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# Beneficial Properties of Probiotics

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**Abstrak:** Probiotik ialah mikroorganisma hidup yang boleh didapati dalam makanan fermentasi dan susu kultur, dan digunakan secara meluas dalam penyediaan makanan bayi. Probiotik dikenali sebagai "bakteria baik" yang memiliki pelbagai manfaat untuk kesihatan seperti pencegahan penyakit usus, peningkatan sistem imun, intoleransi laktosa dan keseimbangan mikrob usus, menunjukkan kesan antihiperkolesterolemik dan antihipertensi, meredakan gangguan menopaus, dan mengurangkan cirit-birit pengembara. Kajian baru-baru ini juga telah memberi tumpuan kepada kegunaan probiotik dalam merawati penyakit kulit dan mulut. Di samping itu, modulasi paksi gut-otak dengan probiotik telah dicadangkan sebagai penyelesaian terapeutik baru bagi gejala kebimbangan dan kemurungan. Oleh itu, kajian ini membincangkan mengenai produk-produk semasa yang mengandungi probiotik di Malaysia, kriteria pemilihan probiotik, dan bukti-bukti yang diperolehi daripada kajian lepas tentang bagaimana probiotik telah digunakan untuk mencegah gangguan usus melalui peningkatan sistem imun, bertindak sebagai faktor antihiperkolesterolemik, meningkatkan kesihatan mulut dan kulit, dan berperanan sebagai ejen anti-kebimbangan dan anti-kemurungan.

**Kata kunci:** Probiotik, Hiperkolesterolemik, Stres, Oral, Derma

**Abstract:** Probiotics are live microorganisms that can be found in fermented foods and cultured milk, and are widely used for the preparation of infant food. They are well-known as "health friendly bacteria", which exhibit various health beneficial properties such as prevention of bowel diseases, improving the immune system, for lactose intolerance and intestinal microbial balance, exhibiting antihypercholesterolemic and antihypertensive effects, alleviation of postmenopausal disorders, and reducing traveller's diarrhoea. Recent studies have also been focused on their uses in treating skin and oral diseases. In addition to that, modulation of the gut-brain by probiotics has been suggested as a novel therapeutic solution for anxiety and depression. Thus, this review discusses on the current probiotics-based products in Malaysia, criteria for selection of probiotics, and evidences

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obtained from past studies on how probiotics have been used in preventing intestinal disorders via improving the immune system, acting as an antihypercholesterolemic factor, improving oral and dermal health, and performing as anti-anxiety and anti-depressive agents.

**Keywords:** Probiotic, Hypocholesterolemic, Stress, Oral, Derma

## INTRODUCTION

Probiotics are live microorganisms which upon ingestion in sufficient concentrations can exert health benefits to the host. This definition of probiotics was derived in 2001 by the United Nations Food and Agriculture Organization (FAO) and the World Health Organization (WHO), and has been the term of reference for science and regulation thereafter (FAO/WHO 2002). Demand for food containing probiotics are expanding globally due to the continuous generation of research evidence indicating their potential health benefits to consumers. This growing market has pulled in the probiotics research into the Malaysian mainstream in line with government policies promoting healthly living styles and related products are being marketed as functional food products. Functional food products resemble conventional food in terms of appearance but are composed of bioactive compounds that may offer physiological health benefits beyond nutritive functions (Emms & Sia 2011; Arora *et al.* 2013). Food processing companies that are widely involved in the manufacturing of probiotics or cultured drinks in Malaysia are Yakult (M) Sdn. Bhd., Nestlé Malaysia, Malaysia Milk Sdn. Bhd., and Mamee-Double Decker (M) Berhad.

Hundreds of different bacteria species are the natural and predominant constituents of intestinal microbiota. Among the numerous intestinal microbes, those anticipated to exhibit potential health benefits to the host through modulation of the intestinal microbiota are commonly selected as probiotics. Species belonging to the genera *Lactobacillus* and *Bifidobacterium* have been reported to be the beneficial probiotic bacterial strains. The representative species include *L. acidophilus*, *L. casei*, *L. plantarum*, *B. lactis, B. longum,* and *B. bifidum* (Kailasapathy & Chin 2000; Ishibashi & Yamazaki 2001). Some of the major health benefits attributed to probiotics include improvement of gastrointestinal microflora, enhancement of immune system, reduction of serum cholesterol, cancer prevention, treatment of irritable bowel-associated diarrhoeas, antihypertensive effects as well as improvement of lactose metabolism (Saarela *et al*. 2000; Nagpal *et al*. 2012). This article reviews on the past studies involving the use of probiotics in strengthening the immune system, prevention of bowel diseases, modulation of hypocholesterolemic effect as well as promoting dermal and oral health. Besides that, potential uses of probiotics for the management of anxiety and depression as well as boosting dermal and oral health are also discussed.

