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Probiotics as a Harpoon for Targeting Oral Cancers: A Brief Update

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Keywords
oral cancer, probiotic, lactobacillus, squamous cell carcinoma

Abstract
Aim: To review different strains of probiotic bacteria and their role in the carcinogenesis process.
Background: Oral cancer is the sixth most prevalent malignancy in the world in terms of prevalence and death rates. Although oral cancer is treated most commonly with chemotherapy and immunotherapy, the formation of resistance to these treatments is a major downside that leads to disease recurrence. Probiotics are currently being advised as adjuvant and complementary therapeutic strategies for boosting the effects of chemotherapy and immunotherapy medications. Probiotics, or friendly microflora in our bodies, aid in the manufacture of beneficial compounds that protect the immune system from diseases such as cancer.
Review Results: In a detailed review, it was found that many probiotic strains of Lactobacillus species took an active participation in the management of oral cancers, leading to their decreased

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frequency in occurrence, along with few other probiotic species like Acetobacter syzygii and Bifidobacterium species.

Conclusion: Probiotics have anti-cancer properties that help in the prevention and inhibition of cancers, focusing mainly on oral cancers. They aid in the reduced occurrence of oral cancers, with the help of certain strains of the lactobacillus species mostly, by restoring the balance of the oral microbiota to its normal healthy state in various cases.

Clinical Significance: Oral probiotics can be used as a cure to manage dysbiosis in the oral environment as well as restore the normal function of the oral microbiome, in cases of head and neck cancers, during the processes of treatment and recovery. Therefore, further studies regarding the actual mode of action of probiotics in the disease progression and management of oral cancers should be investigated, so as to understand the functioning of the probiotics in its recovery.

1. Introduction

Around the world, oral cancer is quite possibly the most well-known form of cancer, with 350,000 new cases each year. It is classified as squamous cell carcinoma of the head and neck (HNSCC). HNSCC is the sixth biggest reason of cancer death all throughout the world. Squamous cell carcinoma of the oral cavity is responsible for up to 90% of all oral malignancies. (OSCC). It is the most aggressive and fatal of all oral malignancies, in addition to having a high incidence rate.[1]

Probiotics are microorganisms that, according to WHO and FAO (2001), give health benefits when taken in sufficient amounts. Probiotics were redefined in 2004 by the International Scientific Association for Probiotics and Prebiotics (ISAPP) to **"live microorganisms which when administered in adequate amounts, confer a health benefit on the host"**.[2] One of the health advantages of consuming probiotics is the remodelling of the immune system and the production of antibacterial and adhesion-preventing substances that fight microorganisms.[3] Probiotics can also have anti-neoplastic characteristics, which could aid in the prevention of oral cancers.[4]

