(6)}$ colony forming per unit, twice a week. The procedure involved hematoxylin and eosin staining, high-performance liquid chromatography, and Western blotting to evaluate aberrant crypt foci, urinary polyamines, and ornithine decarboxylase expression in the colon. The data showed that *L. casei* (ATCC 393) delayed the onset of cancer as it significantly reduced the number of DMH-induced aberrant crypt foci, the levels of putrescine, and the expression of ornithine decarboxylase. As a result, this probiotic strain has a potential role in protection against colon carcinogenesis[20].

2.2 Current colorectal cancer research

Currently, *Lactobacillus bacteria* is incorporated in ice-cream production and other dairy products (Elvivie, et al., 2017). Very recently in 2018, a probiotic snack was developed, consisting of dried apple cubes impregnated with *Lactobacillus casei* NRRL B-442. Apple cubes were impregnated with probiotic microorganisms and dried under different temperatures (10–60 °C), with or without application of ultrasound. The concentration of probiotics in the apple snacks was comparable to the concentration of microorganisms in commercial probiotic dairy products when the apples were dried at 60 °C, or when ultrasound-assisted air-drying was applied. This proves that the production of dried probiotic apple snacks is possible and technically viable. Interestingly, an intake of about 100 g of dried probiotic apple would impart in an intake of about 100 million (CFU) of the probiotic bacteria[21].

Results from a study published in February, 2018 found that spore-based carriers have a large potential in treating colon cancer. The experiment produced a new probiotic *Bacillus* spore-based oral carrier loading curcumin for colon cancer treatment. *In vitro* and *in vivo* studies confirmed that spore-based carriers loading curcumin have strong anti-colon cancer effect by inhibiting tumor growth. The *Bacillus* spores acted as carrier loading drugs by covalently linking curcumin to its rigid coat and folate, and still maintained high bacterial spore activity. The spore-based carriers released drugs in the intestinal tract, mainly in the colon area through surging the gastric barrier, by means of germination and degrading the outer coat. The released complexes from spore-based carriers could form nanomicelles by self-assembly and targeted the HT-29 colon cancer cell line and lead to apoptosis. Pharmacokinetic studies confirmed that *Bacillus* spore-based delivery system could significantly enhance the oral bioavailability of curcumin and prolong the retention time of curcumin *in vivo*. This colon-targeted *Bacillus* spore drug delivery system improved the therapeutic efficacy of anticancer drugs after oral administration[22].

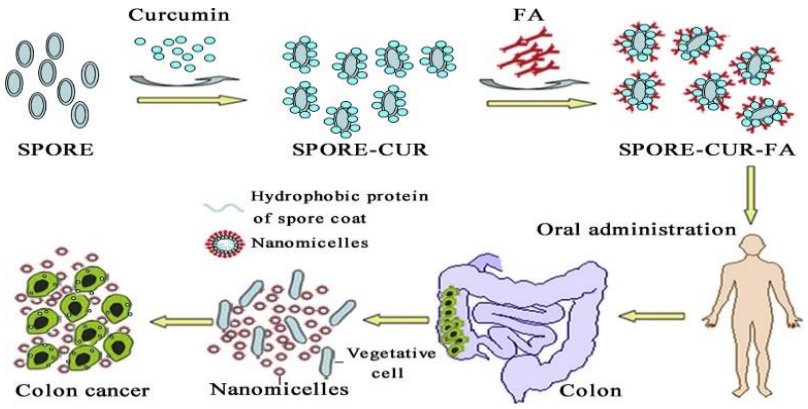

Figure (2): *Bacillus* as curcumin carrier[22]

Another interesting study published in October 2017 presented very promising results in regards of linking histamine production to antitumorigenic effect on colon cancer. It has been shown that histidine decarboxylase (HDC) deficiency promotes colorectal cancer by not converting $_{L}$- histidine to histamine. As illustrated below, mice with induced colorectal cancer, *Lactobacillus reuteri hdc+* was administered to their guts and resulted in luminal *hdc* gene expression and histamine production which suppressed tumorigenesis and tumor necrosis factor production. These findings give insight into probiotic immunomodulant effect in colorectal neoplasia[23].