### Current Probiotics-based Products in the Malaysian Market

Mostly probiotics products in Malaysia are marketed in the form of fermented milk and yoghurt (Ting & DeCosta 2009). However, in recent years, the probiotics products from non-dairy based sources are gaining attention due to the ongoing trend of vegetarianism and also to meet the demands of those who are lactose intolerant (Vasudha & Mishra 2013). The following examples represent some of the dairy based-products with certain types of probiotics that can be found currently in the Malaysian market. Nestlé Bliss, marketed by Nestlé Malaysia, is made up from real fruit juices added with live cultures of *Streptococcus thermophillus*, *B. lactis,* and *L. acidophilus* (as on Feb 22, 2015, http://www.nestle.com.my/brands/chilled_dairy/nestle_bliss). Vitagen is a cultured milk drink manufactured by Malaysia Milk Sdn. Bhd. and is composed of live probiotics such as *L. acidophilus* and *L. casei* that are imported from Chr. Hansen Laboratory, Denmark (as on Feb 22, 2015, http://www.vitagen.com.my/benefits.html). Yakult (M) Sdn. Bhd. produces Yakult Ace cultured milk drink that contains a strain named *L. casei* Shirota strain (as on Feb 22, 2015, http://www.yakult.com.my/html/about_yakult.html). HOWARU Protect™ is a non-dairy product containing patented probiotic formulation in the form of powder which contains *B. lactis* Bi-07™ and *L. acidophilus* NCFM®, and is marketed by Cambert (M) Sdn. Bhd. (as on Feb 22, 2015, http://www.danisco.com/product-range/probiotics/howarur-premium-probiotics/howarur-protect-probiotics/).

Nutriforte Lactoghurt is a product by Cell Biotech, a Danish-Korean bio-venture enterprise that introduces the dual coating technology, Duolac®, in order to increase the viability of the probiotics during manufacturing, shelf life, and during passage through the gastrointestinal tract (GIT). The product is based on the synergistic combination of 5 dual-coated live bacteria strains of *L. acidophilus, L. rhamnosus, B. longum, B. lactis, and S. thermophilus* (as on 16 Oct, 2015, http://www.nutriforte.com.my/Lactoghurt+Probiotics_20_1.htm). Hexbio© is a probiotic formulation consisting of *L. acidophilus* BCMC™ 12130, *L. lactis* BCMC™ 12451, *L. casei* BCMC™ 12313, *B. longum* BCMC™ 02120, *B. bifidum* BCMC™ 02290, and *B. infantis* BCMC™ 02129 that is manufactured by B-Crobes group of companies (as on 16th Oct, 2015, http://www.bcrobes.com/hexbioproduct).

## Selection of Probiotics

There are a number of criteria that must be met during the selection of a probiotic bacterial strain with utmost importance placed on safety issues. Strains of the *Lactobacillus* and *Bifidobacterium* genera are usually regarded as safe from the basis of long-term human use. Members of other genera such as *Bacillus licheniformis* have also been investigated to be used as probiotics. However, it should not be concluded that all members belonging to the *Bacillus* genus can be used as probiotics. This is because there are some strains from the *Bacillus* genus that are associated with diseases such as *Bacillus cereus*, which can cause food-borne illnesses. It is critical to perform safety assessment when the probiotics are not from the genera of *Lactobacillus* or *Bifidobacterium* (European Food Safety Authority [EFSA] 2007; Leuschner *et al*. 2010).