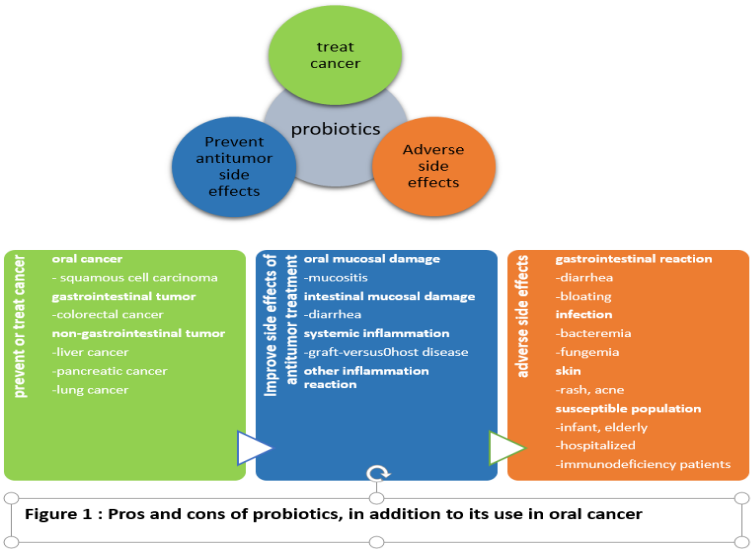

Figure 1 : Pros and cons of probiotics, in addition to its use in oral cancer

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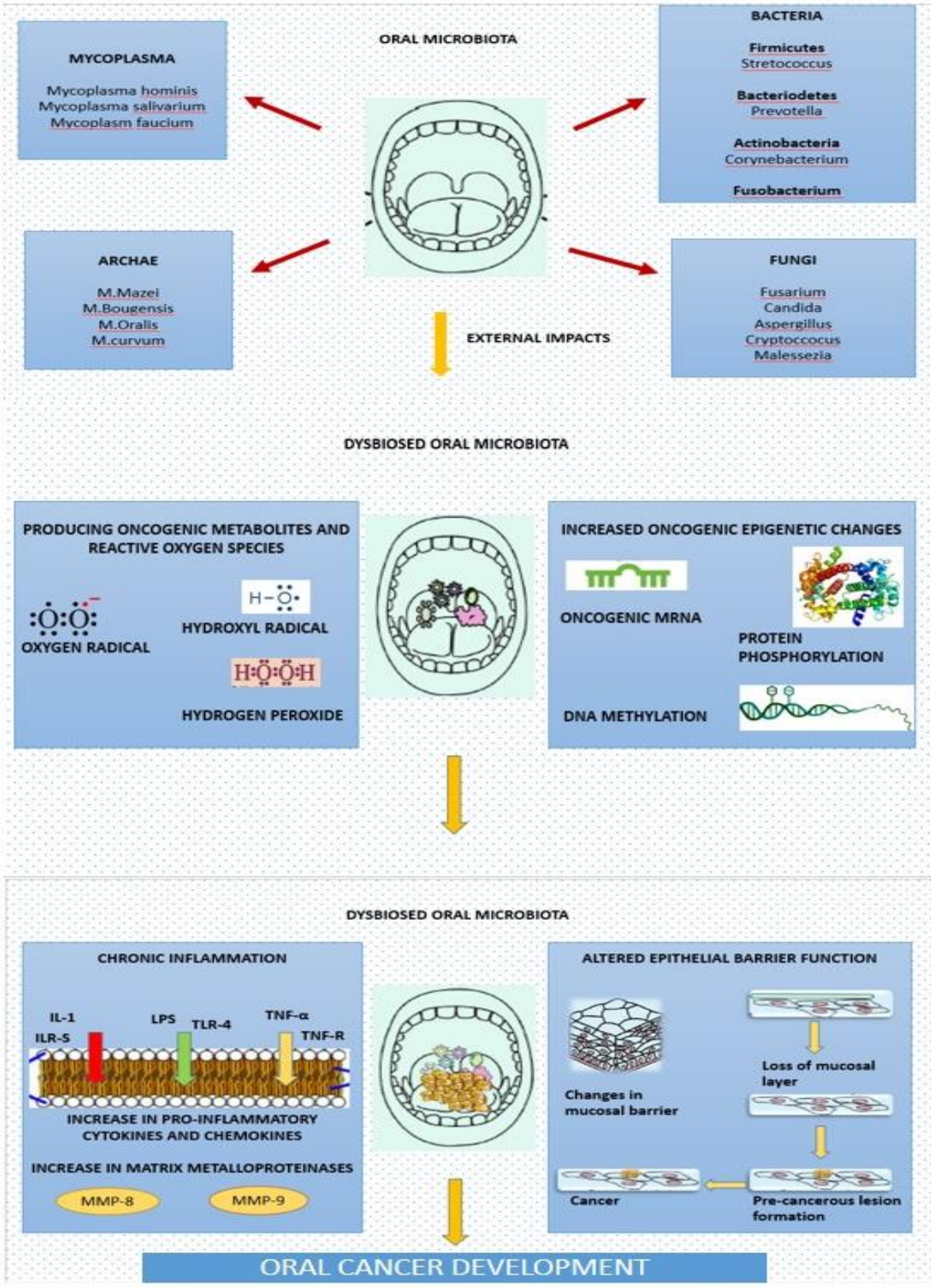

Figure 2 : The diagram represents oral microbiota belonging to different groups and the possible connection between oral microbiota dysbiosis and cancer progression via several mechanisms such as the release of pro-inflammatory cytokines and matrix metalloproteinases, production of ROS and RNS, which induce DNA damage, alteration of the integrity of epithelial barrier resulting in the development of pre-cancerous lesions and increase in the oncogenic epigenetic alterations such as the production of oncogenic miRNAs and increased DNA methylation. (TNF- α: Tumor Necrosis Factor-α; IL: Interleukin; MMP: Matrix Metalloproteinases)

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2. Review Results

In a detailed review, it was found that many probiotic strains of Lactobacillus species took an active participation in the management of oral cancers, leading to their decreased frequency in occurrence, along with few other probiotic species like Acetobacter syzgii and Bifidobacterium species.

3. Discussion

Probiotics In Inhibiting Carcinogenesis

Poor dental hygiene, smoking, and alcohol are all associated with chronic inflammation and infection, which are the primary causes of oral cancer.[5] The tongue, buccal mucosa, lips and floor of the mouth are the most common sites for oral cancer. Heavy alcohol use and cigarette smoking are two etiological risk factors for oral cancer.[6] The oral microbiota, which keeps the oral environment in balance, is also important for oral cell growth and proliferation. Porphyromonas gingivalis, Fusobacterium nucleatum and Prevotella intermedia are some of the bacteria found in the oral environment. Other bacterial strains like Enterobacteriaceae, Haemophilus, Fusobacterium, Prevotella, Streptococcus spp., Porphyromonas and Veillonella have also been linked to precancerous lesions and mouth cancer. The bacterial makeup of patients suffering from oral cancer and the controls vary considerably at both levels of phylum and genus. Firmicutes along with Actinobacteria were dramatically decreased in the diseased samples, while Fusobacteria, Spirochaetes and Bacteroidetes were particularly abundant. The cancer samples contained Treponema, Mycoplasma, Eikenella, Campylobacter, Centipeda, Lachnospiraceae G7, Fusobacterium, Alloprevotella, Selenomonas, Dialister, Peptostreptococcus, Filifactor, Catonella, Peptococcus, Parvimonas, Peptostreptococca and Capnocytophaga.[7]

The most frequent types of probiotics include lactic acid bacteria or bacterial strains, yeasts and non-lactic acid bacteria strains. Bacterial probiotics include Lactobacillus, Bifidobacterium, Enterococcus and Lactococcus. Some possible probiotics are Clostridiales, Bacillus spp., Escherichia coli, Bacteriodales and Weissella spp.along with Candida, Enterococci, Kluyveromyces, Debaryomyces, Picchia, Metschnikowia, and Hanseniaspora which are all considered as possible probiotic yeasts. Probiotics suppress mutagen binding, degradation, and inhibition; procarcinogen prevention and conversion of dangerous, toxic, and highly reactive carcinogens; Short chain fatty acids (SCFAs) produced during the breakdown of non-digestible carbohydrate reduce intestinal pH; and modification and augmentation of the innate immunity of the host by substances that are anti-inflammatory in nature, are all major probiotic mechanisms of action.[7]

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Table 2: Micro-organisms used as probiotics

Lactic acid producing bacteria	Nonlactic acid producing bacteria	*Bifidobacterium* species	Nonpathogenic Yeast	Non spore forming
Lactobacillusacidophilus	*Enterococcus faecalis*	*Bifidobacterium adolescentis*	*Saccharomyces boulardii*	*Coccobacills*
Lactobacillus bulgaricus	*Enterococcus faecium*	*Bifidobacterium animalis*		
Lactobacillus casei	*Escherichia coli Nissle*	*Bifidobacterium bifidum*		
Lactobacillus crispatus	*Streptococcus thermophiles*	*Bifidobacterium breve*		
Lactobacillus fermentum	*Propionibacterium*	*Bifidobacterium infantis*		
Lactobacillus gasseri	*Bacillus cereus*	*Bifidobacterium lactis*		
Lactobacillus johnsonii		*Bifidobacterium longum*		
Lactobacillus lactis				
Lactobacillus plantarum				
Lactobacillus reuteri				
Lactobacillus rhamnosus GG				

