

## Metabiotics and their Health Benefits

Aijaz M. Shaikh and Sreeja V.\*

Dairy Microbiology Department, SMC College of Dairy Science, AAU, Anand, India

\*Corresponding author: sreeja\_p70@rediffmail.com

---

### Abstract

Probiotics are said to confer a number of health benefits on the host through their varied mechanisms of action in the human GIT. But a number of limitations exist with use of live probiotics. We are yet to be sure about the optimal dosage of probiotics, their specific mode of action, duration of the beneficial effects and the nature of the final results. The metabolic substances elaborated by probiotics and or their structural components, popularly called as metabiotics are said to provide more precise results in the above said aspects. These substances are said to possess better absorption, metabolism, distribution, and excretion abilities compared with classic probiotics based on live microorganisms. Hence use of metabiotic products may provide a more precise approach for treatment of pathological conditions associated with the imbalance of host microbiota.

**Keywords:** Probiotics, GIT, metabiotics, health benefits, metabolites

---

Scientific studies are increasingly proving the importance of gut microbiota and their interactions in human health. Recent decades saw emergence of probiotics as one of the most relevant tools to manipulate gut microbiota for human health benefits. Although, use of probiotics has shown them to be safe and beneficial, we are yet to define the optimal amount of bacteria for probiotic effects. Also, there is no single mechanism of action for all probiotics (Pflughoeft *et al.*, 2012, Yazdankhah *et al.*, 2009).

Moreover, the beneficial effects of probiotics may be short-lived, inconsequential, or ambiguous (Kinross *et al.*, 2011 Van Reenen *et al.*, 2011, Kiseleva *et al.*, 2011). Although the history of live probiotic use does not high-light any area of serious concern, recent well-documented events of adverse effects and uncertainty about the level of their risk require new alternative approaches in prophylaxis and treatment of pathological conditions associated with the imbalance of host microbiota. Metabiotics,

the metabolic substances elaborated by probiotic organisms, may be a step towards that.

### WHAT ARE METABIOTICS?

Metabiotics are the structural components of probiotic microorganisms and/or their metabolites and/or signaling molecules with a known chemical structure that can affect the microbiome and/or human metabolic and signaling pathways, optimizing the composition and function of indigenous microbiota and host-specific physiology, immunity and neuro-hormonbiology, and regulating metabolic and/or behavior reactions connected with the activity of host indigenous microbiota. Different probiotic strains can become the source for metabiotic substances. Metabiotics (Shenderov, 2012, Shenderov, 2011) are also known by different names such as 'metabolic probiotics' (Vahitov *et al.*, 2006 and Vahitov *et al.*, 2005), 'postbiotics' (Tsilingiri and Rescigno, 2013), 'ghostprobiotic' (Taverniti *et al.*, 2011), 'Heat-killed probiotic' (Indriyani *et al.*, 2012), 'biological drugs'

(Sonnenburg *et al.*, 2011), or ‘pharmacobiotics’ (Caselli *et al.*, 2011).

Metabiotics have certain advantages over classic probiotics such as defined chemical structure, dosage, safety and long shelf-life. Besides, metabiotics possess better absorption, metabolism, distribution, and excretion abilities compared with classic probiotics based on live microorganisms. A detailed molecular understanding of metabiotics can turn them into significant, specific, and active contributors to the benefits derived from probiotics (Shenderov, 2011 and Sonnenburg *et al.*, 2011). Metabiotics display wide inhibitory activity against various species of pathogens. Metabiotic substances contain various metabolites and signaling molecules which display broad antibacterial spectrum and immunomodulatory actions (Savadogo *et al.*, 2006, Liasi *et al.*, 2009, Gaggia *et al.*, 2010 and Cicienia *et al.*, 2014).

#### Types of metabiotics and their health benefits

Probiotic strains can produce different sets of Low Molecular Weight (LMW) bioactive molecules which can be attractive candidates for metabiotic construction. Some groups of LMW compounds of probiotic microbe origin that may become the basis for manufacture of potential metabiotics are mentioned here under.

#### Bacteriocins

Bacteriocins are an abundant and diverse group of ribosomally synthesized antimicrobial peptides produced by bacteria and archaea (Alleson *et al.*, 2012). They make up a heterogeneous family in terms of heat stability, molecular mass, mode of release and action, microbial target, and mechanism conferring protection to the producing strain (Gordon *et al.*, 2007 and Heng *et al.*, 2007). A number of research studies have shown that bacteriocins have the potential to fight skin infections as well as oral, respiratory, gastrointestinal, pneumonia (Piper *et al.*, 2011, Kwaadsteniet *et al.*, 2010), candidiasis infections, mastitis infection (Akerey *et al.*, 2009), halitosis (Iwamoto *et al.*, 2010), *Clostridium* infection

(Rea *et al.*, 2010), infection with *L.monocytogenes* (Corr *et al.*, 2007, Svetoch *et al.*, 2011) and urogenital tract infections (Turovskiy *et al.*, 2009, Sutyak *et al.*, 2012). Many bacteriocins have been assessed for potential application as therapeutic agents some of which are mentioned in Table 1.

**Table 1:** Bacteriocins which have been studied for potential application as therapeutic agents

Bacteriocins	Producer strain	Potential Pharmaceutical applications
Ancovenin	<i>Streptomyces spp.</i>	Treating high blood pressure
Epidermin	<i>Staphylococcus epidermidis</i>	Treating skin infections
Lacticin 3147	<i>Lactococcus lactis</i>	Treating mastitis infections
Mutacin	<i>Streptococcus mutans</i>	Treating dental carries
Nisin	<i>Lactococcus lactis</i>	Treating peptic ulcer
E1, E4, E7, E8, K & S4	<i>Escherichia coli</i>	Treating hemorrhagic colitis and hemolytic uremic syndrome

Source: Gillor *et al.*, 2005, 2009; van Heel *et al.*, 2011, Brand, 2013.

#### Short chain fatty acids and organic acids

Short-chain fatty acids (SCFA) are the major anions within the intestinal lumen and are mainly produced by anaerobic fermentation of undigested carbohydrates and, to a lesser extent, proteins (Topping and Clifton, 2001). Clinical studies have showed that the administration of SCFAs such as butyrate, acetate and propionate has a positive effect on the treatment of ulcerative colitis, crohn’s disease, antibiotic-associated diarrhoea and obesity (Binder, 2010; Chambers *et al.*, 2014). Several studies have showed that the administration of short-chain fatty acids or dietary fibre to both rats and humans causes a decline in the plasma concentrations of cholesterol (Fushimi *et al.*, 2006, Aritsuka *et al.*, 2016). Proposed health benefits of some of the short chain fatty acids and organic acids are shown in Table 2. Propionate

is a gluconeogenic substrate which inhibits the utilisation of acetate for lipid and cholesterol synthesis (den Besten *et al.*, 2013). Moreover it has been shown to inhibit inflammation and modulate adipokine production in adipose tissue (Al-Lahham *et al.*, 2010b, 2012). It has also improved insulin resistant in the inulin control group when taken with inulin (Chambers *et al.*, 2014). The oral administration of acetate improved glucose tolerance and suppressed obesity (Yamashita *et al.*, 2007). Acetate reduces the appetite by changing the expression profiles of appetite regulatory neuropeptides in the hypothalamus through activation of citric acid pathway (Frost *et al.*, 2014). Microbially produced lactate is generally converted into propionate or butyrate by a subset of lactate-utilizing bacteria

(Flint *et al.*, 2012). Lactate can have diverse metabolic and regulatory properties such as immune function, being an energy source for cell turnover, Histone deacetylase (HDAC) inhibitor, and signalling molecules. Microbially produced lactate may affect physiological functions in the vagina either through HDAC modulation or G protein coupled receptor 81(GPR81) signaling (Boskey *et al.*, 2001). A study by Haraguchi *et al.* (2014) showed that polyphenols in conjunction with high-fat diet raised cecal succinate levels and inhibited growth and proliferation of colon cancer cells.

