

A Review on Recently Explored Functional Aspects of Probiotics

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Received: 3.09.2020 | Revised: 11.10.2020 | Accepted: 14.10.2020

ABSTRACT

Probiotics are the widely explored dietary supplements for a variety of benefits. The most common and known functions include protective effects against gastrointestinal disorders such as irritable bowel syndrome, diarrhea, ulcerative colitis and many others. Recently, scientists have been very keen on exploring the multiple other aspects of probiotic functions. A few of them are, their ability to improve mental health, protection against neurodegenerative disorders, the ability to reduce the symptoms associated with arthritis and most important of all the potential of probiotics to work as anticancer agents. Another major function of probiotics is their ability to detoxify the harmful contaminants in the atmosphere such as heavy metals including lead, cadmium. Studies involving the experiments conducted to explore the functions of probiotics have clearly emphasized their exceptional potential to be used as therapeutic agents in various health conditions. Some of the recent studies have indicated towards their ability to be used as antiviral agents. This can be a very useful aspect to be investigated as the COVID-19 pandemic situation demands exploration of probiotics, that can be used widely even amongst the healthy subjects as immunity boosters.

Keywords: Probiotics, Antidepressants, Neuroprotectants, Anticancer, Bioremediation.

INTRODUCTION

Probiotics are very well established functional foods, whose consumption can be traced back to the early years of human civilization. The fermented foods such as cheese, wine, bread and beer are a rich source of probiotic microorganisms. (Ozen & Dinleyici, 2015). The human gut microbiota contains a repertoire of microorganisms, mostly in the small intestine and colon (Sender et al., 2016). Probiotic microorganisms form a major population of the gut microbiota that plays a

key function in regulating metabolism and conferring health benefits (Butel, 2014). The word “probiotic” is of Greek origin; that means “for life”, was coined by Ferdinand Vergin in 1954. The currently accepted definition of probiotics was formulated by WHO and FAO in 2002 that states that probiotics are “live strains of strictly selected microorganisms which, when administered in adequate amounts, confer a health benefit on the host” (FAO, 2002).

Cite this article: Mishra, V., Sharma, R., Jaiswal, M., Subramani, S. K., Yadav, A., Rana, S., & Bisen, P. S. (2020). A Review on Recently Explored Functional Aspects of Probiotics, *Ind. J. Pure App. Biosci.* 8(5), 213-226. doi: <http://dx.doi.org/10.18782/2582-2845.8359>

The benefits of probiotics are very well explored in maintenance of gastrointestinal health in adults and children. In adults, the infections that can be reduced by probiotic consumption are acute infectious and antibiotic associated diarrhea, pouchitis, *Clostridium difficile* associated diarrhoea and helicobacter pylori infection. In children the probiotics are known to cure inflammatory bowel disease, antibiotic associated diarrhea, acute gastroenteritis, colic and other functional gastrointestinal diseases (Barnes, D., & Yeh, A. M., 2015; Sebastian Dominyo, J. J., 2017; & Verna, E. C., 2010). The probiotics especially bacteria of *Lactobacillus* species have been studied widely for the large number of benefits they possess and the market potential they exhibit has drawn attention of industries (Sharma et al., 2012; & Jaiswal et al., 2020). Owing to the spectrum of benefits exhibited by probiotics, they have been evaluated recently for different other functions since they seem to be promising therapeutic tools (Raghuwanshi et al., 2018).