Anticarcinogenic properties of Lactobacilli

There are several research conducted over the past two decades that state about the anticarcinogenic properties of LAB and fermented dairy products. Several kind of model trials have been carried out so as to determine the anticarcinogenic efficacy of yoghurt and other cultured dairy products. Bifidobacterium infantis, Bifidobacterium bifidum, Corynebacterium, Vibrio anguillarum, Propionibacterium acnes and Listeria monocytogenes are only a few of the Gram-positive and Gram-negative bacteria that reduce tumorous cells. They are divided into two categories: cancer prevention and cancer suppression.[8]

i) **Prevention of cancer initiation**

However, it has been claimed that procarcinogenic chemicals taken through diet may play a role in the development of cancerous tumours.[9] The lower incidence of colon cancer is linked to the cultured dairy products that are consumed. The LAB can work by reducing procarcinogenic chemicals in two ways: (a) directly reducing procarcinogens and (b) indirectly reducing procarcinogens.

1. **Direct reduction of procarcinogens**

In the digestive tract, carcinogenic nitrosamines are being converted from nitrites that have been available from processing of foods. There is a resultant chemical and enzymatic depletion due to lactobacilli cellular absorption of nitrites.[10] The role of nitrite reductase activity of Lactobacillus delbrueckii subsp.lactis was described by Dodds and Collins-Thompson, who further discovered about the nitrite absorption by cells which reduced their ability to convert nitrites to nitrosamines. As a result, LAB may lessen the risk of tumour initiation by metabolising procarcinogens.[11]

2. **Indirect reduction of procarcinogens**

There are some bacterial enzymes that are procarcinogenic in nature, present in faeces, like nitroreductase, azoreductase and B-glucuronidase that are likely to change procarcinogens to carcinogens,

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which are further been utilized to supervise carcinogenesis of mucosal membranes.

The risk of carcinogenesis is risen by the presence of high levels of the enzymes mentioned above. As mentioned by Goldin and Garbach and Goldin et al, the number of these faecal enzymes reduces after consuming fermented dairy products.[12,13] Sinha saw a decrease in faecal B-glucuronidase after using L. acidophilus.[14]

ii) Suppression of initiated cancer

It has been discovered that tumour growth can be slowed by injecting LAB near the tumour or feeding yoghurt and lactic organisms to tumours. In one- to two-week investigations, Ayebo et al. discovered a considerable reduction of the Ehrlich ascites tumour in mice. On the other hand, studies that were conducted over an extended period of time revealed no significant variation in the survival rate of mice after tumour implantation.[17] Lee used a model long-term study in which he chemically created colonic cancers in rats and then supplemented their diet with L. acidophilus to see how this diet affected cancer onset. During the initial phase of the trial, rats on the L. acidophilus diet had fewer tumours and had lower rate of ornithine decarboxylase activity than the control rats. However, there were no variations in tumorous locations or ornithine decarboxylase activity between the experimental and control groups at the end of the study. L. acidophilus may be effective as an anticancer drug during tumour beginning because it has fewer tumorous sites and reduced ornithine decarboxylase activity.[18] In short-term investigations, intact dead cells, lactobacilli cell wall fragments and intact viable entire cells have all been found to inhibit tumours.

The insoluble fraction of sonicated cells contained the anti-tumor growing component of L.delbrueckii subsp.bulgaricus; whereas it had no action on tumor cell proliferation, as stated by Friend et al.The anticancer component has also been linked to Bifidobacterium infantis' cell wall and entire cells, as well as Streptococcus thermophilus' insoluble fraction.[19] According to Kohwi et al., the cell wall retrieved by sonication of deceased B. infantis reduced tumours in mice.[20] Bogdanov et al. discovered that L. delbrueckii subsp. bulgaricus suppressed tumours by producing peptidoglycan, a component of bacteria's cell walls. The cell walls of other lactobacilli comprise of Peptidoglycan which is made up of muramyl peptides. As a result, peptidoglycan could be to blame for tumour suppression. This could explain why cancers can be suppressed by both dead and alive LAB.[21]

a) Lactobacillus salivarius as an anticarcinogenic auxillary

Many studies have shown that there is a decrease in the multiplication of oral cancer cells by probiotics. In one of the investigations, L. salivarius REN was known to suppress COX-2 upregulation. The PTGS2 gene encodes the COX-2 enzyme.[22] COX-2 expression is typically upregulated in malignancies of various sorts. As a result of COX-2, PGE2 is produced, which has been shown to aid in the spreading of cancer. Thus, inhibiting COX-2 is an effective therapy to prevent oral cancer.[23] Lactobacillus salivarius REN (L. salivarius

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REN) is found to be a novel virus which was discovered in the faeces of the healthy centenarians in Bama (China), which is one of the world's five longevity settlements.[24] It was also discovered that L. salivarius REN inhibite d the growth of squamous cell carcinoma in humans (TCA-8113). Anti-tumour action was induced by high dosages of L. salivarius REN. As a result, L. salivarius REN's anti-tumor activity was found to be dose-dependent when tested on the TCA-8113 cancer cell line. This in-vitro study was a follow-up to Zhang, Wang et al.(2013) and Zhang, Sun et al.(2013), and conducted probiotic in-vivo experiments. The result that probiotics reduces the frequency of carcinomas of the tongue in rats was found out in the first study conducted, by inhibiting 4-nitroquioline-1-oxide(4NQO). Previously, a study was carried out by Kanojia and Vaidya, in which they found out that 4-nitroquioline-1-oxide(4NQO), being a water-soluble carcinogen, can cause DNA adducts(2006). 4NQO results in oxidative mutation and damage, mostly in an oral environment away from curd and behaves as a carcinogen, consequently. In the cancer cell lines of the human oral cavity (KB cell lines), it was discovered to have anti-neoplastic characteristics. In normal epithelial cell lines, however, the bacteria had no cytotoxic action (KDR cell lines).[26]