### Proteins, peptides, amino acids

Amino acids are the constructive components of proteins and peptides. Amino acids can serve as

**Table 2:** Proposed health benefits of short chain fatty acids and organic acids

SCFA	Proposed health benefits	References
SCFAs	Treatment of ulcerative colitis, Crohn's disease, AAD and obesity Decline in the plasma concentrations of cholesterol	Chambers <i>et al.</i> , 2014 Binder, (2010) Aritsuka <i>et al.</i> , 2016
Butyrate	Anti-colon cancer Anti-inflammatory Anti-colorectal cancer Anti-inflammatory Efficient HDAC inhibitor Decreases intestinal epithelial permeability	Fushimi <i>et al.</i> , 2006 Hamer <i>et al.</i> , 2008; 2012 Flint <i>et al.</i> , 2012 Donohoe <i>et al.</i> , 2012 Van Immerseel <i>et al.</i> , 2010
Acetate	Improved insulin sensitivity Improved glucose tolerance Suppresses obesity Reduces the appetite	Gao <i>et al.</i> , 2009 Yamashita <i>et al.</i> , 2007 Frost <i>et al.</i> , 2014
Propionate	Act as gluconeogenic substrate Inhibits the utilisation of acetate for lipid and cholesterol synthesis Anti-inflammatory	den Besten <i>et al.</i> , 2013 Al-Lahham <i>et al.</i> , 2010a Al-Lahham <i>et al.</i> , 2010b, 2012
Lactate	Immune function Energy source HDAC inhibitors Signalling molecules	Flint <i>et al.</i> , 2012 Boskey <i>et al.</i> , 2001
Succinate	Anti-colon cancer	Haraguchi <i>et al.</i> , 2014

precursors for the synthesis of SCFA by bacteria (Tome *et al.*, 2013), suggesting an interplay between microbial activity and host amino acid and SCFA homeostasis. Glutamate/ glutamine is a key compound in the cellular metabolism, it therefore serves as a unique brain fuel and performs some other important functions such as detoxification of ammonia, as a hepatoprotective agent, to aid in peptic ulcer healing, and others (Zareian *et al.*, 2012). One of the leading roles of glutamic acid in pharmaceuticals is that of a neurotransmitter. Lysine is required by the body to synthesize L-carnitine, which is a substance required for the conversion of fatty acids into energy. Lysine also helps in calcium absorption and collagen formation which are important for muscle and bone health. It also supports or acts as a precursor in the synthesis of enzymes, antibodies, and some hormones as well. Methionine is an excellent natural

lipotropic agent that processes and eliminates fats from the liver and acts as a natural detoxifying agent removing heavy metals from the body and excess histamine from the brain.

In addition, it has antioxidant properties as well and thus protects the body against free radicals (Chaitow, 1985). Tryptophan is an essential amino acid with a unique indole side chain which indicates its use as a precursor for a number of neurotransmitters in the brain, for example, serotonin, melatonin, and niacin associated with appetite, sleep, mood, and pain perception. Its application lies in the chemical synthesis of some antidepressant drugs and in the treatment of schizophrenia (Porter *et al.*, 2005; Heijden *et al.*, 2005).  $\gamma$ -Aminobutyric acid (GABA) acts as the major inhibitory neurotransmitter in the mammalian central nervous system. GABA improves the plasma

**Table 3:** Bioactive peptides identified in fermented milk products

Dairy Products	Identified bioactive peptide	Activity
Cheese type	$\beta$ -CN (8–16), $\beta$ -CN (58–77),	Phosphopeptides, precursor of
Parmigiano- Reggiano	$\alpha$ s2-CN(83–33)	$\beta$ -casomorphin
Cheddar	$\alpha$ s1-CN fragments	Several
	$\beta$ -CN fragments	Phosphopeptides
Italian varieties:	$\beta$ -CN (58–72)	ACE-inhibitory
Mozzarella, Crescenza,		
Gogonzola, Italico		
Gouda	$\alpha$ s1-CN (1–9), $\beta$ -CN (60–68)	ACE-inhibitory
Festivo	$\alpha$ s1-CN (1–9), $\alpha$ s1-CN (1–7), $\alpha$ s1-CN (1–6)	ACE-inhibitory
Emmental	$\alpha$ s1-CN fragments	Immuno-stimulatory,
	$\beta$ -CN fragments	several
		phosphopeptides,
		antimicrobial
Manchengo	Ovine $\alpha$ s1-CN, $\alpha$ s2-CN, $\beta$ -CN fragments	ACE-inhibitory
Fermented milks	$\beta$ -CN (74–76), $\beta$ -CN (84–86),	Antihypertensive
Sour milk	$\kappa$ -CN (108–111)	
Yogurt	Active peptides not Identified	Weak ACEinhibitory
Dahi	Ser-Lys-Val-Tyr-Pro	ACE-inhibitory

Source: Korhonen, 2009; Haque *et al.*, 2009.

concentration, growth hormones and the protein synthesis in the brain (Cho *et al.*, 2007). GABA intake can regulate sensations of pain and anxiety, and lipid levels in serum (Kono *et al.*, 2000, Miura *et al.*, 2006).

Furthermore, consumption of GABA-enriched foods can inhibit cancer cell proliferation (Park *et al.*, 2007) and improve memory and the learning abilities (Miura *et al.*, 2006). Some proteins secreted by the commensal microbiota might be responsible for the anomalous immune response observed in the framework of inflammatory bowel disease (Adams *et al.*, 2008; Ivison and Steiner, 2008, Schoepfer *et al.*, 2008). It secretes different effector molecules such as chemokines, cytokines or antibacterial peptides (defensins), mucus secretion, and modulation of the immune function and the response of the gut-associated lymphoid tissue (GALT) cells.

Probiotics when used as starter cultures are known to liberate certain specific protein fragments that have a positive impact on body functions and conditions and may ultimately influence health. These peptides are called bioactive peptides. Peptides with various

bioactivities (Table 3) have been identified in several dairy-products such as milk protein hydrolysates, fermented milks and many cheese varieties (Gobbetti *et al.*, 2002; Korhonen and Pihlanto-Leppälä, 2004; Sieber *et al.*, 2010). Some commercially available dairy products with bioactive peptides are listed in Table 4.