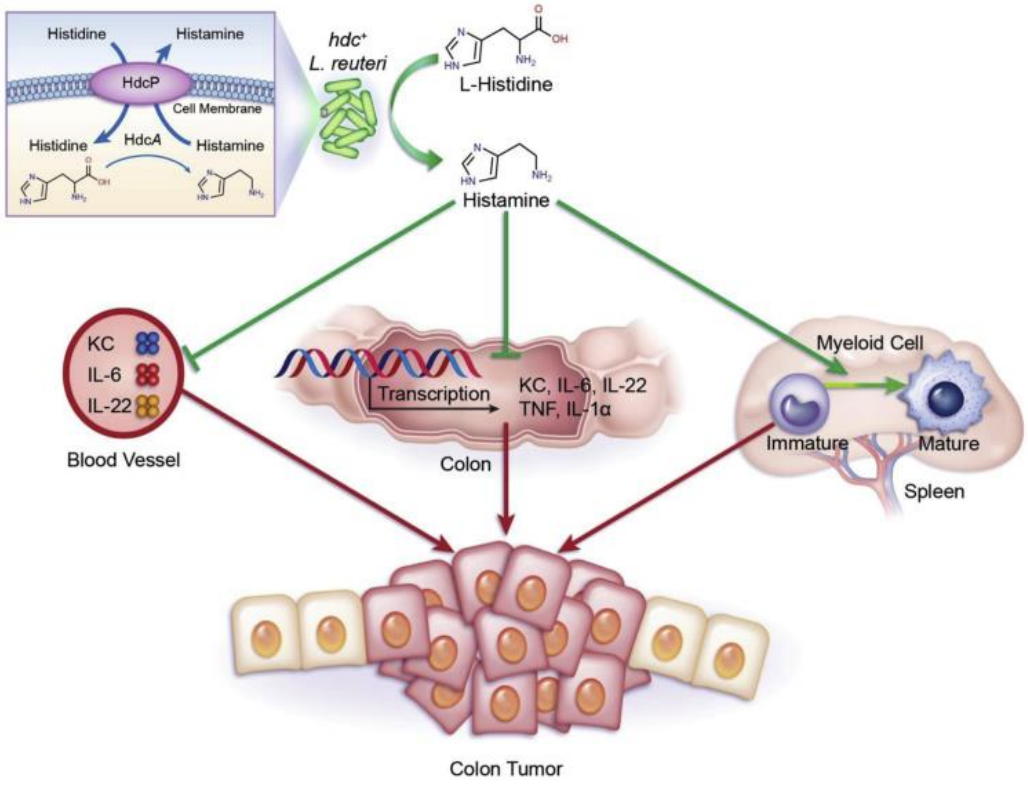

Figure (3): Proposed mechanism of gut microbe mediated suppression of colon carcinogenesis by bacteria histamine production[23]

2.3 Prospects in probiotics and colorectal cancer

There are no current studies to bridge the high potential translational gap between previous promising (in vitro) studies results and clinical studies. Therefore, a study published in 2017 aimed to bridge this translational gap in to explore the role of the human intestinal microbiota in CRC treatment. This was done by studying the intestinal microbiota composition during chemotherapy in patients who has metastatic CRC. The study followed a treatment protocol with all the patient participants and fecal samples were collected accordingly. Multiple data analysis was performed to compare microbiota composition before, during, and after three treatment cycles with systemic therapy between responders and non-responders. CT/MRI was used to compare microbiota composition between those experienced chemo-toxic effects and those who had

limited chemo-toxic effects. This protocol was designed to predict systemic treatment response and/or chemotoxicity based on the patients' intestinal microbiota composition, it will be developed by selecting bacteria and their abundance associated with response and/or chemotoxicity. To limit chemotoxicity and increase effects of systemic treatment, the role of the intestinal microbiota needs to be explored. In vitro studies already suggest that intestinal microbiota plays a promising role in CRC treatment, by exploring the microbiota composition and changes in relation to response and chemotoxicity, the favorable microbiota composition can be detected. In the future, low-burden fecal microbiota transplantation might result in more time and improved for cancer patients[24].

Further studies are needed to take place to identify the actual effector molecules in probiotics that produce the clinical effect in humans. In addition, the exact immunological outcome of each specific probiotic strain applied varies, because the sum of the interactions of proteins, DNA, RNA, and others, is strain-specific**.**

Genome editing tools including single stranded DNA recombineering and CRISPR-Cas genome editing, show great promise. These techniques can develop probiotics with increased stress tolerance, or enhanced metabolic activity[25].