Proliferation and apoptosis are important processes in cell death. Multistage carcinogenesis is a term used to describe the development of cancer in multiple stages It was discovered that several probiotics may also slow tumour growth and increase tumour cell death, however research is limited because the majority of the research was focused on colon cancers.[27,28,29] The outcomes of their research revealed antiproliferative and proapoptotic effects. inhibition of 4NQO-induced oral cancer incidence as a result of dietary Lactobacillus salivarius REN which are in agreement with these findings. There was no detectable apoptosis in response to treatment with Lactobacillus salivarius REN alone, implying that it had no deleterious impact on healthy and normal cells.[26]

b) Acetobacter syzygii as an anticancer probiotic tool

Similarly, A. syzygii metabolites were observed to affect KB cell lines more than KDR cell lines. The prophylactic effects of Acetobacter syzygii isolated from curd, which has typical probiotic features, were investigated in this study by Aghazadeh et al. 2017 on the KB cancer cell line of human oral cavity.[30] On KB malignant cell lines, the cytotoxic finding revealed that A. syzygii secretions had acceptable anticancer activity. Furthermore, based on the findings of our research, Pronase and lipase, which are found in A. syzygii, interacted with cancer cell lines and most likely caused the toxicity. These metabolites produced effects that were similar to cisplatin, a common medicine used to treat oral cancer. In normal epithelial cell lines, however, A. syzygii was found to be less hazardous than cisplatin (KDR cells). A. syzygii was also compared to cisplatin and L.acidophilus in the treatment of normal cell lines and cancer cell lines of oral cavity.

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Eight distinct gram-positive probiotic bacteria strains combine to form AJ2 (Bifidobacterium breve, Bifidobacterium longum, Lactobacillus casei, Streptococcus thermophiles, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus bulgaricus and Lactobacillus plantarum).These possible bacteria were employed to get pro-inflammatory and anti-inflammatory cytokinesin NK cells to secrete at their maximum levels.[31] Natural Killer cells are well-known for their capacity to fight blood malignancies.[6]

Human oral squamous carcinoma stem cells (OSCSC) from hu-BLT mice were implanted in the oral cavity's floor and divided into two groups: "NK cells not injected" and "NK cells injected." When NK cells were administered into hu-BLT mice, the researchers found that the morbidity rate was lower. They retained the capacity to eat as well. On the other hand, Hu-BLT mice that did not receive an NK cell injection rapidly lost weight. When the tumour sizes of the two groups were compared, the tumour in the hu-BLT mice injected with NK cells was found to be smaller. Furthermore, comparing with the group of non-injected NK cells, the proliferation of tumour cells of the oral mucosa was inhibited in the hu-BLT mice that were injected with NK cells that were fed with AJ2. As a result, the prevention of tumour formation was most likely due to a combined action of NK injection and AJ2.[6] Probiotics have been shown to have pro-apoptotic or anti-proliferative properties in human cancer cell lines. Two probiotic strains, Bifidobacterium adolescentis SPM0212 and L. rhamnosus strain GG (LGG), inhibited the proliferation of gastric cancer cells from the human gastrointestinal system and three cancer cell lines from the colon, including SW 480, HT-29, and Caco-2. When Lactobacillus kefiri-containing kefir was utilised against myeloid leukaemia cell lines, it displayed an apoptotic impact. In another investigation, Enterococcus lactis IW5 protected harmful gut bacteria and cancer cells from colonising the gut, including HeLa, MCF-7, AGS, HT-29, and Caco-2, demonstrating probiotic bacteria's anticancer capabilities.[32]

c) Lactobacillus plantarum as an effective modulator in oral cancers

In a recent study, the effect of Lactobacillus plantarum was examined in relation to the alteration of the PTEN gene and the MAPK pathway in cancer cells.[33] The MAPK pathway is made up of three protein kinases that are activated in a specific order. They are essential components of transduction pathways that control critical biological processes such as differentiation, cell proliferation, the immune response and death. Following the activation of a MAPK kinase (MAPKK) and a MAPK kinase-kinase (MAPKKK), the MAPK cascade is activated by specific extracellular signaling.[34] On the other hand, PTEN is a protein that is found to be coded by PTEN gene. This protein assists in production of a protein called protein phosphatise, which is found to be essential for suppression of the tumor. Phosphatase also plays a role in cell cycle regulation by resulting in prevention of cell multiplication and cell division.[35] PTEN gene mutations and deletions prevent the synthesis of protein phosphate, resulting in

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cancer cell growth and a reduction in cell death. As a result, mutations in the PTEN gene can lead to the onset of a variety of cancers, also including cancer of the oral cavity. The MAPK pathway actively participates in the formation of tumours, in contrast to the PTEN gene, which is thought to be involved in the suppression of cancer. Both PTEN and MAPK are observed to be increased and downregulated in cancer cells after L. plantarum promotes their mRNA expression. The decreased MAPK expression raises the possibility that Lactobacillus plantarum can block the cascade of MAPK pathway, leading to a slow development of cancer. PTEN has been activated, as evidenced by Lactobacillus plantarum expressing more PTEN. In short, their studies showed that L. plantarum regulates the expression of PTEN and MAPK pathways, which helps to prevent oral cancer.[33]

d) Lactobacillus brevis as a supplement to cure oral mucositis after anti-cancer treatment