Pathogenicity and infectivity, intrinsic properties as well as virulence factors related to toxicity and metabolic activity of the microorganisms are factors that need to be addressed during the safety assessment process of probiotics (Ishibashi & Yamazaki 2001). Viability and activity of probiotics during storage and when passing through the GIT is also essential. Stomach and the surroundings of the GIT have the highest acidity; therefore it is critical to establish the behaviour and fate of the microorganism during the passage through this condition. In vitro tests typically resembling the conditions in the GIT are commonly used as a screening tool to identify potential probiotics. This is because colonisation and potential health benefits can only be anticipated when these viable cells are able to survive through the natural barriers that exist in the GIT such as low pH conditions and degradation by digestive enzymes as well as by bile salts (Kailasapathy & Chin 2000; Ishibashi & Yamazaki 2001). The viable cell numbers of probiotics in a product should be at least $10^6$ CFU/mL at the expiry date for health and functional claiming as the recommended minimum effective dose per day is $10^8$–$10^9$ cells. Many factors such as pH, titrable acidity, molecular oxygen, redox potential, hydrogen peroxide, flavouring agents, packaging materials, and packaging conditions are associated with viable cell count of a microorganism in a product throughout the manufacturing and shelf-life periods (Mortazavian *et al*. 2012). Another important selection criterion for a probiotic is the ability to adhere to host tissues especially to the intestinal mucus and epithelial cells to promote efficient host-microbial interactions. This interaction is particularly important to prolong the retention period of the specific strain in the gut. However, continuous intake of orally administered probiotics is necessary because permanent colonisation of probiotics is uncommon. Many factors are involved in the adhesion of probiotic microorganisms to the host tissues. Microbial cell density, buffer components, fermentation duration, and growth medium are associated to the in vitro culture parameters while intestinal microflora, digestion, and the food matrix are referred to in vivo conditions (Ouwehand & Salminen 2003; Forssten *et al*. 2011).

There are ongoing studies on the identification of new strains for potential exploitation as probiotics concurrently with existing strains being explored for novel applications. These new strains need to be evaluated and assessed based on established selection criteria which include safety and, functional and technological characteristics prior to the selection of a particular strain for probiotic application.

## IN VITRO AND IN VIVO STUDIES ON THE BENEFICIAL EFFECTS OF PROBIOTICS

### Bowel Diseases and the Immune System

Ulcerative colitis and Chron's diseases are types of bowel diseases that have been linked to the gut's microbial genetic predisposition and environment. Breaking the balance between the intestinal immunity and microbiome may lead to these bowel diseases (Khor *et al*. 2011). Enteric bacteria may change the equilibrium of pro-inflammatory and anti-inflammatory cytokine level of the intestine that becomes the predisposing factor for intestinal disorders. Pro-inflammatory cytokines that are produced by Th1 cells and anti-inflammatory cytokines that are secreted by Th2 cells are important in maintaining the homeostasis of the immune system in the intestinal barrier (Elgert 2009).

Probiotic organisms are increasingly known for its ability to prevent and/or treat intestinal disorders and improve the immune system in both in vitro and animal models. Peran *et al.* (2005) investigated the role of *L. salivarius* CECT 5713 in colitis induced rats. The research showed that orally administered probiotics were able to exert anti-inflammatory effects and reduced the necrosis in the treated group which subsequently ameliorated the colonic condition. It was proved with histological findings where the affected intestine of the treated group showed a pronounced recovery and the markers of inflammation and necrosis such as MPO, TNF-α, and iNOS expressions have been greatly reduced. This result also matches with the research conducted on human peripheral blood mononuclear cells (PBMCs) that certain probiotic bacteria such as lactobacilli exert anti-inflammatory effects where the highest level recorded was with *L. salivarius* Ls-33. The inflammatory status was assessed by the ratio of IL10/IL12 whereby a high ratio indicates an anti-inflammatory effect whereas a low ratio shows a pro-inflammatory effect. In addition to that, the ranking of the tested strains' ability to improve experimental colitis that was obtained on the basis of an in vitro IL-10/IL-12 cytokine stimulation ratio closely resembles the order in an animal model such as mice (Foligne *et al*. 2007).

Additionally, a downregulation of TNF-α and COX-2, and upregulation of anti-inflammatory cytokines for instance IL-4, IL-6, and IL-10 were observed in colitis mouse fed with *L. plantarum* 91 (Duary 2011). A similar in vivo result was also obtained where an increase in anti-inflammatory cytokine IL-10 and a decrease in pro-inflammatory cytokine were found in dextran sulphate sodium (DSS) induced colitis mouse treated with *L. kefiranofaciens* M1. In the same study, anti-colitis effect was also examined using in vitro assays. Results showed that *L. kefiranofaciens* M1 was able to increase the amount of apical and basolateral chemokines, and CCL-20, and strengthen the barrier function of epithelia via improving the transepithelial electrical resistance (TEER) (Chen *et al*. 2011). In addition to that, Ganguli *et al.* (2013) conducted a study to investigate the effect of probiotics in necrotising enterocolitis (NEC). NEC is considered a lethal condition in premature infants. The effect of probiotics was observed on developing human intestinal xenografts and the research proved that *L. acidophilus* ATCC 53103 and *B. infantis* ATCC 15697 were able to modulate intestinal inflammatory response. The secreted glycolipid or glycan could be the reason for the anti-inflammatory effect.