#### Nucleic acids and nucleotides

DNA and RNA act as the genetic code and translators for the proteins. Nucleotides are the constitutive units of DNA and RNA. Nucleotides are true nutraceuticals or functional ingredients frequently used to improve the disease resistance, to decrease mortality and to promote the growth rate. They are widely utilized in clinical nutrition and in mother milk substitutes. Nucleotides have beneficial effects on early infant growth (Singhal *et al.*, 2010), small intestinal growth and development (Rodriguez-Serrano *et al.*, 2010), intestinal microflora and immune function (Hawkes *et al.*, 2006; Gutierrez-Castrellon *et al.*, 2007). DNA vaccines have been used to prevent allergic response (Horner *et al.*, 2001). DNA aptamers have demonstrated promise in intervention of pathogenic

**Table 4:** Some commercially available products containing bioactive peptides

Brand name	Product type	Health claims	Bioactive peptide	Manufacturer
Calpis	Sour milk	Reduction of blood pressure	VPP, IPP from $\beta$ -casein and $\kappa$ -casein	Calpis Co., Japan
Evolus	Fermented milk, calcium enriched	Reduction of blood pressure	VPP, IPP from $\beta$ -casein and $\kappa$ -casein	Valio, Finland
BioZate	Hydrolysed whey protein isolate	Reduction of blood pressure	Whey peptides	Davisco, USA
BioPURE-GMP	Whey protein Hydrolysate	Anticariogenic, Antimicrobial, Antithrombotic	Glycomacropeptide $\kappa$ -casein fb(106–169)	Davisco, USA
Recaldent	Chewing gum	Anticariogenic	Caseinphosphopeptides	Cadbury Enterprises
Festivo	Fermented low-fat hard cheese	Reduction of blood pressure	$\alpha$ s1-casein f(1–6) RPKHPI, f(1–7)	MTT Agrifood Research, Finland
CholestBlock	Drink powder	Hypocholesterolemic	Soy peptides bound to Phospholipids	Kyowa Hakko, Japan

*Source:* Korhonen, 2009; Haque *et al.*, 2009; Tidona *et al.*, 2010; Sharma *et al.*, 2011.

protein biosynthesis against HIV-1 integrase enzyme (de Saultrait *et al.*, 2002). Small interfering RNAs are being investigated to inhibit HIV (Martinez *et al.*, 2002), hepatitis (Zamore and Aronin 2003), and influenza infection (Ge *et al.*, 2003). Supplements containing good levels of nucleic acids have been recommended to retard aging, improve memory, or improve the immune or other protein functions.

**Polysaccharides, peptidoglycans and other surface molecules**

Many strains of probiotics are capable of elaborating EPS which are said to play an important role in conferring health benefits (Table 5). Orally administrated fermented milk containing either exopolysaccharide (EPS) producing *Lb. delbrueckii* ssp. *bulgaricus* or EPS-producing *S. thermophilus* has resulted in the reduction of colon cancer in male Fisher rats and exhibited a chemo-preventive effect *in vivo* (Purohit *et al.*, 2009). Kefiran, an EPS produced by *Lactobacillus* spp. increased T-cell activity and thereby decreased tumor growth in mice (Zubillaga *et al.*, 2001). Bacterial polysaccharides have been reported to exhibit antitumor activity; however the potency of activity depends on the branching structure (Yoon *et al.*, 2004).

Peptidoglycans determines the shape and preserves the integrity of the bacterial cell. Purified

polysaccharide-peptidoglycan complex (PSPG) from *Lb.casei Shirota* has anti-inflammatory actions in chronic intestinal inflammatory disorders (Matsumoto *et al.*, 2009).The peptidoglycan extracted from *Lb.paracasei* subsp. *paracasei*X12 (X12-PG) may have played an important role in its inhibitory effects on colon cancer (Wang *et al.*, 2014). Peptidoglycans of probiotic *L. rhamnosus* GG *viz.*, Msp1 (p75) and Msp2 (p40), were found to promote the survival and growth of epithelial cells under pro-inflammatory conditions (Yan *et al.*, 2007).

Many bacteria possess nanoscale fibrous extracellular appendages known as pili on their surfaces (Telford *et al.*, 2006).Pili-mediated bacteria-host interactions have been demonstrated in the probiotic Gram-positive bacterium *Lactobacillus rhamnosus* GG (Kankainen *et al.*, 2009). The pili identified in *L. rhamnosus* GG confer the ability to adhere to the intestinal epithelial cells (Caco-2) and human intestinal derived mucus; they also promote biofilm formation (Lebeer *et al.*, 2012). Furthermore, pili of *L. lactis* allowed the strain to adhere to intestinal epithelial cells (Caco-2) (Meyrand *et al.*, 2013). *L. rhamnosus* GG pili are involved in reducing IL8 mRNA expression provoked by other cell surface components, such as lipoteichoic acids (LTAs) in intestinal epithelial cells (Lebeer *et al.*, 2012). The roles of pili in bacterial adhesion, invasion, aggregation, formation of biofilms, and modulation

**Table 5:** Proposed health benefits of microbial polysaccharides

Potential health benefits	Producer strain	References
Antioxidant potential by inhibiting hydroxyl and superoxide anion radicals	<i>Streptococcus spp.</i> and <i>B. animalis</i>	Kanmani <i>et al.</i> , 2011; Xu <i>et al.</i> , 2011
Reduction of plasma cholesterol by ~33%	<i>Lb. mucosae</i>	London <i>et al.</i> , 2014
Reduction of colon cancer	<i>Lb. delbrueckii</i> ssp. <i>bulgaricus</i> , <i>S. thermophilus</i>	Purohit <i>et al.</i> , 2009
Antitumor	<i>Lb. acidophilus</i> , <i>S. thermophilus</i> <i>Lactobacillus delbrueckii</i> subsp. <i>Lactococcus lactis</i> ssp.	Kim <i>et al.</i> , 2010 Hassan, (2008)
Obesity induced Type 2 Diabetes	Levan ( <i>Bacillus licheniformis</i> )	Dahech <i>et al.</i> , 2011 Xiu <i>et al.</i> , 2010
Protection from intestinal inflammation induced by <i>Helicobacter hepaticus</i>	Polysaccharide A (PSA) of <i>Bacteroides fragilis</i>	Mazmanian <i>et al.</i> , 2008

of immunity are well established (Lebeer *et al.*, 2012; Danne *et al.*, 2012).

### Plasmalogens and vitamins

Plasmalogens are a unique class of membrane glycerophospholipids containing a fatty alcohol with a vinyl ether bond at the sn-1 position, and enriched in polyunsaturated fatty acids at the sn-2 position of the glycerol backbone. Plasmalogens have been proposed to act as antioxidants in membrane physiology *via* protection of unsaturated fatty acids and membrane proteins from harmful oxidation (Wang and Wang 2010). Reduced brain plasmalogens can be demonstrated in various neurodegenerative disorders. These include Alzheimer disease (Han *et al.*, 2001), Parkinson's disease (Fabelo *et al.*, 2011), Down

syndrome (Murphy *et al.*, 2000) and experimental autoimmune encephalomyelitis (Singh *et al.*, 2004). Plasmalogens are a significant component of the cytoplasmic membrane of *B. animalis* subsp. *lactis* (Taylor *et al.*, 2012).