Previous research has looked at the impact of probiotics on patients suffering from cancer who were receiving anti-cancer medication. Lactobacillus brevis CD2 delivers huge amounts of arginine deiminase and sphingomyelinase, specifically.[36] Separately, arginine may be converted to nitric oxide and polyamines by nitric oxide synthase and arginase in eukaryotic human cells. A bacterial enzyme called arginine deiminase competes with nitric oxide synthase and converts arginine to ammonia and citrulline, delaying arginine to nitric oxide conversion and lowering levels of numerous inflammatory markers (cytokines IL-1a, IL-6, IL-8, TNF-a, IFN-y, PGE2, and matrix metalloproteinases).[37] The inflammatory cytokine platelet activating factor (PAF), which has been associated to oral mucositis in radiation therapy, can be hydrolyzed by bacterial sphingomyelinase. In 2009, Atul Sharma et al.performed a randomized controlled study in order to estimate the effectiveness of Lactobacillus brevis CD2 lozenges which were found to reduce mucositis which was caused by radiation methods and chemotherapy procedures in patients suffering from cancer of the head and neck. Lactobacillus brevis CD2 was found to be beneficial in decreasing mucositis caused by radiotherapy and chemotherapy in patients with head and neck cancer in a double-blind randomized controlled trial. Patients who were given Lactobacillus brevis CD2 lozenges had a decreased incidence of mucositis than those who received a placebo. The placebo group had a 50% higher risk of grade III and IV mucositis, while 28% of patients administered Lactobacillus brevis CD2 lozenges were free of mucositis, compared to just 7% in the placebo group; these differences were highly significant (P.001) in the distribution. In the Lactobacillus brevis CD2 arm, 31 percent more patients were able to tolerate and complete anticancer therapy than in the placebo arm (P<.001). Patients in the L. brevis CD2 arm discontinued cancer treatment due to radiotherapy or chemotherapy-induced side effects such as nausea or vomiting and dysphagia. (P=.001). In patients with HNSCC who were receiving a combination of radiation and

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chemotherapy, Lozenges containing Lactobacillus brevis CD2 were found to be both reliable and effective in decreasing the development and progression of severe oral mucositis conditions. This might be beneficial for patients suffering from head and neck cancer who are not able to proceed with their treatment because of the toxicity caused by chemotherapy and radiation.[38] This observation was in agreement with Riccia et alprior's findings on the anti-phlogistic actions of Lactobacillus brevis CD2 on the diseases of the periodontium.[39]

e) Lactobacillus fermentum as a preventive measure against tongue cancer

Lactic acid bacteria causes an increase in the activity of mononuclear phagocytic cells (macrophages and monocytes) and polymorphonuclear leukocytes, improved the phagocytosis of mononuclear phagocytic system by increasing the secretion of mononuclear factors and lysosomes, and also causing a promotion in the production of reaction nitrogen and oxygen. Lactic acid bacteria elicit distinct immunological responses, primarily via cell-mediated immunity and humoral immunity.[39] The body produces humoral immunity by producing antibodies and increasing the levels of IgM, IgA, and IgG in the mucosa and blood. Activating macrophages, natural killer (NK) cells, and B lymphocytes, as well as encouraging the production of cytokines like interferon, is how cell-mediated immunity is done (IFN).[40] G-CSF and GM-CSF are effective treatments for cancer-related neutropenia. The results of the investigation showed that LF-CQPC08 reduced the effects of carcinogenic chemicals on the thymic and splenic indices in a mouse model.[41] LF-CQPC08 also helped to reverse the reduction in serum GM-CSF, G-CSF, IgM, and IgG levels induced by oral cancer. Normal mice in this study had serum levels of IgM and IgG that were identical to those found in a prior study.[42] As a consequence, LF-CQPC08 outperformed the commonly used LDSB in controlling the lowered immunity caused by tongue cancer in mice and boosting the immunity of tumor-bearing animals. The results of the tests revealed that LF-CQPC08 considerably caused a reduction in the effects of experimental tongue cancer on animals by protecting mice from 4NQO-induced experimental tongue cancer and boosting their resistance to it. The impact of LF-CQPC08 on mouse tongue cancer may be attributed to metabolites or an improvement in the animal's immune. Furthermore, tongue cancer may be suppressed by LF- CQPC08's inhibitory effects on oxidative stress damage in mouse model because they may help to repair damage caused by tongue cancer. Lactobacillus fermentum CQPC08 (LF-CQPC08) is a strain that belongs to the bacterial family that was recently discovered and recognized in Sichuan, China. According to a study conducted by Bihui et al, they discovered that L. fermentum prevented tongue cancer caused by 4-nitroquinoline 1-oxide in mouse models. Their findings revealed that LF-CQPC08 successfully prevents the fall of the thymus index, splenic index, phagocytic index, and proportion of phagocytic macrophages. LF-CQPC08 caused an increase in granulocyte-

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macrophage-CSF (GM-CSF), serum granulocyte-colony stimulating factor (G-CSF), immunoglobulin (Ig)M and immunoglobulin (Ig)G, levels of serum interleukin (IL)-4, IL-12, interferon-gamma levels and tumour necrosis factor-alpha, in mice, preventing immunity decline caused by tongue cancer. Nuclear factor erythroid 2-related factor 2 (Nrf2), Heme oxygenase-1 (HO-1), Bcl-2-associated X protein (Bax), and glutathione-S-transferases (GSTs) were all upregulated while p63, p73, p53, tensin, and phosphatase were downregulated in the tongue tissues of the tongue cancer mouse treated with LF-CQPC08. The microbial resource LF-CQPC08 might be used to prevent tongue cancer.[43]

f) Anticancer power of Lactobacillus rhamnosus coupled with Geniposide

The active component of Gardenia jasminoides Ellis, a member of the Gardenia genus, is geniposide. The primary benefits of gardenia fruit are liver and gallbladder nourishment and protection. [44] In addition, they are abundant in additional components like pigments, volatile oils, and organic acids, to name a few.[45] Glucosidase generated by intestinal microbes hydrolyzes geniposide to form genipin.[46] In addition to reducing inflammation, lipid peroxidation, and angiogenesis, studies have shown that genipin has minimal cytotoxicity, good biocompatibility, and a high anti-degradation capacity.[47,48]