On the other hand, a clinical trial was conducted involving 187 ulcerative colitis patients where *L. rhamnosus* GG (LGG) was given at the dosage of $18 \times 10^9$ viable bacteria/day with and without standard treatment of mesalazine at the dosage of 2400 mg/day. Administration of LGG or a combination of LGG and mesalazine to the subjects increased the relapse-free time compared to the standard treatment (Zocco *et al*. 2006). As shown in both in vitro and in vivo studies, probiotic treatment may alleviate bowel diseases through modulating the immune responses.

Although probiotic treatments improve the severity of the diseases by decreasing inflammation, it did not treat the actual root cause. Moreover, there is fear of opportunistic infection by probiotic strains as they modulate the inflammatory status of a subject. Thus, more clinical trials will be needed to disclose the controversies regarding the effectiveness and safety issues in order to provide better understanding on the control mechanisms of diseases. Longer duration of studies are also required to prove the sustainability of the positive effects on human health.

**Hypocholesterolemic Effect**

Probiotics have been suggested to have hypocholesterolemic effects through numerous mechanisms such as assimilation of cholesterol, binding of cholesterol to cellular surface (Lye *et al.* 2010), co-precipitation of cholesterol (Zhang *et al*. 2008), interference with the formation of micelle for intestinal absorption, and bile acids deconjugation through the secretion of bile salt hydrolase (BSH) (Lambert *et al.* 2008).

Hypocholesterolemic effects exhibited by probiotics is mostly claimed due to BSH activity and it can be detected in all lactobacilli and bifidobacteria strains. The major role of BSH is deconjugation of bile acid, which makes the bile salt less soluble and be excreted out as free bile acid via faeces. This will reduce the cholesterol in serum and increase the de novo synthesis to replace the lost bile acid (Nguyen *et al*. 2007). Besides that, cholesterol could be removed in greater amount in the presence of bile as it acts as a surfactant and allows cholesterol to attach onto bacterial cell membrane. Additionally, Lye *et al.* (2010) reported that the attachment of cholesterol on the bacterial cell membrane was growth dependent. However, the efficacies of treatment of each probiotic strain have not been explored in detail with respect to dose and duration. Table 1 shows the summary of findings for the hypocholesterolemic effects of probiotics.

**Dermal Health**

Probiotics have been proven to have some new benefits for skin health. Recent studies showed that probiotic could improve atopic eczema, wound and scar healing, and help skin-rejuvenation.

To date, effects of probiotics on skin diseases are extensively studied via both administration and topical application methods. However, research data are still inconclusive to support the concerned potential of probiotics. Results from the clinical trial of probiotic treatments are conflicting due to differences in dosage, probiotic strain, duration of application, length of follow-up, and time slot of administration.

A recent study done by Yesilova *et al*. (2012) revealed that probiotics treatment containing *B. bifidum*, *L. acidophilus*, *L. casei,* and *L. salivarius* was effective in reducing atopic dermatitis patients' SCORing Atopic Dermatitis (SCORAD) index and in stimulating cytokine production. The authors suggested that the impact of probiotics on SCORAD could be due to the modification of immunogenicity of potential allergens. On the other hand, *Escherichia coli* Nussle 1917 (EcN, serotype O6: K5: H1) has been evaluated to be beneficial for the treatment of several chronic inflammatory diseases. Weise *et al*. (2011) demonstrated that oral administration of EcN induced the immune regulatory mechanisms in allergen-induced dermatitis mouse model (BALB/c mice) via stimulating the cytokine production.