Probiotic bacteria that live in your intestinal tract also produce vitamins, including B-vitamins like folate, biotin and vitamin B12. The production of vitamin B1 and B2 by bacteria contributes to the total intake of vitamin B1 and B2 (Fabian *et al.*, 2008). It was reported that *Lactobacillus reuteri* CRL1098 was able to produce B12 (Taranto *et al.*, 2003). Vitamin K as well as vitamin D production by bacteria in the gut is also reported (Jones *et al.*, 2013). *In vitro* studies have demonstrated the production of high levels of folate (about 100 µg/L) by strains of *Lactobacillus*. Bifidobacteria strains

**Table 6:** Some of the commercially available metabiotic products

Product	Description	Reference
Hylak Forte	Manufactured by Ratiopharm/Merckle, Germany. It contains <i>Escherichia coli</i> DSM 4087, <i>Streptococcus faecalis</i> DSM 4086, <i>Lactobacillus acidophilus</i> DSM 4149 and <i>L. helveticus</i> DSM 4183. Presence of SCFA, lactic acid, and some other non-identified microbial metabolites in this drug. Health benefits for adults and children by producing positive shifts in intestinal microbiota, host acid-alkaline balance, water-salt metabolism, vitamins B and K balance and energy provision to intestinal epithelia and local immune cells.	(Belousova <i>et al.</i> , 2005)
Zakofalk	Prepared by Dr. Falk Germany. It contains supplements inulin and butyric acid. Recommended for the treatment of mild to moderately active inflammatory intestinal diseases.	(Roda <i>et al.</i> , 2007)
Bactistatin	It contains <i>B.subtilis</i> strain, Vitamin E. Recommended for increasing the immune defense function of the human body, selectively adsorbs and removes toxins and allergens, reduces bloating and cramps and improves the functional state of the gastrointestinal tract.	(www.bactistatin.com)
Aktoflor C	It is made up of lactic acid, lysine, succinic acid and mainly helpful for reducing intestinal disorder symptoms (diarrhea, constipation, bloating) and it prevents side effects of antibiotics.	(www.amt.allergist.ru)
Acilact	It is made up of <i>Lactobacillus</i> , Fructo-oligosaccharides, Lactoferrin. It is suitable for reducing the cholesterol level in the blood and for treatment of bacterial vaginosis.	(www.medicatione.com)
Nagipol	It consists of yeast autolysate beer containing proteins, amino acids (including the 8 essential) and vitamins of group B (B1-B6). Increased physical activity, reduced resistance to colds disease, anaemia and infectious diseases of the gastrointestinal tract and hepatitis are reported.	(www.noillen.bitballoon.com)
Lacteol Forte	It is heat killed product of <i>Lb.fermentum</i> and <i>Lb.delbruekii</i> . It can be prescribed for infants and patients with positive H.I.V. and immunodeficient patients.	(www.medicinep.com)

also contribute to folate intake by the synthesis and secretion of folates in the human intestine (Strozzi & Mogna, 2008).

#### Various messenger or signal molecules

Symbiotic gut microorganisms release various soluble LMW molecules of different chemical nature. These LMW molecules are able to sense environment, interact with corresponding cell surface, membrane, cytoplasm and nucleic acid receptors, to reply quickly and coordinately by induction of special sets of genes and playing an important role in the control for many genetic and physiological functions, biochemical and behavior reactions, in supporting host health in general. Bacteria-host cells cross talk is mainly based on the exchange of signal molecules in both directions (Yuan *et al.*, 2008, Khmel & Metlitskaya, 2006 and Atkinson & William, 2009). Lectins are active regulators of metabolism and functional food ingredients (Shenderov & Lakhtin, 2004). They participate in adhesion processes and other functions (Lakhtin *et al.*, 2006). Probiotic lectins can function as cell surface building constituents, protecting and communicating components and growth and signal factors. The signal molecule autoinducer-2 (AI-2) and its cognate synthase LuxS are considered to be attractive candidates for multispecies communication at the gastrointestinal level (Lebeer *et al.*, 2008). AI-2 molecules produced by *E. coli* Nissle are found to influence the expression of cytokines in the mucosa of the colon in the mice.

#### Products containing metabiotics

A number of products containing metabiotics are commercially available. Some of which are shown in Table 6.

#### CONCLUSION

Metabiotics are a natural evolution of the probiotic concept and are considered to be one step ahead of live probiotics because of their well-defined chemical structure, dosage, safety, specificity, metabolic aspects and long shelf-life. Metabiotics are said to impart a plethora of health benefits through varied

mechanisms. But this warrants more and more in-depth studies to understand the mechanisms of action at molecular level to validate the health claims. This may promote further development of the probiotic concept and reduce health hazards of the current approaches in the prevention and treatment of diseases associated with imbalance of host microbiota. Further to market the metabiotic products, proper regulatory frame work is essential to prevent false claims.

#### REFERENCES

- Adams, R.J., Heazlewood, S.P., Gilshenan, K.S., O'Brien, M., McGuckin, M.A. and Florin, T.H. 2008. IgG antibodies against common gut bacteria are more diagnostic for Crohn's disease than IgG against mannan or flagellin. *Am J Gastroenterol.*, **103**: 386–396.
- Akerey, B., Le-Lay, C., Fliss, I., Subirade, M. and Rouabhia, M. 2009. *In vitro* efficacy of nisin Z against candida albicans adhesion and transition following contact with normal human gingival cells. *J Appl Microbiol*, **107**: 1298–1307.
- Al-Lahham, S., Roelofsen, H., Rezaee, F., Weening, D., Hoek, A., Vonk, R. and Venema, K. 2012. Propionic acid affects immune status and metabolism in adipose tissue from overweight subjects. *Eur.J. Clin. Invest*, **42**: 357–364.
- Al-Lahham, S.H., Peppelenbosch, M.P., Roelofsen, H., Vonk, R.J. and Venema, K. 2010a. Biological effects of propionic acid in humans; metabolism, potential applications and underlying mechanisms. *Biochim. Biophys. Acta*, **1801**: 1175–1183.
- Al-Lahham SH, Roelofsen H, Priebe M, Weening D, Dijkstra M, Hoek A, Rezaee F, *et al.* 2010b. Regulation of adipokine production in human adipose tissue by propionic acid. *Eur. J. Clin. Invest*, **40**: 401–407.
- Alleson D, Cotter PD, Ross RP and Colin H 2012. Bacteriocin production: a probiotic trait? *J.ASM.org*, **78**: 1-6.
- Aritsuka T, Tanaka K and Kiriyama S 2016. Effect of beet dietary fibre on lipid metabolism in rats fed a cholesterol-free diet in comparison with pectin and cellulose. *J. Japn. Soc. Nutr. Food Sci*, **11**: 19-89.
- Atkinson S and William P 2009. Quorum sensing and social networking in the microbial world. *J Royal Soc Interface*, **40**: 59-78.
- Belousova EF, Nikitina YV, Mishurovskaya NC and Zlatkina AR 2005. Possibilities of microbial metabolite preparations for intestinal microbiota restoration. *Consilium Medicum*, **7**: 9-13.
- Binder HJ 2010. Role of colonic short-chain fatty acid transport in diarrhea. *Annu. Rev. Physiol*, **72**: 297–313.