Evaluating new strains of probiotics and their applicability in biomedical/clinical research, is progressing to pave a new direction for discovering probiotics to improve human health[26].

In an accepted article, it is suggested that the *Streptomyces* bacteria produces antiproliferative, immunosuppressive compounds such as rapamycin and tacrolimus that contribute to the rapamycin resistance of certain mucosal tumors like colon cancer. This type of bacteria has low abundance in the human microbiome maybe due to the current hygienic lifestyle. The insufficient of exposure to these compounds, due to the current lifestyle might be an underlying reason for the increase of inflammatory diseases, such as inflammatory bowel diseases. A future investigation on adding certain species like S. *hygroscopicus* and *S. tubercidicus to* the list of probiotics against inflammatory diseases would be an interesting research area[27 2].

Due the many draw backs in designing effective delivery systems to target the colon cancer cells in situ, researchers are prompted to a new approach. Wang et al have developed a lipoic acid esterified polysaccharide inulin (IN) delivery system to treat colorectal cancer in vitro. Inulin is a naturally occurring polysaccharide composed of a mixture of oligomers and polymers, and a great portion of dietary (IN) cannot be digested in the upper gastrointestinal tract. Inulin also has potential health benefits, such as promoting immune system function, supporting the cardiovascular system, and increasing the absorption of minerals. Many studies have conducted chemical modification of IN to obtain biocompatible drug delivery systems. IN was modified with lipoic acid (LA), and the hydrophobic core was cross-linked by the thiol–disulfide exchange reaction between the LA rings, thereby increasing the stability of the micelles and producing a glutathione-responsive disulfide bond[28].

As illustrated in figure 4, the modified IN-LA conjugate was successfully subjected to self-assembly into nano-sized micelles with hydrophobic pockets, which can encapsulate hydrophobic anticancer drug; Tanshinone IIA (TAN), which is a lipophilic compound isolated from *Salvia miltiorrhiza*. Investigation of the hydrodynamic sizes, zeta potentials, drug entrapment efficiency, drug release behavior in vitro, anti-tumor efficiency and proliferative activity to the probiotic bacteria was done.

In vitro cytotoxicity analysis demonstrated that the TAN-loaded CR micelles produced a more potent anticancer efficiency than an equivalent concentration of free TAN after incubation for 48 hours.

The drug delivery system promoted the growth of *B. longum*, which was beneficial for CRC treatment. The delivery system can selectively release loaded drugs to tumor cells and protect probiotic bacteria. This work was

a proof-of-concept study that examined the potential of a novel drug delivery system that utilized microbiota. The findings of this study could serve as a basis for further optimization and promote the development of drug delivery systems in treatment of colorectal cancer[28]

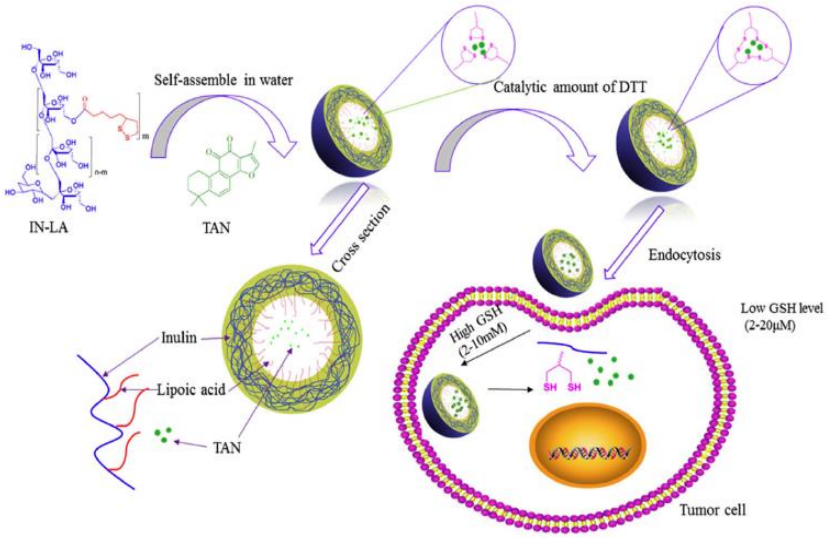

Figure (4): Drug loading and drug release from CR micelles at a high concentration of GSH in cancer cells[28]

Very recently, a study was conducted to deliver probiotics orally, González-Ferrero et al encapsulated probiotics using a by-product coacervation of soybean protein concentrate (SPC) by using calcium salts and spray-drying. SPC was extracted from soybean flour, produced during the processing of soybean milk. Two probiotic strains were selected for encapsulation.