Lactobacillus rhamnosus GG strain(LGG) has the ability to increase the effects of anticancer properties of geniposide on HSC3 human oral squamous cells, according to the investigation carried out by Cheng et al. On one side, LGG($1.0x10^3$ CFU/ml) had no effect on its own in human oral keratinocytes and HSC3 cancer cells, whereas Geniposide (25 or 50 g/ml) had no action on human oral keratinocytes but it resulted in the prevention of growth of HSC3 cancer cells, upon addition of LGG. These findings stated that geniposide caused increase in mRNA and protein expression of caspases 9, 3, and 8, as well as Bcl2 associated X protein, p21, p53, inhibitor of nuclear factor B (NFB), Fas ligand, and Fas, while resulting in a decrease in Bcl extra large protein, Bcl2, inhibitor of apoptosis 1 & 2, NFB, cyclooxigenase2, and inducible nitric oxide LGG in HSC3 cells. Genipin is a potent anticancer drug created through the transformation of geniposide by lactic acid bacteria's glycosidase. A study carried out by Cheng et al concluded that LGG was found to be capable of converting geniposide to genipin, resulting in a stronger inhibitory effect on oral cancer cells. There were different methods to study anticancer effects of Lactobacillus rhamnosus GG strain on geniposide in HSC3 cancer cells such as MTT, western blot, RTqPCR and flow cytometry. It was found out that upon addition of LGG in a smaller amount also led to the stronger anticancer effect of geniposide on HSC3 cancer cells. These findings suggest that Lactobacillus rhamnosus GG strain increases the anticancer effects of geniposide, raising the possibility that this formulation could be employed to treat carcinoma.[49]

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PROBIOTIC ORGANISMS	CONCLUSIONS	STUDIES
Lactobacillus salivarius	Lactobacillus salivarius REN and its secretions have been shown to have potent inhibitory effects on 4NQO-induced oral cancers, and these actions may be connected to 4NQO metabolism, DNA protection from oxide damage, cell proliferation suppression, cell death initiation, and/or expression of COX-2 downregulation.	Zhang et al.[26]
Acetobacter syzygii	Showed that the metabolites of A. syzygii were also found to be more toxic to KB cell lines compared to KDR cell lines	Aghazadeh et al.[30]
AJ2(Bifidobacterium breve, Bifidobacterium longum, Lactobacillus casei, Streptococcus thermophiles, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus bulgaricus and Lactobacillus plantarum)	Showed that the combined action of NK injection and AJ2 proved to be effective in cancer inhibition	Kamaluddin et al.[6]
Lactobacillus plantarum	Showed that L. plantarum regulates the expression of PTEN and MAPK pathways, which helps to prevent oral cancer	Asoudeh-Fard et al.[33]
Lactobacillus brevis	Showed that Lozenges containing Lactobacillus brevis CD2 were found to be both reliable and effective in oral mucositis conditions	Riccia et al. [37]
Lactobacillus fermentum	demonstrated that LF-CQPC08 improved immunity and antioxidant capacity, reducing tongue cancer's negative effects on the immune system and oxidative balance.	Liu et al.[43]
Lactobacillus rhamnosus	When coupled with geniposide, can be used to treat cancer	Cheng et al.[49]

Table 2: Studies showing different probiotic organisms and their application in oral cancers

4. Conclusion

Therefore, in patients suffering from head and neck cancer and also undergoing the treatment for the same, the considerable effects of use of probiotics should be further investigated in order to get

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educated more about the mode of actions in activating the body's defense responses. According to the findings of a 2013 study by Zhang, Wang, and colleagues, Lactobacillus salivarius REN and its secretions have potent inhibitory effects on 4NQO-induced oral cancers, and these actions could be associated with cell proliferation suppression, cell death initiation, 4NQO metabolism, DNA protection from oxide damage and/or expression of COX-2 down regulation.[9]

L. plantarum can both upregulate and downregulate the PTEN and MAPK pathways, according to findings by Abbas Asoudeh Fard et al.2017. Based on these findings, this microbe appears to have a crucial role in preventing development of cancer in oral cavity. As a result, L. plantarum has been proposed as a candidate for cancer probiotic therapy.[12]

It was discovered that combining three probiotics (Enterococcus faecium, Bifidobacterium longum, and Lactobacillus lactis) improved patients' immunity and as a result, reduced the frequency of oral mucositis. The mechanism of action that is underlying, however, is unknown. Probiotics' apoptosis-inducing and anti-proliferative properties in cancer cells provide compelling evidence that they can be employed as a therapy for prevention of oral cancer. Lactobacillus salivarius REN was discovered to be related to a lower incidence of oral cancer in a quantitative synthesis.[6]

Anticancer therapy has greatly improved over the last 20 years, and new treatments are less harmful than older ones. Probiotics can be used to alter the oral microbiota of cancer patients in order to help the oral microbiome regain its balance and functionality after being damaged by treatment. It is possible to treat oral dysbiosis with oral probiotics without suffering any harmful effects. It is known that probiotics can help treat cancer completely.[6] Contrarily, probiotics raise the risk of opportunistic infections and antibiotic resistance in cancer patients with impaired immune systems. Probiotics have been proven to be an efficacious adjunct in the treatment of cancer in spite of the hazardous conditions. Probiotics can also be used in combination with anticancer drugs to assist people with oral cancer in maintaining and improving their oral health conditions both during and after treatment.[50]

References

[1] Vigneswaran, N., & Williams, M. D. Epidemiologic trends in head and neck cancer and aids in diagnosis. Oral and Maxillofacial Surgery Clinics of North America. (2014);26:123–141.

[2] Zendeboodi, Fatemeh & Khorshidian, Nasim & Mortazavian, Amir & Cruz, Adriano. Probiotic: conceptualization from a new approach. Current Opinion in Food Science.2020;32.