- Boskey ER, Cone RA, Whaley KJ and Moench TR 2001. Origins of vaginal acidity: high D/L lactate ratio is consistent with bacteria being the primary source. *Hum. Reprod*, **16**: 1809–1813.
- Brand MA 2013. Therapeutic properties of the lantibiotic nisin F. Dissertation presented for the degree of Doctor of Science in the faculty of science at Stellenbosch University. Stellenbosch University, 7-32.
- Caselli M, Vaira G, Calo G, Papini F, Holton J and Vaira D 2011. Structural bacterial molecules as potential candidates for an evolution of the classical concept of probiotics. *Adv Nutr*, **2**: 372-380.
- Chaitow L 1985. Amino acids in therapy. Thorsons publishers limited, Wellingborough, Northamptonshire, pp. 43–106.
- Chambers ES, Viardot A, Psichas A, Morrison DJ, Murphy KG, Zac-Varghese SE, MacDougall K *et al.* 2014. Effects of targeted delivery of propionate to the human colon on appetite regulation, body weight maintenance and adiposity in overweight adults. *J Gut*, **30**: 13-45.
- Cho YR, Chang JY and Chang HC 2007. Production of gamma aminobutyric acid (GABA) by *Lactobacillus buchneri* isolated from kimchi and its neuroprotective effect on neuronal cells. *J. Microbiol. Biotechnol*, **17**: 104–109.
- Cicenia A, Scirocco A, Carabotti M, Pallotta L, Marignani M and Severi C 2014. Postbiotic activities of lactobacilli-derived factors. *Journal of Clinical Gastroenterology*, **48**: 18-22.
- Corr SC, Li Y, Riedel CU, O'Toole PW, Hill C and Gahan CGM 2007. Bacteriocin production as a mechanism for the anti-infective activity of *Lactobacillus salivarius* UCC118. *Proc. Natl. Acad Sci*, **18**: 17-21.
- Dahech I, Belghith KS, Hamden K, Feki A, Belghith H and Mejdoub H 2011. Oral administration of levan polysaccharide reduces the alloxan-induced oxidative stress in rats. *International Journal of Biological Macromolecules*, **49**: 942–947.
- Danne C and Dramsi S 2012. "Pili of Gram-positive bacteria: roles in host colonization." *Research in Microbiology*, **163**: 645–658.
- deKwaadsteniet M, van Reenen C and Dicks L 2010. Evaluation of nisin F in the treatment of subcutaneous skin infections, as monitored by using a bioluminescent strain of *Staphylococcus aureus*. *Probiotics Antimicrob Proteins*, **2**: 61–65.
- den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud DJ and Bakker BM 2013. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. *J. Lipid Res*, **54**: 2325–2340.
- denBesten G, van Eunen K, Groen AK, Venema K, Reijngoud DJ and Bakker BM 2013. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. *J. Lipid Res*, **54**: 2325–2340.
- deSaultrait VR, Lozach PY, Altmeyer R, *et al.* 2002. DNA aptamers derived from HIV-1 RNaseH inhibitors are strong anti-integrase agents. *J Mol Biol*, **324**: 195–203.
- Donohoe DR, Collins LB, Wali A, Bigler R, Sun W and Bultman SJ 2012. The Warburg effect dictates the mechanism of butyrate-mediated histone acetylation and cell proliferation. *Mol. Cell*, **48**: 612–626.
- Fabelo N, Martin V, Santpere G, Marin R, Torrent L, Ferrer I and Diaz M 2011. Severe alterations in lipid composition of frontal cortex lipid rafts from Parkinson's disease and incidental Parkinson's disease. *Mol. Med*, **17**: 1107–1118.
- Fabian E, Majchrzak D, Dieminger B, Meyer E and Elmadfa I 2008. Influence of probiotic and conventional yoghurt on the status of vitamins B1, B2 and B6 in young healthy women. *Ann NutrMetab*, **52**: 29-36.
- Flint HJ, Scott KP, Louis P and Duncan SH 2012. The role of the gut microbiota in nutrition and health. *Nat. Rev. Gastroenterol. Hepatol*, **9**: 577–589.
- Frost G, Sleeth ML, Sahuri-Arisoylu M, Lizarbe B, Cerdan S, Brody L, Anastasovska J *et al.* 2014. The shortchain fatty acid acetate reduces appetite via a central homeostatic mechanism. *Nat. Commun.*, **5**: 11-36.
- Fushimi T, Suruga K, Oshima Y, Fukiharu M, Tsukamoto Y and Goda T 2006. Dietary acetic acid reduces serum cholesterol and triacylglycerols in rats fed a cholesterol-rich diet. *Br.J. Nutr*, **95**: 916–924.
- Gaggia F, Mattarelli P and Biavati B 2010. Probiotics and prebiotics in animal feeding for safe food production. *Int J Food Microbiol*, **141**: 515–528.
- Gao Z, Yin J, Zhang J, Ward RE, Martin RJ, Lefevre M, Cefalu WT, *et al.* 2009. Butyrate improves insulin sensitivity and increases energy expenditure in mice. *Diabetes*, **58**: 1509–1517.
- Ge Q, McManus MT, Nguyen T *et al.* 2003. RNA interference of influenza virus production by directly targeting mRNA for degradation and indirectly inhibiting all viral RNA transcription. *Proc Natl Acad Sci USA*, **100**: 2718–2723.
- Gillor O, Etzion A, and Riley MA 2009. The dual role of bacteriocins as anti- and probiotics. *Appl Microbial Biotechnol*, **81**: 591-606.
- Gillor O, Nigro LM, and Riley MA 2005. Genetically engineered bacteriocins and their potential as the next generation of antimicrobials. *Current Pharmaceutical Dign*, **11**: 1067e1075.
- Gobbetti M, Stepaniak L, De Angelis M, Corsetti A and Di Cagno, R. 2002. Latent bioactive peptides in milk proteins: Proteolytic activation and significance in dairy processing. *Critical Reviews in Food Science and Nutrition*, **42**: 223–239.
- Gordon DM, Oliver E and Littlefield-Wyer J 2007. The diversity of bacteriocins in Gram-negative bacteria. In: Riley MA, Chavan M(eds). *Bacteriocins: ecology and evolution*. Springer, Berlin, pp.5-18.