Probiotics as neuroprotectants

The probiotics have recently been widely explored for their neuroprotective effects and their ability to modify progression of aging (Lye et al., 2018). In patients with Alzheimer's disease, a study was carried out where the patients were randomly divided into two groups, and were treated with a combination of *L. acidophilus*, *L. casei*, *B. bifidum* and *L. fermentum* (2×10^9 CFU/g each) for 12 weeks. Positive effects of the probiotic combination was observed on the cognitive function and metabolic status of the patients (Akbari et al., 2016). Probiotics consumption has the ability to prevent cognitive impairment associated with Alzheimer's disease (Boon W et al., 2018). The TLR ligands that are derived from probiotics have the ability to suppress inflammation by the production of cytokines that have anti-inflammatory properties. The probiotics restore the normal gut microflora, thereby maintaining a healthy gut-brain axis (Caputi & Giron, 2018). The probiotic strains *L. salivarius* LS01 and *L. acidophilus* have the ability to reduce pro-inflammatory cytokines

significantly and increase the concentration of anti-inflammatory cytokines. The probiotics also reduced oxidative stress and overgrowth of pathogenic bacteria (Magistrelli et al., 2019).

Role of probiotics in combating stress and depression

Stress has been associated with various health problems. It has been studied for its ability to affect various aspects of human health. Extreme levels of stress can lead to the suppression of the immune system that can lead to malignancy. Stress has also been reported to cause cardiovascular complication such as myocardial infarction (Yaribeygi et al., 2017). The benefits of probiotics as anti-stress agents have been reported extensively in various subjects. In athletes performance related mental stress has been found to be a root cause of weak immunity and disturbances in the gastric function. A combination of *Lactobacillus* and *Bifidobacterium* strains has proved to be useful in controlling a range of stress related conditions in athletes such as gastrointestinal disorders (Blum-Menzes et al., 2019).

Probiotics have a very strong influence in improving the working memory and cognition in individuals suffering from stress (Papalini et al., 2019). The consumption of probiotics has a positive effect on a person's mood and sleep ability. From a study conducted by Marotta et al., in 2019, it was observed that there were improvements in different areas of mood profile like fatigue, anger, sadness in individuals that were healthy and consumed probiotics (Marotta et al., 2019). Another set of clinical trials have emphasised the importance of probiotics in relieving symptoms associated with psychological stress (Ning Zhang et al., 2019). The gut-brain axis plays an important role in the maintenance of overall well-being of an individual. The gut microbiota influences the two way communication between the nervous system of the gut and the central nervous system that ultimately links centers of brain responsible for emotions and cognition to the peripheral intestinal functions (Carabotti et al.,

2015). The probiotics have also been found to have antixylotic effects in patients suffering from depression. A combination of *Lactobacillus* and *Bifidobacterium* have significant protective effects against the symptoms of depression. (Nikolova V et al., 2019).

Probiotics against skin problems:

The skin works as a first line of defense against infections. Skin damage generally occurs due to several factors such as surgery. The antibiotics are generally used to prevent the infections that are caused by bacteria such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae* etc.

The skin microflora is interestingly responsible for maintaining the homeostasis by preventing the inflammation and promoting the cells of the immune system that work against infection. It has been studied that the pathogenic organisms such as *S. aureus* or *P. aeruginosa* result in negative balance of the microbiota present on the skin. The topical probiotics exert beneficial effects against the immune dysregulation that has been related to atopic dermatitis (AD). The treatment involving topical probiotics leads to an increase in ceramides of skin, improvement in pruritus, erythema and scaling. It also decreases the concentration of pathogenic bacteria *S. aureus*. *Propionibacterium* is the major pathogen that is responsible for acne. A combination of probiotic bacteria such as *L. acidophilus*, *L. delbrueckii* and *B. bifidum* was found to decrease the number of lesions that were associated with acne. These probiotics also led to an improvement in functioning of skin barrier. The treatment with topical probiotics did not show any side effects (Knacksted et al., 2019). There are several immunomodulatory functions of topical probiotics that have shown to reduce the severity of symptoms associated with atopic dermatitis. The probiotics inhibit the response mediated by T-helper cell type-2 (Th-2). The probiotics reduce the inflammation caused by inflammation inducing cytokines such as IL-4, IL-6 and tumor necrosis factor- α . It has been concluded

from various randomized controlled trials that the administration of probiotics for at least 8 weeks reduces the severity scoring of symptoms linked to atopic dermatitis (Rusu et al., 2019).