[3] Maria Carmen Collado, Miguel Gueimonde, Seppo Salminen, Probiotics in Adhesion of Pathogens: Mechanisms of Action. Bioactive Foods in Promoting Health,Academic Press. 2010;353-370

[4] Kumar, Manoj & Kumar, Ashok & Nagpal, Ravinder & Mohania, Dheeraj & Behare, Pradip & Verma, Vinod & Kumar, Pramod & Poddar, Dev & Aggarwal, P.K. & Henry, Jeya & Jain, Shalini & Yadav,

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

Hariom. Cancer-preventing attributes of probiotics: An update. International journal of food sciences and nutrition.2010; 61. 473-96.

[5] Singh D, Khan MA, Siddique HR. Therapeutic implications of probiotics in microbiota dysbiosis: A special reference to the liver and oral cancers. Life Sci. 2021 Nov 15;285:120008.

[6] Wan Mohd Kamaluddin WNF, Rismayuddin NAR, Ismail AF, Mohamad Aidid E, Othman N, Mohamad NAH, Arzmi MH. Probiotic inhibits oral carcinogenesis: A systematic review and meta-analysis. Arch Oral Biol. 2020 Oct;118:104855.

[7] Legesse Bedada T, Feto TK, Awoke KS, Garedew AD, Yifat FT, Birri DJ. Probiotics for cancer alternative prevention and treatment. Biomed Pharmacother. 2020 Sep;129:110409.

[8] Fernandes CF, Shahani KM. Anticarcinogenic and Immunological Properties of Dietary Lactobacilli. J Food Prot. 1990 Aug;53(8):704-710.

[9] Gadelle, D., P. Raibaud, and E. Sacquet. 1985. B-Glucuronidase activities of intestinal bacteria determined both in vitro and in vivo in gnotobiotic rats. Appl. Environ. Microbiol. 49:682-685.

[10] Dodds, K. L., and D. L. Collins-Thompson. 1984. Incidence of nitritedepleting lactic acid bacteria in cured meats and in starter cultures. J. Food Prot. 47:7-10.

[11] Dodds, K. L., and D. L. Collins-Thompson. 1985. Characteristics of nitrite reductase activity in Lactobacillus lactis TS4. Can. J. Microbiol.31:558-562.

[12] Goldin, B. R., and S. L. Gorbach. 1983. The effect of oral administration of Lactobacillus and antibiotics on intestinal bacterial activity and chemical induction of large bowel tumors. Dev. Ind. Microbiol.25:139-150.

[13] Goldin, B. R., L. Swenson, J. Dwyer, M. Sexton, and S. L. Gorbach. 1980. Effect of diet and Lactobacillus acidophilus supplements on human fecal bacterial enzymes. J. Natl. Cancer Inst. 64:255-261.

[14] Sinha, D. K. 1979. Development of a nonfermented acidophilus milk and testing its properties. Ph.D. Dissertation. The University of Nebraska-Lincoln.

[15] Fernandes, C. F., K. M. Shahani, and M. A. Amer. 1987. Therapeutic role of dietary lactobacilli and lactobacillic fermented dairy products.FEMS Microbiol. Rev. 46:343-356.

[16] Ayebo, A. D., K. M. Shahani, R. Dam, and B. A. Friend. 1982. Ion exchange separation of the antitumor component(s) of yogurt dialyzate. J. Dairy Sci. 65:2388-2390.

[17] Reddy, G. V., B. A. Friend, K. M. Shahani, and R. E. Farmer. 1983. Antitumor activity of yogurt components. J. Food Prot. 46:8-11.

[18] Lee, H. 1989. Effect of Lactobacillus acidophilus on colon carcinogenesis.Ph.D. Dissertation. The University of Nebraska-Lincoln.

[19] Friend, B. A., R. E. Farmer, and K. M. Shahani. 1982. Effect of feeding and intraperitoneal implantation of yogurt culture cells on Ehrlich ascites tumor. Milchwissenschaft 37:708-710.

[20] Kohwi, Y., K. Imai, Z. Tamura, and Y. Hashimoto. 1978. Antitumor effect of Bifidobacterium infantis in mice. Gann 69:613-618.

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

[21] Bogdanov, I. G., P. G. Dalev, A. I. Gurevich, M. N. Kolosov, V. P. Mal'Kova, L. A. Plemyannikova, and I. B. Sorokina. 1975. Antitumor glycopeptides from Lactobacillus bulgaricus cell wall. FEBS Lett.57:259-261.

[22] Hla, T., & Neilson, K. (1992). Human cyclooxygenase-2 cDNA. Proceedings of the National Academy of Sciences of the United States of America, 89, 7384–7388.

[23] Menter, D. G., Shilsky, R. L., & Dubois, R. N. Cyclooxygenase-2 and cancertreatment: Understanding the risk should be worth the reward. Clinical CancerResearch. (2010);16:1384–1390.

[24] Wang F, Jiang L, Liu AP, Guo XH, Ren FZ. Analysis of antigenotoxicity of Lactobacillus salivarius by high performance liquid chromatography. Chinese J Anal Chem 2008;36:740–4.

[25] Kanojia D, Vaidya MM. 4-nitroquinoline-1-oxide induced experimental oral carcinogenesis. Oral Oncol 2006;42:655–67.

[26] Zhang, M., Wang, F., Jiang, L., Liu, R., Zhang, L., Lei, X., et al. Lactobacillus salivarius REN inhibits rat oral cancer induced by 4-nitroquioline 1-oxide. Cancer Prevention Research. (2013);6:686–694

[27] Chen CC, Lin WC, Kong MS, Shi HN, Walker WA, Lin CY, et al. Oral inoculation of probiotics Lactobacillus acidophilus NCFM suppresses tumour growth both in segmental orthotopic colon cancer and extraintestinal tissue. Br J Nutr 2012;107:1623–34.