- Gutierrez-Castrellon P, Mora-Magana I, Diaz-Garcia L, Jimenez-Gutierrez C, Ramirez-Mayans J and Solomon-Santibanez GA 2007. Immune response to nucleotide-supplemented infant formulae: systematic review and meta-analysis. *Brit J Nutr.*, **98**: 64–67.
- Hamer HM, De Preter V, Windey K and Verbeke K 2012. Functional analysis of colonic bacterial metabolism: relevant to health? *Am. J. Physiol.*, **30**: 1–9.
- Hamer HM, Jonkers D, Venema K, Vanhoutvin S, Troost FJ and Brummer RJ 2008. Review article: The role of butyrate on colonic function. *Aliment. Pharmacol. Ther.*, **27**: 104–119.
- Han X, Holtzman DM and McKeel DW 2001. Plasmalogen deficiency in early Alzheimer’s disease subjects and in animal models: molecular characterization using electrospray ionization mass spectrometry. *J. Neurochem.*, **77**: 1168–1180.
- Haque E, Chand R, and Kapila S 2009. Biofunctional properties of bioactive peptides of milk origin. *Food Reviews International*, **25**: 28–43.
- Haraguchi T, Kayashima T, Okazaki Y, Inoue J, Mineo S, Matsubara K, Sakaguchi E et al. 2014. Cecal succinate elevated by some dietary polyphenols may inhibit colon cancer cell proliferation and angiogenesis. *J. Agric. Food Chem.*, **62**: 5589–5594.
- Hassan AN 2008. ADSA Foundation Scholar Award: Possibilities and challenges of exopolysaccharide producing lactic cultures in dairy foods. *Journal of Dairy Science* **91**: 1282–1298,
- Havenaar R 2011. Intestinal health functions of colonic microbial metabolites: a review. *Benef. Microbes*, **2**: 103–114.
- Hawkes JS, Gibson RA, Roberton D and Makrides M 2006. Effect of dietary nucleotide supplementation on growth and immune function in term infants: a randomized controlled trial. *European Journal of Clinical Nutrition*, **60**: 254–264.
- Heijden FM, Fekkes D, Tuinier S, Sijben AE, Kahan RS and Verhoeven, WM 2005. Amino acids in schizophrenia: Evidence for lower tryptophan availability during treatment with atypical antipsychotics. *J. Neural Transm.*, **112**: 577–585.
- Heng NCK, Wescombe PA, Burton JP, Jack RW and Tagg JR 2007. The diversity of bacteriocins in Grampositivebacteria. In: Riley MA, Chavan M(eds). *Bacteriocins: ecology and evolution*. Springer, Berlin, pp. 45-92.
- Horner AA, van Uden JH, Jubeldia JM et al. 2001. DNA-based immune therapeutics for the treatment of allergic disease. *Immunol Rev*, **179**: 102–118.
- <http://noillen.bitballoon.com/medicine2/nagipol-instructions1572>. Accessed 2016 December 02.
- <http://www.medications.com/?c=drug&s=acilact&ingredient=lactobacillus%20acidophilus> Accessed 2016 December 02.
- [https://amt.allergist.ru/analogi\\_zamena/aktoflor-c](https://amt.allergist.ru/analogi_zamena/aktoflor-c). Accessed 2016 December 02.
- <https://www.medicinep.com/lacteol-fort-lactobacillus-lb-sachets-antidiarrheal-of-microbial-origin-545>. Accessed 2016 December 08.
- Indriyani A, Juffrie M and Satyati A 2012. Effect of live versus Heat killed probiotics on acute diarrhea in young children. *Paediatrica Indonesiana*, **52**: 249-254.
- Iverson SM and Steiner TS 2008. Anti-flagellin antibodies in irritable bowel syndrome: another attack on our commensals? *Neurogastroenterol Motil*, **20**: 1081–1085.
- Iwamoto T, Suzuki N, Tanabe K, Takeshita T and Hirofujii T 2010. Effects of probiotic Lactobacillus salivarius WB21 on halitosis and oral health: an open-label pilot trial. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol*, **110**: 201–208.
- Jacobi CA, Grundler S, Chih-Jen H, Fick JS, Adam P, Lamprecht G et al. 2012. Quorum sensing in the probiotic bacterium *Escherichia coli* Nissle 1917 (Mutaflor)- evidence that furanosyl borate diester (AI-2) is influencing the cytokine expression in the DSS colitis mouse model. *Gut Pathogens*, **4**: 1-8.
- Johnston SA, Talaat AM and McGuire MG 2002. Genetic immunization what’s in a name? *Arch Med Res*, **33**: 325–329.
- Jones ML, Martoni CJ and Prakash S 2013. Oral supplementation with probiotic *L. reuteri* NCIMB 30242 increases mean circulating 25-hydroxyvitamin D: A post hoc analysis of a randomized controlled trial. *J Clin Endocrinol Metab*, **98**: 2944-2951.
- Kankainen M1, Paulin L, Tynkkynen S, von Ossowski I, Reunanen J, Partanen P, Satokari R et al. 2009. Comparative genomic analysis of *Lactobacillus rhamnosus* GG reveals pili containing a human mucus binding protein. *Proc.Natl. Acad.Sci.USA*, **106**: 17-25.
- Kanmani P, Kumar RS, Yuvaraj N, Paari KA, Pattukumar V and Arul V 2011. Production and purification of a novel exopolysaccharide from lactic acid bacterium *Streptococcus phocae* PI80 and its functional characteristics activity *in vitro*. *Bioresourcetchnology*, **102**: 4827–4833.
- Khmel IA and Metlitskaya AZ 2006. Quorum sensing of gene expression-perspective drug target against bacterial pathogenicity. *MolBiology*, **40**: 195-210.
- Kim PI, Sohng JK, Sung C, Joo HS, Kim EM, Yamaguchi T, Park D and Kim BG 2010. Characterization and structure identification of an antimicrobial peptide, hominicin, produced by *Staphylococcus hominis* MBBL. *Biochem Biophys Res Commun*, **399**: 133–138.

