REVIEW

Probiotics and their beneficial effects against various diseases

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Abstract: Joint FAO/WHO expert's consultation report defines probiotics as: Live microorganisms which when administered in adequate amounts confer a health benefit on the host. Most commonly used probiotics are Lactic acid bacteria (LAB) and bifidobacteria. There are other examples of species used as probiotics (certain yeasts and bacilli). Probiotic supplements are popular now a days. From the beginning of 2000, research on probiotics has increased remarkably. Probiotics are now day's widely studied for their beneficial effects in treatment of many prevailing diseases. Here we reviewed the beneficiary effects of probiotics in some diseases.

Keywords: *Probiotics, Lactic acid Bacteria (LAB), Bifidobacteria, Probiotic supplements*

INTRODUCTION

The emergence of resistance and tolerance to the existing drugs has created a decreased efficacy of these drugs in use. Along with the advancement in other fields of medicine (Qadir *et al.,* 2006; Qadir *et al.,* 2007; Qadir *et al.,* 2008), the problem of resistance has been tried to be overcome by increasing the drug delivery to the target site by the use of polymers (Khalid *et al*., 2009; Hussain *et al*., 2011) or through nanotechnology (Naz *et al*., 2012; Ehsan *et al*., 2012), synthesis of new drugs, either by the use of proteomics (Qadir and Malik, 2010; Qadir, 2011; Qadir and Malik, 2011), or synthesis from lactic acid bacteria (Masood *et al*., 2011), or marine microorganisms (Javed *et al*., 2011). However, now a days, the trend is being changed from synthetic drugs to the natural drugs either from plants or microbes to control the diseases. The natural products are constantly being screened for their possible pharmacological value particularly for their anti-inflammatory (Qadir, 2009), hypotensive (Qadir, 2010), hepatoprotective (Ahmad *et al*., 2012; Ali *et al.,* 2013), hypoglycaemic (Qadir *et al*., 2009; Nisa *et al.*, 2010), amoebicidal (Asif and Qadir, 2011), anti-diarrheal (Janbaz *et al*., 2013a), anti-fertility, cytotoxic, antibiotic (Amin *et al*., 2012), spasmolytic, bronchodilator (Janbaz *et al*., 2013b), antioxidant (Janbaz *et al*., 2012) and anti-Parkinsonism properties. As a natural product, probiotics have been emerged as new management tools for the control of different diseases.

The gastrointestinal tract of human, at different site is habited by beneficial bacteria. These bacteria have a relationship of symbiosis with the host. There are sites where the potentially beneficial micro-organisms are more in number than potentially harmful bacteria. This type of ecosystem composition is called Normobiosis. The environment where the potentially harmful bacteria dominate over health beneficial bacteria is called dysbiosis (Roberfroid *et al*., 2010). The potentially beneficial bacteria are called probiotics.

Probiotics (derived from Latin and Greek) means ''for life'' is defined in many ways. It was defined first time 50 years ago. The most recent and accepted definition of probiotics is "live micro-organisms administered in adequate amounts which confer a beneficial physiological effect on the host". Joint FAO/WHO experts consultation report defines probiotics as: Live microorganisms which when administered in adequate amounts confer a health benefit on the host.

There are some substances normally oligosaccharides which serve as substrate for probiotics and thus important for their growth. These are called prebiotics. Prebiotics are those substances that are not used or metabolized by non-probiotic bacteria like *Bacteroides* spp and *Escherichia coli*. Prebiotics are found in breast milk and some vegetables (Hamilton and Miller, 2004).

Many of the publications define probiotics with reference to more or less same source. Most publications say that term probiotics is attributed to Lilly and Stillwell who had coined the term first in 1965. They defined probiotic as: a substance produced by one microorganism stimulating the growth of another microorganism. They understood a probiotics as opposite to an antibiotic. Parker (1974) gives a totally different overview: Organisms and substances which contribute to intestinal microbial balance. Most commonly, Kollath may be credited for the term

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'probiotics'. In 1953, he coined probiotics as 'Probiotika', active substances that are essential for a healthy development of life.