**Table 1:** Summary of findings for hypocholestrolemic effects of probiotics.

| | Probiotic organism | Experimental system | Major findings | Reference |
|---|---|---|---|---|
| In vivo | Yogurt (unknown) | Human | Reduced total cholesterol and LDL | Agerholm-Larsen *et al.* (2000) |
| | Fortified buffalo milk-yogurts with *B. longum* | Rat | Reduced total cholesterol, LDL-cholesterol, and triglyceride | Abd El-Gawad *et al.* (2005) |
| | *L. plantarum* | Mice | Reduced blood cholesterol<br>Decreased triglycerides | Nguyen *et al.* (2007) |
| | *L. plantarum* | Rat | Decreased total cholesterol and LDL-cholesterol<br>Increased HDL-cholesterol | Kumar *et al.* (2011) |
| | *L. plantarum* | Rat | Decreased LDL, VLDL, and increased HDL with decrease in deposition of cholesterol and triglyceride in liver and aorta | Mohania *et al.* (2013) |
| In vitro | *L. fermentum* | Culture media | BSH activity | Pereira *et al.* (2003) |
| | *L. plantarum* | Culture media | Cholesterol assimilation | Kumar *et al.* (2011) |
| | *L. acidophilus*<br>*L. bulgaricus*<br>*L. casei* | Culture media | Assimilation of cholesterol<br>Attachment of cholesterol onto cell surface<br>Disrupt the formation of cholesterol micelle<br>Deconjugation of bile salt<br>Exhibited bile salt hydrolase activity | Lye *et al.* (2010) |
| | *L. reuteri*<br>*L. fermentum*<br>*L. acidophilus*<br>*L. plantarum* | Culture media | Cholesterol assimilation | Tomaro-Duchesneau *et al.* (2014) |

Furthermore, a few evidences suggesting that nonviable bacteria as well as extract component from bacteria could also exert health potentials. Research findings showed that bacterial compounds can evoke certain immune responses and improve skin barrier functions. Stability of the cell components and metabolites at room temperature when compared to viable cell make them more suitable for topical applications (Gueniche *et al*. 2010). Furthermore, Lew and Liong (2013) reported that some of the bacterial compounds such as hyaluronic acid, lipoteichoic acid, peptidoglycan, and sphingomyelinase exhibited beneficial dermal effects with some possible mechanism actions. However, the exact mechanisms remain unclear, and more research should be directed to explore the potential in fulfilling the demand for probiotic dermal formulations.

Lactic acid bacteria can produce bioactive peptides known as bacteriocins that possess antimicrobial activity against pathogenic bacteria. Iordache *et al*. (2008) revealed that in the presence of soluble molecules produced by lactic bacteria with probiotic potential, the expression of opportunistic bacterial virulence factors could be suppressed. These findings could lead to a new alternative treatment for bacterial infections although the exact mechanism of action remains to be ascertained.

Based on the studies that have been done, probiotics pose a promising potential although its effects could be strain specific, dosage dependent, and application reliance.

**Oral Health**

The emergence of antibiotic-resistance bacteria has recently attracted the attention of researchers for potential application of probiotics in boosting oral health. To date, research findings suggested that probiotic is useful in preventing oral diseases such as dental caries, periodontal infection, and halitosis (Cildar *et al.* 2009; Shimauchi *et al.* 2008; Masdea *et al.* 2012).

**Dental caries**

Dental caries is a bacterially mediated process that is characterised by acid demineralisation of the tooth enamel (Selwitz *et al.* 2007). In the event of preventing dental caries, probiotics need to adhere to the dental surfaces and antagonise the cariogenic species such as mutans streptococci and lactobacilli. Probiotics that are incorporated into a dairy product such as cheese could neutralise the acidic condition in the mouth and prevent demineralisation of the enamel (Jensen & Wefel 1990).

An in vitro study done by Ahola *et al*. (2002) has revealed that *L. rhamnosus* GG could potentially inhibit the colonisation by streptococcal cariogenic pathogens, thus helping to reduce tooth decay incidences in children. Nase *et al*. (2001) demonstrated a significant decrease in dental caries and lowered salivary counts of *S. mutans* in patients after consumption of dairy products containing *L. rhamnosus* for seven months. An in vitro study done by Haukioja *et al*. (2008) also revealed that lactobacilli and bifidobacteria were able to modify the protein composition of salivary pellicle and thus, specifically prevent the adherence of *S. mutans*.

In addition, Nikawa *et al*. (2004) revealed that the consumption of yogurt containing *L. reuteri* for 2 weeks reduced the concentration of *S. mutans* in saliva up to 80%.

**Periodontal disease**

Primary pathogenic agents such as *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia* possess a variety of virulent characteristics that allow them to colonise the subgingival site, interfere with the host's immune system, and cause tissue damage. Hojo *et al*. (2007) reported that *L. salivarius*, *L. gasseri*, *L. fermentum*, and *Bifidobacterium* are among the common prevalent species residing in the oral cavity and are significant for the oral ecological balance.