Skin is the largest organ of the body that acts as an effective barrier against the harmful substances and microorganisms. (Sivamaruthi et al., 2018). The probiotic supplementations have been explored widely for their ability to treat skin diseases such as atopic dermatitis, rosacea and acne (Knackstedt et al., 2020). Atopic dermatitis is a skin disease that is characterised by inflammation and dryness of the skin, also cutaneous lesions that are eczematous. This disease is generally chronic in nature, manifested by pruritic papules with progression towards lichenification. The probiotic bacteria *Lactobacilli* and *Bifidobacteria* when present in the gut microbiome in suitable concentrations, have the ability to produce bioactive isomers of conjugated linoleic acid. These isomers possess immune modulating properties that reduce proinflammatory cytokines. Probiotics such as *Bifidobacterium bifidum* modulate microflora of the intestine thereby reducing manifestation of allergic phenomenon. The most common inhabitant of healthy skin is *Staphylococcus epidermidis* and *Staphylococcus cohnii* have proved to possess protective effects in children against atopic dermatitis. A randomized, double blind, placebo-controlled trial where a combination of *Bifidobacterium lactis* CECT 8145, *Bifidobacterium longum* CECT 7347 and *Lactobacillus casei* when administered to 50 children was helpful in reducing SCORAD index in the experimental subjects. The probiotic supplementation in adults have also been very helpful in reducing the severity of atopic dermatitis. A combination of the probiotics viz., *Lactobacillus paracasei*, *Lactobacillus acidophilus* and *Bifidobacterium animalis subsp. lactis* for 8 weeks decreased the SCORAD index in adults (Rusu et al., 2019). Supplementaton of *Lactobacillus lactis* in combination with *Bifidobacterium bifidum*,

1 X 10⁹ CFU of each strain per day to pregnant women for 6 weeks before delivery and 12 months continued for infants after birth prevented the eczema incidence in infants for upto 2 years. The supplementation of *Bifidoacterium animalis* subsp. lactis LKM512 (6 X 10⁹ CFU) in patients suffering from atopic dermatitis in combination with prebiotics viz., dextrin, glucose, inulin, silicon dioxide mixed with skim milk, reduced the levels of kynurenic acid and itching in patients which makes LKM512, a potent anti-pruritus therapeutic agent (Sivamaruthi et al., 2018). The probiotic supplementation also helps in reducing transepidermal water loss (TEWL). *Lactobacillus paracasei* NCC241 supplementation for 2 months decreased sensitivity of the skin and TEWL, this effect was observed due to an increase in the levels of transforming growth factor- beta (TGF-β), a cytokine that exerts effect on epidermal barrier integrity (Alesa et al., 2019). In a case where conventional treatment with methotrexate, steroids and dapsone was not effective in treating pustular psoriasis, supplementation of *Lactobacillus sporogenes*, 3 times a day for 4 weeks, cured the disease completely. A study conducted in BALB-c mice helped in concluding that the treatment of probiotic strain *Lactobacillus pentosus* GMNL-77 decreased the mRNA levels of cytokines that are proinflammatory in nature such as tumor necrosis factor- alpha IL-23/IL-17A axis associated cytokines, and interleukin (IL-6). The reduction in the pro-inflammatory cytokines indicates towards reduction in the severity of psoriasis (Chen et al., 2017). In a recent clinical trial of 12-weeks that was randomized, double-blind and placebo-controlled, the aim was to analyse the efficiency of a probiotic mixture in reducing the severity of psoriasis. The probiotic mixture consisted of *Bifidobacterium longum* CECT 7347, *Bifidobacterium lactis* CECT 8145 and *Lactobacillus rhamnosus* CECT 8361 containing a total of 1X10⁹ colony-forming units (CFU) per capsule, formulated on maltodextrin. After 12-weeks of probiotic