There are different types of bacteria which are used as probiotics (fig. 1). Commonly used bacteria include *Lactobacilli* and *Bifidobacteria* (Macfarlane *et al*., 2004). These bacteria show symbiotic relationship with human. They are present in the mucus membrane present on epithelial cells of the gut (Holzapfel and Schillinger, 2002) where they inhibit the growth and attachment of harmful bacteria by producing bactericidal chemicals against these bacteria. With the development of evidences regarding usefulness and safety of probiotics, these bacteria are replacing the traditional prophylactic and treatment regimes.

Sources of probiotics

Yogurt is the most common source of probiotics. Yogurt consists of milk (usually from the cow, goat or sheep) fermented by bacteria that modify lactose into lactic acid. Lactic acid is responsible for giving yogurt its characteristics (sharp taste usually changed into good taste by using sweeteners and flavouring) and also denatures and precipitates casein, resulting in a semisolid consistency. ''Bioyoghurts'' are produced in a similar way, but bacteria used for fermentation are of different strains, usually L acidophilus. Fermented milk and fortified fruit juice are common sources of probiotics. Probiotics are also available in supplements consisting of freeze dried bacteria in tablets, capsules and powders. Selection of probiotic product depends on type of bacteria and type of beneficial effect expected. There are thousands of strains of probiotics and all of them show different beneficial effects.

Regulation of probiotics

It was usually understood that probiotics are not regulated (Sanders, 2008). But bacteria used as probiotics require a careful safety assessment (Wassenaar *et al*, 2008). FDA has established a regulatory authority to regulate probiotics production, manufacturers, labeling and safety of products. Of note, on 24 August 2007, the FDA issued rules that require current GMP for dietary supplements. Although these regulations do not address verification of efficacy claims, hopefully they will improve the compositional quality (identity, purity, and strength) of probiotic supplements in the market. Normally, the FDA Does not challenge the labeling or safety of a probiotic product except where the product is mentioned as a drug (i.e., to treat, cure, prevent, mitigate, or diagnose disease) and lacks approval as a drug (Sanders, 2008).

FDA regulations on probiotics depend on intended use of the product (indicated on Label). In FDA there are 4 regulatory categories for probiotics and each of these has different regulatory requirements. These are (1) Drug or biological products, (2) Dietary supplements, (3) food or