Krasse *et al.* (2006) found that after two weeks of ingesting chewing gum containing *L. reuteri*, oral cavity of the patients with a moderate-to-severe gingivitis has been colonised by the strain and a significant reduction of plaque index was observed. In addition, Riccia *et al.* (2007) evaluated the anti-inflammatory effects of *L. brevi* in a group of patients with chronic periodontitis. The result demonstrated a positive improvement in plaque index, gingival index, bleeding, and probing for all patients after four days of treatment with lozenges containing *L. brevis*. Moreover, substantial reduction of the salivary level prostaglandin $E_2$ ($PGE_2$) and matrix metalloproteinases (MMPs) were also observed and these could be due to ability of *L. brevis* in preventing the production of nitric oxide, thus suppressing $PGE_2$ expression and MMPs activation.

Recent studies have reported the ability of lactobacilli flora to inhibit the growth of periodontopathogens such as *P. gingivalis*, *Prevotella intermedia*, and *Aggregatibacter actinomycetemcomitans*. According to Koll-Klais *et al*. (2005), isolated oral lactobacilli suppressed the growth of *S. mutans*, *A. actinomycetemcomitans*, *P. gingivalis*, and *P. intermedia* up to 69%, 88%, 82%, and 65%, respectively. In a recent study, Chen *et al*. (2012) determined the antagonistic growth effects of *L. salivarius* and *L. fermentum* on the growth inhibition of periodontal pathogens including *S. mutans*, *S. sanguis*, *and P. gingivalis*. A similar finding was also reported by Ishikawa *et al*. (2003) on the in vitro inhibition of *P. gingivalis*, *P. intermedia*, *and Prevotella nigrescens* by daily oral administration of a tablet containing *L. salivarius*.

Comprehensive studies are required to clarify the correlation between regular consumption of the product containing probiotics and periodontal health. Further clinical investigation on the dosage of probiotic, mean of administration, and safety aspects are required in order to establish the potential of probiotics in the treatment of periodontal diseases.

**Halitosis**

The unpleasant odour from the oral cavity in halitosis is due to the volatile sulphur compounds (VSC) which are produced by anaerobic bacteria that degrade food proteins. *Fusobacterium nucleatum, P. gingivitis, P. intermedia,* and *T. denticola* are the bacteria that are responsible for VSC production. Kang *et al*. (2006) suggested that the production of hydrogen peroxide by *Weisella cibaria* caused the growth inhibition of *F. nucleatum*. They also found that the gargle solution containing *W. cibaria* reduced the production of hydrogen sulphide and methanethiol by *F. nucleatum*. Moreover, another species, *S. salivarius* is known to produce bacteriocins that could colonise with and suppress the growth of volatile sulphide-producing species (Burton *et al.* 2005).

Preliminary data obtained by numerous studies have been encouraging, but apparently more clinical studies are necessary to establish probiotics' potential application in oral health. More studies are required to identify the most safe and functional probiotic strains, optimal target population, optimal dosage, and mode of administration. The effects of probiotic on oral health and its maintenance remain unclear. The exact mechanisms of action for immuno-modulation in host and its interaction with pathogenic species need further clarification. Long-term effects of probiotics consumption remain ambiguous. Thus, well-designed long-term clinical trials are needed to evaluate the potential of probiotics. Promising strains need to be tested in an extended clinical trial with various methods of applications in order to prove conclusively the effectiveness of oral disease treatment using probiotics.

## MODULATION OF GUT-BRAIN AXIS USING PROBIOTIC

In a human body, the GIT is the most heavily colonised organ by various species of bacteria such as *Bactroidetes, Firmicutes,* and *Actinobacteria* (Vyas & Ranganathan 2012). The human GIT is inhabited with $10^{13}$ to $10^{14}$ microorganisms, which is tenfold greater than the human cell number and carries 150 times more genes than that of the human genome (Cryan & Dinan 2012).

On the other hand, gut-brain axis is the bidirectional interactions between the GIT and the brain (Grenham *et al*. 2011). It is regulated at the hormonal, neural, and immunological levels for maintaining homeostasis and dysfunction of the axis causes pathophysiological consequences. The frequent co-occurrence of stress-related psychiatric disorders for instance gastrointestinal disorders and anxiety has also further emphasised the importance of this gut-brain axis (Cryan & Dinan 2012; Matsumoto *et al*. 2013).

The scaffolding of the gut-brain axis consists of the central nervous system (CNS), the enteric nervous system (ENS), the sympathetic and parasympathetic arms of the autonomic nervous system (ANS), the neuroendocrine and neuroimmune systems, and also the gut microbiota (Grenham *et al*. 2011). A complex reflex network is formed to facilitate signalling along the axis, with afferent fibre projections to integrative CNS structures and efferent fibre projections that project to smooth muscle in the intestinal wall (Cryan & Dinan 2012). Through this bidirectional communication network, brain signals can affect the motor, sensory, and secretory functions of the GIT and contrarily, the GIT signals can affect the brain function (Grenham *et al*. 2011).