administration there was a deduction in Psoriasis Area and Severity Index in 66.7% of patients in the probiotic group (Vicente et al., 2019). Extracts from probiotic organisms such as an ethanol extract (SEL 001) from *Lactobacillus sakei* was evaluated for its ability to cure imiquimod psoriasis in the mouse model. The treatment of imiquimod caused histopathological changes in the dorsal ear skin tissues. There was an increase in the number of inflammatory cells in the epithelial tissues due to the imiquimod treatment. There was also an increase in the expression of genes of inflammatory cytokines, as observed from Real-Time PCR. However, the treatment of SEL 001 inhibited the changes associated with imiquimod induced psoriasis. There was a decrease in the levels of gene expression of interleukins viz., IL-1A, IL-19 and IL-23 (Rather et al., 2018). The probiotic treatment has the ability to increase the levels of interleukin in acne vulgaris that shows potential in the use of oral probiotic as a therapeutic agent for acne. It is also an effective therapy because the side effects are tolerable and safe. This was evident from a study conducted in 33 subjects where the oral probiotic mixture containing rice starch, maltodextrin, *Bifidobacterium lactis*, *Lactobacillus acidophilus*, *Lactobacillus salivarius*, *Lactobacillus casei* and *Lactococcus lactis* were administered to the subjects under study (Total bacterial cell count >10⁸ colony forming units) (Rahmayani, 2019). The probiotic microorganisms that have been found to be potentially beneficial for the treatment of acne, as evident from *in vitro* and *in vivo* test are following: *Staphylococcus epidermidis*, *Streptococcus salivarius*, *Lactococcus species HY449*, *Streptococcus thermophilus*, *Lactobacillus paracasei*, *Enterococcus faecalis*, and *Lactobacillus plantarum*. *Streptococcus thermophilus* has been very well established for its activity against gastrointestinal disorders and different other functions such as protective effects against pathogenic organisms and cholesterol assimilation (Sharma et al., 2014). All the

mentioned microorganisms possess inhibitory actions against *Cutibacterium acnes* (*C. acnes*, formerly called *Propionibacterium acnes*) (Lee et al., 2019). Several prebiotics have been found useful in the treatment of skin diseases. Fructo-oligosaccharides have been found to be helpful in the treatment of allergic contact dermatitis. Konjac glucomannan hydrolysates (GMH) have been found to be useful in the inhibition of *Acne vulgaris* and *P. acnes*, the causative bacteria of acne and in turn promote the growth of lactic acid bacteria. The galactooligosaccharides are helpful in the treatment of photoaging as they prevent transepidermal water loss (TEWL), reduction in the erythema of skin, increase in the mRNA expression of CD44, Tissue inhibitor of metalloproteinases 1 and collagen 1. The oligosaccharides also have beneficial role to play in the treatment of photoaging, as they modulate the expression of elastase-type proteases through elastin receptors (Lolou & Panayiotidis, 2019).

Probiotics against rheumatoid arthritis

From a study conducted in rats, the ameliorating effects of probiotics were analysed. The probiotics pretreatment reduced the interleukin-IP serum levels, edema, hyperalgesia and activity of p38MAPK pathway. The probiotic administration increased the expression of μ -opioid receptor (MOR) expression during the chronic stages of arthritis induced by Complete Freund's Adjuvant (CFA) (Shadnoush et al., 2018). A review on rheumatoid arthritis describes the ability of disease modifying antirheumatic drugs (DMARDs) in modulating the microbiota of host. These drugs reduce the levels of healthy microbiota as they possess antibiotic properties. There has been an increased interest in patients suffering from arthritis, to consume dietary supplements such as probiotics, to restore normal flora of beneficial microorganisms (Bodhke et al., 2019). The functions of probiotics are not just limited to protection against rheumatoid arthritis but they also extend to other autoimmune disorders such as systemic lupus erythematosus

(SCE), multiple sclerosis (MS) (Liu et al., 2018).