- Kinross JM, Darzi AW and Nicholson JK 2011. Gut microbiome-host interactions in health and diseases. *Genome Med*, **3**: 1-14.
- Kiseleva EP, Mikhailopulo KI, Sviridov OV, Novik GI, Knirel YA and Dey ES 2011. The role of components of *Bifidobacterium* and *Lactobacillus* in pathogenesis and serologic diagnosis of autoimmune thyroid diseases. *Benef Microbes*, **2**: 139-154.
- Kono I and Himeno K 2000. Changes in g-aminobutyric acid content during beni-koji making. *Biosci. Biotechnol. Biochem*, **64**: 617-619.
- Korhonen H 2009. Milk-derived bioactive peptides: from science to applications. *Journal of Functional Foods*, **1**: 177-187.
- Korhonen H and Pihlanto-Leppala A 2004. Milk-derived bioactive peptides: Formation and prospects for health promotion. In *Handbook of Functional Dairy Products* (eds Shortt, C. & O'Brien, J.), pp. 109-124.
- Lakhtin VM, Aleshkin VA, Lakhtin MV, Afanasyev SS, Pospelova VV and Shenderov BA 2006. Lectins, adhesins and lectinlike substances of lactobacilli and bifidobacteria. *Vestnik of Russian Academy of Medical Sciences*, **81**: 28-34.
- Lebeer S, Claes I, Tytgat HLP *et al.* 2012. Functional analysis of *Lactobacillus rhamnosus* GG pili in relation to adhesion and immunomodulatory interactions with intestinal epithelial cells. *Applied and Environmental Microbiology*, **78**: 185-193.
- Lebeer S, Vanderleyden J and De Keersmaecker SCJ 2008. Genes and molecules of lactobacilli supporting probiotic action. *Microbiol Mo l Biol Rev*, **72**: 728-734.
- Liasi SA, Azmi T, Hassan MD, Shuhaimi M, Rosfarizan M and Ariff AB 2009. Antimicrobial activity and antibiotic sensitivity of three isolates of lactic acid bacteria from fermented fish product. *Budu. Malays J Microbiol*, **5**: 33-37.
- London LEE, Kumar AH, Wall R, Casey PG, Sullivan F, Shanahan C. Hill PD *et al.* 2014. Exopolysaccharide-producing probiotic lactobacilli reduce serum cholesterol and modify enteric microbiota in ApoE-deficient mice. *J. Nutr*, **144**: 1956-1962.
- Martinez MA, Gutierrez A, Armond-Ugon M *et al.* 2002. Suppression of chemokine receptor expression by RNA interference allows for inhibition of HIV-1 replication. *AIDS*, **16**: 2385-2390.
- Matsumoto S, Hara T, Nagaoka M, Mike A, Mitsuyama K, Sako T, Yamamoto M *et al.* 2009. A component of polysaccharide peptidoglycan complex on *Lactobacillus* induced an improvement of murine model of inflammatory bowel disease and colitis-associated cancer. *Immunology*, **128**: 170-180.
- Mazmanian SK, Round JL and Kasper DL 2008. A microbial symbiosis factor prevents intestinal inflammatory disease. *Nature*, **453**: 620-625.
- Meyrand M1, Guillot A, Goin M, Furlan S, Armalyte J, Kulakauskas S, Cortes-Perez NG *et al.* 2013. Surface proteome analysis of a natural isolate of *Lactococcus lactis* reveals the presence of pili able to bind human intestinal epithelia cells. *Mol.Cell.Proteomics*, **12**: 3945-3947
- Miura D, Ito Y, Mizukuchi A, Kise M, Aoto H and Yagasaki K 2006. Hypercholesterolemic action of pre-germinated brown rice in hepatoma-bearing rats. *Life Sci*, **79**: 259-264.
- Murphy EJ, Schapiro MB, Rapoport SI and Shetty HU 2000. Phospholipid composition and levels are altered in Down syndrome brain. *Brain Res*, **86**: 9-18.
- Park KB and Oh SH 2007. Production of yogurt with enhanced levels of gamma-aminobutyric acid and valuable nutrients using lactic acid bacteria and germinated soybean extract. *Biores. Technol*, **98**: 1675-1679.
- Pflughoeft KJ and Versalovich J 2012. Human microbiome in health and disease. *Ann Rev PatholMech Dis*, **7**: 99-122.
- Piper C, Hill C, Cotter PD and Ross RP 2011. Bioengineering of a Nisin A-producing *Lactococcus lactis* to create isogenic strains producing the natural variants Nisin F, Q and Z. *Microb Biotechnol*, **4**: 375-382.
- Porter RJ, Mulder RT, Joyce PR and Luty SE 2005. Tryptophan and tyrosine availability and response to antidepressant treatment in major to antidepressant treatment in major depression. *J. Affect. Disord*, **86**: 129-134.
- Purohit DH, Hassan E, Bhatia X, Zhang and Dwivedi C 2009. Rheological, sensorial, and chemopreventive properties of milk fermented with exopolysaccharide-producing lactic cultures. *Journal of Dairy Science*, **92**: 847-856.
- Rea MC, Sit CS, Clayton E, O'Connor PM, Whittall RM, Zheng J, Vederas JC *et al.* 2010. Thuricin CD, a posttranslationally modified bacteriocin with a narrow spectrum of activity against *Clostridium difficile*. *Proc Natl Acad Sci*, **107**: 9352-9357.
- Roda A, Simoni P, Magliulo M, Nanni P, Baraidini M, Roda G *et al.* 2007. A new oral formulation for the release of sodium butyrate in the ileo-cecal region and colon. *World J Gastroenterol*, **13**: 1079-1084.
- Rodriguez-Serrano F, Rios A, Marchal JA, Caba O, Martinez-Amat A, Prados J *et al.* 2010. Differentiation of intestinal epithelial cells mediated by cell confluence and/or exogenous nucleoside supplementation. *Cells Tissues Organs*, **191**: 478-488.
- Savadogo A, Ouattara AC, Bassole HI and Traore SA 2006. Bacteriocins and lactic acid bacteria-A minireview. *Afr J Biotechnol*, **5**: 678-683.
- Schoepfer AM, Schaffer T, Seibold-Schmid B, Muller S and Seibold F 2008. Antibodies to flagellin indicate reactivity to bacterial antigens in IBS patients. *Neurogastroenterol Motil*, **20**: 1110-1118.