There have been increasing evidences showing that the alterations in the gut microbiota can greatly influence the interaction between the gut and the brain, affect brain function as well as modulate behaviour. The use of germ-free animals is one of the approaches used to study the gut-brain axis. Neufeld *et al*. (2011) carried out a comparison study on the basal behaviour of female germ-free (GF) mice and conventionally reared specific pathogen-free (SPF) mice. A higher plasma corticosterone level was observed in the GF mice which indicated a higher stress response compared to the SPF mice. An altered gene expression level of brain-derived neurotrophic factor (BDNF), glutamate and serotonin receptors which imply anxiety were also observed in the GF mice. This was the first study which demonstrated the effect of intestinal microbiota on the behaviour development and neurochemical changes in the brain (Neufeld *et al*. 2011).

Gut-brain axis modulation has been considered as a potential therapeutic solution to treat disorders like anxiety and depression due to the emergent concern on gut-brain interaction and its ability to affect the development of psychiatric disorders. Studies also supported that probiotics play a role in modulation and improvement of mood, stress response, and anxiety signs in irritable bowel syndrome (IBS) and chronic fatigue patients (Lakhan & Kirchgessner 2010). A number of researches have been conducted to examine the impact of probiotics on gut-brain axis.

An in vivo study on the effect of psychotropic-like properties of probiotic in rat and human subjects was performed by Messaoudi *et al*. (2011). The authors found that the daily consumption of the probiotics mixture of *L. helveticus* R0052 and *B. longum* R0175 ($10^9$ cfu) significantly ($p$<0.05) decreased anxiety-like behaviour in rats and showed a reduced psychological distress in human subjects. The research findings indicated that probiotics are not only able to modulate gut microbiota but are also involved in stress, anxiety, and depression management which can be used as a novel therapy in psychiatric disorders (Messaoudi *et al*. 2011). In another study, a reduction in the post-myocardial infarction depressive behaviour and an improvement in intestinal permeability in rats were observed upon administration of a similar probiotics mixture. The authors postulated that the probiotics mixture might exhibit therapeutic effect on depressive behaviour via reduction of pro-inflammatory cytokines, which subsequently leads to depression induction and restores intestinal integrity by apoptosis inhibition (Arseneault-Breard *et al*. 2012).

In addition, Desbonnet *et al*. (2009) studied the effect of *B. infantis* on 20 Sprague-Dawley rats. The authors reported that an increase in serotonergic precursor (tryptophan) and decrease in pro-inflammatory immune responses, whereby both are implicated in depression, were found in rats upon consumption of *B. infantis* for 14 days. Results showed that *B. infantis* might possess antidepressant properties and might be beneficial in depressive therapies. This was supported by Desbonnet *et al*. (2010) whereby the *B. infantis* treatment enabled the normalisation of the peripheral immune response, reversed behavioural deficits, and restored concentrations of basal noradrenaline in the brain of maternal separation rats (Desbonnet *et al*. 2010).

Moreover, an experiment was performed by Bravo *et al*. (2011) to examine the antidepressant effect of *L. rhamnosus* (*JB-1*) in mice. The authors observed a decrease in stress-induced corticosterone and reduced anxiety- and depression-related behaviours in mice as well as induced region-dependent alterations in gamma-aminobutyric acid receptors ($GABA_A$ and $GABA_B$) mRNA expressions via the vagus nerve. GABA is the main CNS inhibitory neurotransmitter. Pathogenesis of depression and anxiety was implicated by alteration in the expression of the GABA receptor. The results revealed that administration of *L. rhamnosus* (*JB-1*) was able to modulate the GABAergic system and alter anxiety- and depression-related behaviours in mice.