Probiotics functions in promoting sound mental health

The beneficial effects of prebiotics and probiotics have recently been widely explored for different aspects of mental health (Ansari et al., 2020). A possibility of advantages of probiotics and prebiotics supplementation has been reviewed by scientists where the data from clinical trials showed that the administration of prebiotics and probiotics have been effective in alleviating the gastrointestinal disorder symptoms such as dysbiosis, which in turn are associated with autism spectrum disorders. Recently a correlation has been established between the gut and brain via the gut brain axis. Hence, the microbiota of the gut has direct effect on behavioural symptoms (Ng et al., 2019). In a recent study where dietary approaches have been explored for the management of autism spectrum disorders, it has been emphasised that a suitable dietary plan including supplementation of vitamins, minerals, hormones, pre- and probiotics is helpful in managing symptoms of gastrointestinal disorders along with the behavioural symptoms associated with it (Hartman & Patel, 2020). In another study the consumption of gluten-free/ casein free diet has proved to be beneficial in controlling behavioural disorders associated with autism. In addition to that a supplementation of fermentable foods, probiotics, curcumin and camel milk can play an important role in relieving the subjects from the behavioural disorders associated with autism (Cekici & Sanlier, 2019). In a similar study it was found that the ketogenic and gluten-free diet is very effective in reducing the symptoms of autism (Goggou & Kolios, 2018). In a study where rats were exposed to stress, there was a decrease in the corticosterone levels and the parameters of spatial memory were also altered, such as the increased time and distance required to find the hidden platform in Morris water maze. However, the pre and post stress treatment of probiotics reduced the anxiety-like behaviour

and thus reduced the time and distance required by rats to find the hidden maize, which was close to the behaviour of the rats grouped as control. There was also an increase of 50% in the concentration of corticosterone in the stressed rats. However the pre and post treatment of probiotics restored the corticosterone close to normal (Hadizadeh et al., 2019).

Probiotics as anticancer agents

It is known that cancer is on the second position when the causes of worldwide mortality are listed. Scientists are in a constant search for novel therapeutics against this disease. Various therapeutic approaches lead to an increase in gastrointestinal toxicity such as radiotherapy, chemotherapy. Gut microbiota plays a very important role in maintaining the homeostasis in an individual. Hence, clinical studies where cancer patients receiving therapy, had been administered with probiotic supplements such as *Lactobacillus rhamnosus* GG (LGG), showed enhanced efficiency in reducing side effects that were life threatening or gut related (Vivarelli et al., 2019). The benefits of probiotics are evidence based in treated antibiotic associated diarrhea as well as *Clostridium difficile*-associated diarrhea. The respiratory tract infections have also been studied to be treated by probiotic supplementation (Rondanelli et al., 2017). Supplementation with probiotic bacteria helps in restoring the gut microbiota in the patients receiving cancer immunotherapy whose normal microflora is possibly depleted by the antibiotic administration (Zitvogel et al., 2018). Impairment of the immune system and dysbiosis are the side effects that result from immunotherapy in cancer patients that involves the administration of broad spectrum antibiotics and immunosuppressants. Several studies have demonstrated the importance of gut microbiota in maintaining an efficient immune system (Gopalkrishnan et al., 2018). There are increasing evidences where it has been suggested that an abundance of gut microbiota regulates the response towards anticancer immunotherapy in intestinal as well