[28] Lan A, Bruneau A, Bensaada M, Philippe C, Bellaud P, Rabot S, et al. Increased induction of apoptosis by Propionibacterium freudenreichiiTL133 in colonic mucosal crypts of human microbiota-associated rats treated with 1,2-dimethylhydrazine. Br J Nutr 2008;100:1251–9.

[29] Foo NP, Ou Yang H, Chiu HH, Chan HY, Liao CC, Yu CK, et al. Probiotics prevent the development of 1,2-dimethylhydrazine (DMH)-induced colonic tumorigenesis through suppressed colonic mucosa cellular proliferation and increased stimulation of macrophages.J Agric Food Chem 2011;59:13337–45.

[30] Aghazadeh Z, Pouralibaba F, Yari Khosroushahi A. The prophylactic effect of Acetobacter syzygii probiotic species against squamous cell carcinoma. J Dent Res Dent Clin Dent Prospects. 2017 Fall;11(4):208-214.

[31] Kaur, K., Topchyan, P., Kozlowska, A. K., Ohanian, N., Chiang, J., Maung, P. O., et al. (2018). Super-charged NK cells inhibit growth and progression of stem-like/poorly differentiated oral tumors in vivo in humanized BLT mice; effect on tumor differentiation and response to chemotherapeutic drugs. Oncoimmunology, 7, 1–14.

[32] Hendler R, Zhang Y. Probiotics in the treatment of colorectal cancer. Medicines(Basel) 2018;5(3):101

[33] Asoudeh-Fard, A., Barzageri, A., Dehnad, A., Bastani, S., Golchin, A., &Omidi, Y. Lactobacillus plantarum induces apoptosis in oral cancer KB cells through upregulationof PTEN and downregulation of MAPK signalling pathways. BioImpacts. (2017);7:193–198.

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

[34] Morrison, D. K. MAP kinase pathways. Cold Spring Harbor Perspectives in Biology, (2012);4:a011254

[35] Chu, E. C., & Tarnawski, A. S. (2004). PTEN regulatory functions in tumor suppression and cell biology. Medical Science Monitor, 10, 235–242.

[36] Di Marzio L, Russo FP, D'Alo` S, et al. Apoptotic effects of selected strains of lactic acid bacteria on a human T leucemia cell line are associated with bacterial arginine deiminase and/ or sphingomyelinase activities. Nutr Cancer 2001;40:185–96.

[37] Riccia, D. N. D., Bizzini, F., Perilli, M. G., Polimeni, A., Trinchieri, V., Amicosante, G.,et al. Anti-inflammatory effects of Lactobacillus brevis (CD2) on periodontal disease. Oral Diseases. (2007);13:376–385.

[38] Sharma, A., Rath, G. K., Chaudhary, S. P., Thakar, A., Mohanti, B. K., & Bahadur, S. Lactobacillus brevis CD2 lozenges reduce radiation- and chemotherapy-induced mucositis in patients with head and neck cancer: A randomized double-blind placebo-controlled study. European Journal of Oral Cancer,. .(2011);48:875–881.

[39] Zhao, X.; Yi, R.; Qian, Y.; Park, K.Y. Lactobacillus plantarum YS-3 prevents activated carbon-induced constipation in mice. J. Med. Food **2018**, 21, 575–584.

[40] Zhang, Z.J.; Feng, X.; Jiang, J.; Xiao, P. Influence of Pachyman on biosynthesis level of mice serum IgA, IgG and IgM. Chin. J. Immunol. **2013**, 29, 1213–1215.

[41] Chen, S.C.; Zhu, K.;Wang, R.; Zhao, X. Preventive effect of polysaccharides from the large yellow croaker swim bladder on HCl/ethanol induced gastric injury in mice. Exp. Ther. Med. **2014**, 5, 316–322

[42] Zhang, Z.J.; Feng, X.; Jiang, J.; Xiao, P. Influence of Pachyman on biosynthesis level of mice serum IgA, IgG and IgM. Chin. J. Immunol. **2013**, 29, 1213–1215.

[43] Liu B, Zhang J, Yi R, Zhou X, Long X, Pan Y, Zhao X. Preventive Effect of Lactobacillus fermentum CQPC08 on 4-Nitroquineline-1-Oxide Induced Tongue Cancer in C57BL/6 Mice. Foods. 2019 Mar 11;8(3):93.

[44] Kim SJ, Kim JK, Lee DU, Kwak JH and Lee SM: Genipin protects lipopolysaccharide-induced apoptotic liver damage in D-galactosamine-sensitized mice. Eur J Pharmacol 635: 188-193, 2010. 3.

[45] Zhu H, Yin R, Han F, Guan J, Zhang X, Mao X, Zhao L, Li Q, Hou X and Bi K: Characterization of chemical constituents in Zhi-Zi-Da-Huang decoction by ultra high performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry. J Sep Sci 37: 3489-3496, 2014

[46] Gong G, Zheng Z, Liu H, Wang L, Diao J, Wang P and Zhao G: Purification and characterization of a β-glucosidase from aspergillus niger and its application in the hydrolysis of geniposide to genipin. J Microbiol Biotechnol 24: 788-794, 2014

[47] Koo HJ, Song YS, Kim HJ, Lee YH, Hong SM, Kim SJ, Kim BC, Jin C, Lim CJ and Park EH: Antiinflammatory effects of genipin, an active principle of gardenia. Eur J Pharmacol 495: 201-208, 2004.

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

[48] Cho HI, Kim SJ, Choi JW and Lee SM: Genipin alleviates sepsis-induced liver injury by restoring autophagy. Br J Pharmacol 173: 980-991, 2016.

[49] Cheng Z, Xu H, Wang X, Liu Z. Lactobacillus raises in vitro anticancer effect of geniposide in HSC-3 human oral squamous cell carcinoma cells. Exp Ther Med. 2017 Nov;14(5):4586-4594.

[50] Mishra S, Rath S, Mohanty N. Probiotics-A complete oral healthcare package. J Integr Med. 2020;18(6):462-469.