- Sharma B, Srivastava S, Singh N, Sachdev V, Kapur S and Saraya A 2011. Role of probiotics on gut permeability and endotoxemia in patients with acute pancreatitis: a double-blind randomized controlled trial. *J. Clin. Gastroenterol*, **45**: 442–448.
- Shenderov BA 2011. Probiotic (symbiotic) bacterial languages. *Anaerobe*, **17**: 490-495.
- Shenderov BA 2012. OMIC technologies and their importance in the modern prophylactic and regenerative medicine. *Regenerative Med J*, **3**: 70-80.
- Shenderov BA and Lakhtin VM 2004. Lectins - new potential category of physiologically active functional ingredients. *Bulletin of Restoration Medicine*, **4**: 33-7.
- Sieber R, Butikofer U, Egger C, Portmann R, Walther B and Wechsler D 2010. ACE inhibitory activity and ACE-inhibiting peptides in different cheese varieties. *Dairy Science and Technology* **90**: 47-73.
- Singh I, Paintlia AS, Khan M, Stanislaus R, Paintlia MK, Haq E et al. 2004. Contreras, Impaired peroxisomal function in the central nervous system with inflammatory disease of experimental autoimmune encephalomyelitis animals and protection by lovastatin treatment. *Brain Res*, **22**: 1–11.
- Singhal A, Kennedy K, Lanigan J, Clough H, Jenkins W, Elias-Jones A et al. 2010. Dietary nucleotides and early growth in formula-fed infants: a randomized controlled trial. *Pediatrics*, **126**: 946–953.
- Sonnenburg JL and Fischbach MA 2011. Community Health care: therapeutic opportunities in the human microbiome. *Sci Transl Med*, **3**: 12-18.
- Strozzi GP and Mogna L 2008. Quantification of folic acid in human feces after administration of Bifidobacterium probiotic strains. *J Clin Gastroenterol*, **42**: 179-184.
- Sutyak Noll K, Prichard MN, Khaykin A, Sinko PJ and Chikindas ML 2012. The natural antimicrobial peptide subtilisin acts synergistically with glycerol monolaurate, lauricarginate and epoxy-L-lysine against bacterial vaginosis-associated pathogens but not human lactobacilli. *Antimicrob Agents Chemother*, **5**: 8-11.
- Svetoch EA, Eruslanov BV, Levchuk VP, Perelygin VV, Mitsevich EV, Mitsevich IP, Stepanshin J et al. 2011. Isolation of *Lactobacillus salivarius* 1077 (NRRL B-50053) and characterization of its bacteriocin, including the antimicrobial activity spectrum. *Appl Environ Microbiol*, **77**: 2749–2754.
- Taranto MP, Vera JL, Hugenholtz J, De Valdez GF and Sesma F 2003. *Lactobacillus reuteri* CRL1098 produces cobalamin. *J Bacteriol*, **185**: 5643-5647.
- Taverniti V and Guglielmetti S 2011. The immunomodulatory properties of probiotic microorganisms beyond their viability (ghost probiotics: proposal of paraprobiotic concept). *Genes Nutr*, **6**: 261-274.
- Taylor SO, Robert EW, James LS and Jeff RB 2012. Identification of plasmalogens in the cytoplasmic membrane of *Bifidobacterium animalis* subsp. *lactis*. *J.asm.org*, **78**: 880-884.
- Telford JL, Barocchi MA, Margarit I, Rappuoli R and Grandi G 2006. Pili in Gram positive pathogens. *Nat .Rev. Microbiol*, **4**: 509-519.
- Thanh NT, Loh TC, Foo HL, HAIR-BEJO M and Azhar BK 2010. Inhibitory activity of metabolites produced by *Lactobacillus plantarum* isolated from Malaysian fermented food. *Int J Probiotics Prebiotics*, **5**: 37–44.
- Tidona F, Sekse C, Criscione A, Jacobsen M, Bordonaro S, Marletta D and Vegarud GE (2010). Antimicrobial effect of donkeys' milk digested *in vitro* with human gastrointestinal enzymes. *International Dairy Journal*, doi: 10.1016/j.idairyj.2010.10.008.
- Tome D, Gotteland M, Henri B, Andriamihaja M, Sanz Y, Blachier F and Davila AM (2013). Re-print of "Intestinal luminal nitrogen metabolism: Role of the gut microbiota and consequences for the host". *Pharmacol. Res*, **69**: 114–126.
- Topping DL and Clifton PM 2001. Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides. *Physiol. Rev*, **81**: 1031–1044.
- Tsilingiri K and Rescigno M 2013. Postbiotics: what else? *Beneficial Microbes*, **4**: 101-107.
- Turovskiy Y, Ludescher R, Aroutcheva A, Faro S and Chikindas M. 2009. Lactocin 160, a bacteriocin produced by vaginal *Lactobacillus rhamnosus*, targets cytoplasmic membranes of the vaginal pathogen, *Gardnerellavaginalis*. *Probiotics Antimicrob Proteins*, **1**: 67–74.
- Vahitov TY and Petrov LN (2006). Regulatory functions of bacterial exometabolites. *Microbiology (Russ Trans)*, **75**: 415-419.
- Vahitov TYA, Petrov LN and Bondarenko VM 2005. Concept of a probiotic preparation containing original microbial metabolites. *Zh Microbiol*, **73**: 108-114.
- van Heel AJ, Montalban-Lopez M and Kuipers OP 2011. Evaluating the feasibility of lantibiotics as an alternative therapy against bacterial infections in humans. *Exp Opin Drug MetabolToxicol*, **7**: 675–680.
- Van Immerseel F, Ducatelle R, De Vos M, Boon N, Van De Wiele T, Verbeke K, Rutgeerts P et al. 2010. Butyric acid-producing anaerobic bacteria as a novel probiotic treatment approach for inflammatory bowel disease. *J Med Microbiol*, **59**: 141-143.
- van Reenen CA and Dicks LMT 2011. Horizontal gene transfer amongst probiotic lactic acid bacteria and other intestinal microbiota: what are the possibilities? *A review. Arch Microbiol*, **193**: 157-168.
- Waldecker M, Kautenburger T, Daumann H, Busch C and Schrenk D 2008. Inhibition of histone-deacetylase activity

- by short-chain fatty acids and some polyphenol metabolites formed in the colon. *J NutrBiochem*, **19**: 587-593.
- Wang G and Wang T 2010. The role of plasmalogen in the oxidative stability of neutral lipids and phospholipids. *J. Agric. Food Chem*, **58**: 2554-2561.
- www.bactistatin.com. Accessed 2016 December 02.
- Xiu AH, Kong Y, Zhou MY, Zhu B, Wang SM and Zhang JF 2010. The chemical and digestive properties of a soluble glucan from *Agrobacterium* sp. ZX09. *Carbohydrate Polymers* **82**: 623-628.
- Xu RH, Shang N and Li PL 2011. *In vitro* and *in vivo* antioxidant activity of exopolysaccharide fractions from *Bifidobacterium animalis* RH. *Anaerobe*, **17**: 226-231.
- Yamashita H, Fujisawa K, Ito E, Idei S, Kawaguchi N, Kimoto M *et al.* 2007. Improvement of obesity and glucose tolerance by acetate in Type 2 diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats. *Biosci. Biotechnol. Biochem*, **71**: 1236-1243.
- Yan F, Cao H, Cover TL, Whitehead R, Washington MK and Polk DB. 2007. Soluble proteins produced by probiotic bacteria regulate intestinal epithelial cell survival and growth. *Gastroenterology*, **132**: 562-575.
- Yazdankhah SP, Midtvedt T, Narvhus JA, Berstad A, Lassen J and Halvorsen R. 2009. The use of probiotics for critically ill patients in hospitals. *MicrobEcol Health Dis*, **21**: 114-121.
- Yoon EJ, Yoo SH, Cha JH and Lee HG. 2004. Effect of levan's branching structure on antitumor activity. *International Journal of Biological Macromolecules*, **34**: 191-194.
- Yuan J, Wang B, Sun Z, Bo X, Yuan X, He X *et al.* 2008. Analysis of host-Inducing Proteome changes in *Bifidobacterium longum* NCC2705 grown *in vivo*. *J Proteome Res*, **7**: 375-385.
- Zamore PD and Aronin N 2003. siRNAs knock down hepatitis. *Nat Med*, **9**: 266-267.
- Zareian M, Ebrahimpour A, Bakar FA, Mohamed AKS, Forghani B, Safuan M, Kadir A and Saari N 2012. A glutamic acid producing lactic acid bacteria isolated from Malaysian fermented foods. *Int. J. Mol. Sci*, **13**: 5482-5497.
- Zubillaga MR, Weill E, Postaire C, Goldman R and Boccio J 2001. Effect of probiotics and functional foods and their use in different diseases. *Nutrition Research*, **21**: 569-579.