as extra-intestinal tissues. A review of findings has emphasised the administration of specific strains of probiotic bacteria to promote homeostasis of the individual and to promote effective implementation of immunotherapy in the individuals under treatment (Huo et al., 2019). The probiotic bacteria such as *Lactobacillus acidophilus* and *Bifidobacterium bifidum* have been found to maintain optimum pH and bile acid profile that has been found to be an effective tool in prevention of cancer. The putrefying bacteria present in the human gut produces various harmful, carcinogenic compounds with the use of gut enzymes such as nitroreductase. However, the consumption of fermented milk rich in *Lactobacillus acidophilus* protects against the toxic effects of putrefying bacteria such as *Escherichia coli* and *Clostridium perfringens*. The anticancer properties of *Lactobacillus* and *Bifidobacillus* strains have been explored. These probiotic bacteria bind and degrade potential carcinogens. Consumption of *Lactobacillus* strains by human subjects reduced the excretion of heterocyclic aromatic amines in urine and faeces which helped in altering the mutagenic effect of cooked meat rich diet. The probiotic microorganisms have also been found to produce short chain fatty acids by the fermentation of prebiotics. These molecules apart from being an energy source, act as signalling molecules that help in the regulation of cell proliferation, cell death and immune system (Gorska et al., 2019). Two strains of *Streptococcus thermophilus* that were isolated from dairy environment in Italy were isolated and evaluated for their ability to exhibit probiotic potential and anticancer properties. Results showed that both the strains of *S. thermophilus* possessed in vitro probiotic properties, also anticancer properties and exhibited the ability to produce folate (Tarrah et al., 2018). *Lactobacillus plantarum* has been found to be effective in treatment of oral cancer by the up regulation of PTEN pathway and down regulation of MAPK pathways, respectively. Thus they can serve as potential probiotic in cancer therapy (Asaudeh- Farah et

al., 2017). Another important function of *Lactobacillus plantarum* strain 06CC2 was evaluated *in vitro* in Caco 2 colorectal cancer cells where it induces the JNK/p38 MAP pathway and the endoplasmic reticulum stress that ultimately causes apoptosis of the cancer cells (Hiraishi et al., 2019). The common side effect of radiotherapy and chemotherapy is mucositis. A combination of different probiotic bacteria such as *Saccharomyces boulardii*, *Bifidobacterium longum*, *Bifidobacterium breve*, *Lactobacillus acidophilus* and *Bifidobacterium infantis* has been found to be effective in the amelioration of mucositis (Pico- Monllor & Mingot-Ascencao, 2019). A pretreatment of probiotics in a group of patients who received the treatment of radiotherapy and chemotherapy, showed positive results with respect to the restoration of normal microbial flora in the intestine. Similarly, the treatment with probiotics after the chemotherapy and radiotherapy treatment restored the microflora in the intestine, close to that of healthy people. The probiotic combination included *Enterococcus faecium*, *Bifidobacterium longum* and *Lactobacillus lactis*. Hence, the probiotic treatment was very helpful in reducing the severity of oral mucositis associated with cancer treatment (Jiang et al., 2018). Several probiotics, singly and in combination have reduced the severity of breast cancer by being cytotoxic such towards cancerous cells such as *Enterococcus lactis* IW5, *Lactococcus lactis* NK34, *Lactococcus lactis* KC24, *Enterococcus faecalis* and *Staphylococcus hominis*, *Lactobacillus crispatus* and *Lactobacillus rhamnosus*, a combination of *Lactobacillus acidophilus*, *Lactobacillus casei* and *Lactococcus lactis* (Mendoza L., 2019). The probiotic bacteria *Lactobacillus casei shirota* has been evaluated for its ability to reduce the incidence of breast cancer. The frequency of breast cancer incidence has been reported to be lower due to consumption of fermented dairy products such as yoghurt (Ranjbar et al., 2019). Different probiotic bacteria exhibit different mechanisms of action when it comes to work as anti-breast cancer agent, as explored

through various studies, where *Lactobacillus crispatus* and *Lactobacillus acidophilus* have been found to decrease the transcription of different cancer antigens. Cell death by apoptosis is a mode of action exhibited by *Bacillus subtilis* CSY 191 that produces molecule surfactin causes down regulation of ERK and PI3K/Akt that ultimately causes hindrance of growth. Probiotics such as *Lactobacillus casei* have exhibited natural killer cell activity. *Lactobacillus casei shirota* stops the damage to DNA caused in rat model by exposure to mutagenic compound (N-methyl-N-nitro, N-nitrosoguanidine). *Lactobacillus casei* along with soy milk has proved to prevent breast cancer prevention in rats that were exposed to carcinogenic compounds (Malik et al., 2018).