(*Lactobacillus plantarum* CECT 220 and *Lactobacillus casei* CECT 475). To evaluate the ability of SPC to encapsulate and protect bacteria from stress conditions compared with the most common forms commercialized nowadays, the viability of these encapsulated.

strains under in vitro gastrointestinal conditions and shelf-life during storage were tested.

The results showed that SPC is a feasible material for the development of probiotic microparticles with adequate physical and chemical properties and enhanced significantly both probiotic viability and tolerance against simulated gastrointestinal fluids[29, 30]

3. Conclusions

In conclusion, probiotics hold a promising future in the field of preventing colorectal cancer as it was proved by several studies. In addition to their presence naturally in human intestines, they are found in fermented foods and dairy, or taken as supplements. Some mechanism of actions and strains have been identified, nonetheless, further studies are needed to understand their biomedical and clinical applications.

Acknowledgements

The authors would like to acknowledge the support of Middle East University, Amman, Jordan for publication and production of this review.

4. Recommendations

In this literature review, most of the studies and data

collected available focused on colon cancer and not rectal cancer although the combined term refers to both. Despite the idea that probiotics are naturally found in the GI tract and any supplementation of additional probiotics is delivered orally and their distant fate is the colon, and the anatomical continuity of colon to rectum, more attention should be given to rectal polyps alone as an initial site for carcinogenesis. Most of the studies were done in vitro or in mice models due to the close genetic makeup to humans, however, more trials should be performed on humans after taking all necessary safety precautions.

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البروبيوتيك والتقدم التكنولوجي الحيوي في الحد من سرطان القولون والمستقيم والوقاية منه؛ مراجعة مصغرة

هناء ربيع باجس[1]، عماد الدجيلي[1]

[1] كلية الصيدلة، جامعة الشرق الأوسط، عمان، الأردن.

ملخص

خلفيه:

يتم استهلاك البروبيوتيك لإضافة فوائد صحية لجسم الإنسان، ولكن بمساعدة التقنية الحيوية، يتم استخدام البروبيوتيك على وجه التحديد للوقاية من السرطان أو الحد منه. سرطان القولون والمستقيم يمكن أن يكون سببا لعوامل مختلفة. في المقام الأول عدم التوازن من النباتات الطبيعية في الأمعاء. يمكن تناولها عن طريق الأغذية المخمرة ، المكملات الغذائية، أو باعتبارها الناقل لعامل مضاد للسرطان.

الهدف:

الغرض من هذا الاستعراض هو توفير المعلومات ذات الصلة حول تأثير البروبيوتيك على سرطان القولون والمستقيم وآلية عملهم. وقد برهنت بعض البروبيوتيك فعاليتها ضد الالتهابات المنتظمة، من خلال التفاعل مع المسارات الكيميائية التي تؤدي إلى موت الخلايا المبرمج. تم استخراج البيانات ذات الصلة وتقييمها، وأصبح ذلك ممكنًا بواسطة البحث في محركات البحث المختلفة في المقام الأول PubMed و Science Direct باستخدام الكلمات الرئيسية ذات الصلة.

النتائج:

لوحظ في بعض المجتمعات انخفاض معدل انتشار سرطان القولون والمستقيم الذي ارتبط مع نظامهم الغذائي الغني بالبروبيوتيك. تتجه صناعة الأغذية حاليًا نحو ابتكار منتجات جديدة يمكن إثراؤها ببروبيوتيك قابلة للحياة ويهدف البحث المستمر إلى إيجاد طرق فعالة لاستهداف ورم القولون والمستقيم وتقليل انتشاره أو منعه.

الكلمات الدالة: البروبيوتيك، سرطان قولوني مستقيمي، توصيل المخدرات، التسرطن.

تاريخ استلام البحث ٢٠١٨/٥/٢٥ وتاريخ قبوله للنشر ٢٠١٨/١٢/٤.