Chronic fatigue syndrome (CFS) is a complex and debilitating disorder characterised by intense fatigue that may be worsened by physical or mental activities and will not be improved by bed rest. About 97% of CFS patients claimed neuropsychological disturbances such as headaches and symptoms in the emotional realm. The most prevalent emotion-related symptoms are anxiety and depression. In a pilot study, CFS patients receiving *L. casei* strain Shirota (LcS) ($24 \times 10^9$ cfu) daily for two months showed a significant ($p$<0.01) decrease in anxiety symptoms (Rao *et al*. 2009). This study provided further support on the presence of the gut-brain communication which can be mediated by the gut microbiota. In another study, human subjects were required to consume either a cultured drink containing *L. casei* Shirota ($10^8$ cfu/mL) or a placebo control daily for three weeks. Measurements on cognition and mood using questionnaire-based profile of mood states (POMS) were conducted at baseline and after 10 and 20 days of administration. Six basic mood dimensions were measured daily which includes confident/unsure, clearheaded/ muddled, elated/depressed, agreeable/angry, energetic/tired, and composed/anxious on 10 cm visual analogue scales. Every evening subjects were requested to rate their mood all through the day based on the scales. Human subjects with poor mood at the beginning of the experiment exhibited a significant ($p$<0.05) improvement in mood after the probiotic treatment (Benton *et al*. 2007).

It has been reported that an alteration of normal gut microbiota in adult rodents with probiotics can modulate pain, behaviour, and brain biochemistry (Bravo *et al*. 2011). Thus, another study proposed that the alteration of gut microbiota might possess a similar effect on human behaviour and brain function. Tillisch *et al*. (2013) evaluated an effect of consuming fermented milk containing a mixture of probiotics (*B. animalis* subsp *Lactis*, *S. thermophiles*, *L. bulgaricus*, and *Lactococcus lactis* subsp *Lactis*) on gut-brain communication in humans. Results revealed that brain activity, which plays a role in controlling emotion and sensation in healthy women was influenced after administration of the aforementioned fermented milk. This study clearly demonstrates the relationship of consumption of probiotics on the modulation of brain activity and also provides evidence for the modulatory effect of probiotics in the gut-brain interactions.

An increase of experimental data has supported the existence of gut-brain axis and the modulatory effect of probiotics on the axis to treat psychiatric disorders. However, the exact mechanisms involved in the modulation of the gut-brain axis with probiotics remain ambiguous. In a recent research by Bercik *et al*. (2011), administration of *B. longum* NCC3001 was determined to normalise anxiety-like behaviour of the dextran sodium sulphate-induced colitis mice model. The authors hypothesised that it might be the vagal pathways that mediate the anxiolytic signals of *B. longum,* which can be initiated either on vagal afferent terminals innervated with gut or at the enteric nervous system level.

Altogether, accumulating evidences prove the presence of the gut-brain communication and its importance in altering brain function and behaviour. Capabilities of certain probiotics to regulate different aspects of the gut-brain axis simultaneously provide potential benefits in the management of stress, anxiety, and depressive behaviours. However, the findings are still in the preliminary stages and further studies are warranted to examine the exact mechanisms of action involved. In addition to that, investigations on the specific gut microbes, intestinal structure and function should be carried out to better understand the interactions that take place. Evaluation on the signalling pathways between gut microbiota and the brain in humans are also critical to elucidate whether the gut-brain communication plays a homologous role in modulating stress, mood, and anxiety as reported in rodent models. Advance understanding of the interaction that occurs during the gut-brain communication can provide insight into the development of novel treatment strategies for patient with psychiatric disorders or other diseases.

## CONCLUSION

This review has focused on several beneficial properties of probiotics. One of the most known health effects of probiotics is preventing and ameliorating bowel diseases by improving the immune system. Besides that, probiotics are found to exhibit hypocholesterolemic effects via cholesterol assimilation, binding of cholesterol to cellular surface, co-precipitation of cholesterol, interfering with the formation of micelle for intestinal absorption, deconjugation of bile acids by BSH, and improving the lipid profiles. Apart from these conventional beneficial effects, probiotics have been reported to improve atopic eczema, wound and scars healing, and possess skin-rejuvenating properties. It has been suggested that probiotics could exhibit beneficial dermal effects by producing bacterial compounds which evoke certain immune responses and improve skin barrier functions. Probiotics could also be used to prevent and treat oral diseases. They are found to improve/prevent dental caries and periodontal infection via growth inhibition of cariogenic bacteria and periodontopathogens. Additionally, they have been shown to reduce the production of nitric oxide, which subsequently suppresses the prostaglandin and matrix metalloproteinases levels in saliva. Moreover, the unpleasant odour from the oral cavity in halitosis could also be ameliorated by inhibiting the growth of volatile sulphide-producing species. On the other hand, improvement of stress-related psychiatric disorders such as anxiety and depression via modulation of gut-brain axis by probiotics has also further emphasised the importance of probiotics. However, more scientific developments are needed to establish the potential application of probiotics. There is no doubt that the application of probiotics for human health will expand to a greater degree with the current significant research progress.

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