Probiotics in Bioremediation:

Bioremediation is the process of removal of environmental contaminants by the use of microorganisms. It is a beneficial process that removes bioaccumulants from the living organisms (Albert et al., 2017). This function of bioremediation is exhibited by probiotic microorganisms also (Helmy et al., 2019). The probiotics have the property of reducing the concentration of organochlorine pesticides in the fermented beverages that were prepared using cow and goat milk during cold storage, significantly over a period of 14 days, the maximum decrease in concentration was 20.7%. A mixture of monocultures i.e. *L.b. acidophilus* LA- 5 and *Bifidobacterium* BB-12 was very effective in reducing the concentration of pesticides (Witczakwicz- & Mituniewicz-Malek, 2019). Endocrine disruptors are the commonly found compounds that pollute the environment. They generally are components of food packaging and various other food products. They have the ability to affect the functions of the endocrine system adversely altering the hormonal functions in human and animals. The major endocrine disruptors are pesticides, polybrominated diphenyl ethers (PDEs), polychlorinated biphenyls (PCBs), heavy metals. There are several studies where the supplementation of probiotics especially

Lactobacillus have ameliorated the genotoxic effects of endocrine disruptors. Chandel et al., 2019 have demonstrated the anticancer and antigenotoxic potential of *Lactobacillus* probiotic strains against colorectal cancer from enhancement of faecal lactic acid bacteria, reduced faecal pH, reduced aberrant crypt foci, enhanced flora of lactic acid bacteria in the faeces and also an alteration in faecal enzymes (β -glucosidase, nitroreductase, β -glucuronidase). With the observed alteration it was concluded that LAB strains viz. *L.rhamnosus*, *L. plantarum* and *Pediococcus pentosaceus* have the ability to modulate microbiota of the gut so ultimately colon's histoarchitecture is restored (Chandel et al., 2019). Yuan Xet al., 2019 have emphasised the importance of gut microbiota in pesticide induced toxicity, as studied in experimental models i.e. mice. They have explained that the gut microbiota is affected by pesticides, which in turn may be a cause of their toxic actions. There are also evidences where isolates from probiotic organisms have shown to possess cytotoxic and antigenotoxic potential against cells of colon cancer. The SOS Chromo Test Conducted on the CaCO-29 and HT-29 cells using cell free supernatants (CFS), dissolved in different solvents. It was observed that CFS dissolved in carboxymethyl cellulose showed 80-90% cytotoxicity. The extracts were prepared from *L.rhamnosus* MD 14 (Sharma et al., 2020). Lead is a heavy metal that has a tendency to bio-accumulate and can enter the biological system via occupational or environmental exposure. It can affect different vital organs and can lead to associated disorders which include reproductive dysfunctions, haematological, renal, hepatic, pulmonary, cardiovascular, nervous and musculoskeletal. Some studies have explored the potential of probiotic organisms in reducing the toxic effects of lead (Bhattacharya, 2019).

Giri et al. (2018), have demonstrated the protective effects of *L. reuteri* p16 in *Cyprinus carpio*, thereby paving way for the toxicity reduction in aquatic organisms. The supplementation of *L. reuteri* P16 in diet

improved the growth performance, immune system response and reduction in lead accumulation in tissues of the experimental subjects. It also protected the tissues of *C. carpio* against oxidative stress (Giri et al., 2018). In another study, the administration of probiotic *Lactobacillus plantarum* CCFM 866 along with dietary supplements such as vitamin C, calcium carbonate, grape seed extract, zinc acetate and tea polyphenols in another formulation significantly reduced bioaccumulation in mice tissues. The supplementation also protected the antioxidant enzymes such as superoxide dismutase and reduced the levels of malondialdehyde in tissues and blood of mice indicating protection against oxidative stress. These supplements do not exert any side effects as reported from the study (Zhai et al., 2018). Various species of *Bacillus* have the ability to detoxify toxic heavy metals such as lead, cadmium, zinc and copper as evident from the studies. *Bacillus licheniformis*, *Bacillus cereus*, *Bacillus subtilis*, *Bacillus amyloliquefaciens* have been studied to show protective effects against the toxic effects of heavy metals especially lead and cadmium. Different other strains of *Bacillus* are effective against heavy metals are *Bacillus carotarum*, *Bacillus lentus*, *Bacillus thuriengiensis*, *Bacillus sphaericus*, *Bacillus pumilus* and *Bacillus megaterium* (Goyal et al., 2019). The *Bacillus* species BpChIAY was studied for its ability to bio accumulate heavy metals as compared to *Bacillus thuringensis* under different concentrations. It was concluded that BpChIAY was a better metal absorber as compared to *Bacillus thuriengiensis* (Musawi et al., 2019). *Bacillus subtilis* has been studied for its effectiveness to reduce oxidative stress caused by sodium arsenite in normal human keratinocytes. The pretreatment of *Bacillus subtilis* spores in keratinocytes caused activation of genes involved in stress response which resulted in protection against injury caused by sodium arsenite (Petruk et al., 2018). The food based strains of *Lactobacillus plantarum* and yeasts were analysed for their probiotic properties that included survival in gastric conditions

such as tolerance to gastric juice (pH = 2.0), small intestine juice (pH = 8.0), that contained pancreatin (1 mg/ml) and bile extract (0.5%). The selected strains tolerated the acid and bile. The probiotic strains also exhibited the protective effects against the genotoxin 4-nitroquinoline-1-oxide (4-NQO) this property was analysed using SOS- Chromo test (Prete et al., 2017). This in vivo study helped in analysing the potential of the selected strains of *L. rhamnosus* and yeast to work efficiently *in vivo*, hence these probiotics can be safely ingested as a part of diet. A lesser explored probiotic *Pedococcus pentosaceus* has been studied to combat heavy metal toxicity. The bacteria's probiotic property was evident from its ability to survive in the pH range of 3-9, bile salt range of 0.15-0.5%. These bacteria were resistant against antibiotic clindamycin, ampicillin and benzympenicillin. The bacteria *Pedococcus pentosaceus* showed significantly high MIC (1800 & 150 ppm) for lead and cadmium respectively. These beneficial effects of *Pedococcus pentosaceus* indicate towards its use as an agent against bioremediation in fish ponds, where frequent contamination of heavy metals occurs (Jaafar, 2020).

Potential role of probiotics in COVID-19 treatment

Probiotics have shown to reduce the severity of respiratory disorders, as well as gastrointestinal disorders. The prominent symptom of COVID-19 infection is respiratory tract infection and gastrointestinal disorder, the consumption of probiotics can be a part of preventive medicine. The probiotic strains that possess these functions are *Lactobacillus casei*, DN-114001, *Lactobacillus rhamnosus* GG, *Lactobacillus gasseri* PA 16/8. These probiotics can be considered for clinical trials to prove their efficacy against COVID-19 (Baud et al., 2020). Scientists have suggested that more targeted approach is required so that the gut microbioata can be altered with the help of probiotics in order to promote immunity against COVID-19 (Mak et al., 2020). Infusino et al., have reviewed the ability of different probiotics in immunomodulatory functions, thereby

emphasizing their prospects for the use as treatment against COVID-19. But at the same time they have mentioned the necessity of clinical trials (Infusino et al., 2020).

CONCLUSION

This review clearly explains the huge potential that probiotics possess to be used as multifunctional therapeutics. More studies and clinical trials in near future, especially emphasizing their antiviral properties, can prove their beneficial effects and make them widely accepted as health supplements amongst consumers.

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