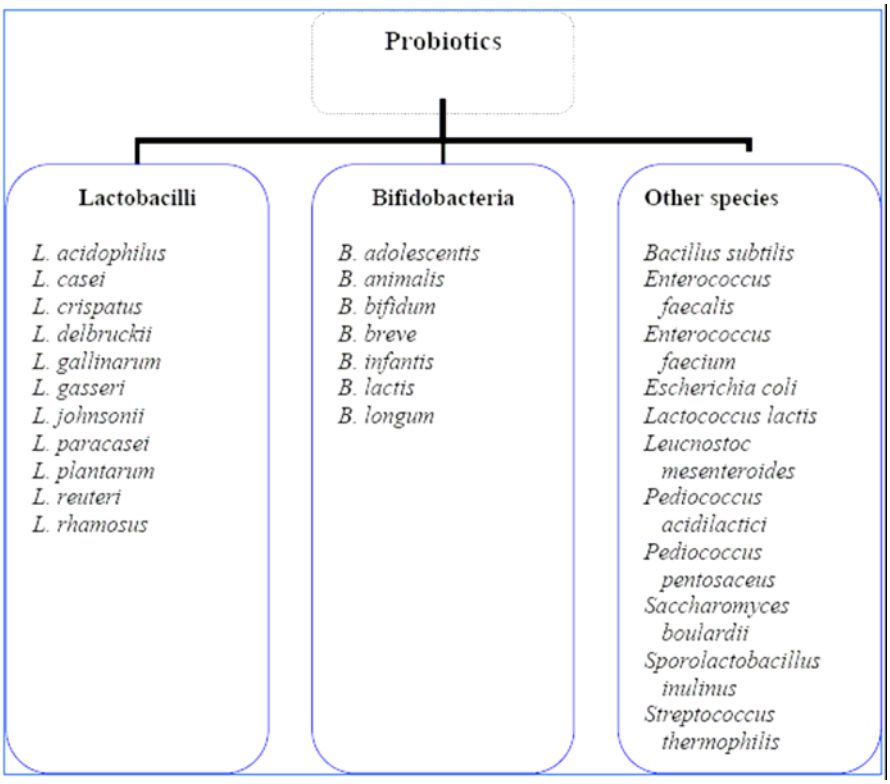

Fig. 1: Different types of bacteria which are recognized as probiotics (Furrie, 2005).

food ingredient, (4) medical food (Degnan, 2008, Hoffman *et al,* 2008).

If probiotics are intended for use as drug, these are also considered as biological products and FDA regulations of biological products will also be applied on probiotics. If these are to be used as "dietary supplements", the manufactures may market it without any pre-approval. But manufacturer must notify FDA the claims of the product. And it will be treated as "new dietary ingredient". If it is launched to be used as food or food ingredient, the FDA only regulates its post-market controls related to adulteration. If the product is launched as medical food, then no pre-market clearance will be required (Degnan, 2008).

In Europe, the probiotic mediated food is not governed by European regulations. But microbial feed additives are subjected to regulations, regarding safety assessment of these additives in animals and humans. Scientific Committee on Animal Nutrition (SCAN) in Europe has launched a "Qualified Perception of Safety" (QPS) concept. According to this concept, the species which have long safety data are allowed to be marketed without extensive safety testing (Wright and Atte, 2005).

Clinical uses of probiotics

Diabetes

World health organization states diabetes as "Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces" Diabetes mellitus is one of the most prevalent diseases in the world with the ranking of 9th with respect to number of deaths. Hyperglycemia, or increased glucose level, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels (.

Diabetes has proved a silent killer for most of the Patients. So the main focus should be to device the best treatment with lesser adverse effects.

Diabetes mellitus is classified into 2 major classes. Type-1 diabetes mellitus is related with destruction of pancreatic beta cells and failure to produce insulin.Type-2 diabetes mellitus is associated with decrease insulin production or increased insulin resistance with is mostly linked with obesity.

Diabetes management includes a large number of medications but none of them could be helpful in complete cure of disorder. Many researches are being carried out at bimolecular and pharmacological level. One of the efforts to cure this disorder is to use symbiotic (probiotic and prebiotics).

At the Start of 20th century, it was thought that probiotics beneficially affect the host by improving balance of gut microbiota. Recent researches show that there is a connection between bacterial population in gut and metabolic disease in human (especially diabetes). Recent studies based on large-scale 16S rRNA gene sequencing, quantitative real time PCR (qPCR) and fluorescent in situ hybridization (FISH), have shown that there is a connection between the composition of the intestinal microbiota and metabolic diseases like obesity and diabetes (Larsen *et al.*, 2010). Danish researches worked on 36 Danish people and came to know that there is a difference in gut microbial flora of diabetic and non diabetic peoples. These men were of different age and body weight and 18 of them are diabetic and 18 are non diabetic they also found 3 types of major phyla of bacteria that reside in gut of human. These are firmicutes (most important is lactobacillus which is beneficial bacteria), proteobacteria and bactereodetes (opportunistic pathogens which can cause gum disease and tooth decay). There was a low level bacteria from phylum firmicutes and greater level of bacteria from phylum bactereodates. Researchers also found that increased level of bactereodetes and decreased level of firmicutes will lead to decreased glucose tolerance which is key problem with diabetes mellitus (Larsen *et al*, 2010). Probiotics are supposed to treat the diabetic patients by balancing microbial gut flora.

Low-fat (2.5%) dahi containing probiotics *Lactobacillus acidophilus* and *Lactobacillus casei* was tested in rats against high fructose-induced type-2 diabetes. Both these bacteria proved beneficial effect in lowering blood glucose by decreasing insulin resistance (Yadav *et al.*, 2006). It is also suggested that the use of probiotics can decrease the insulin resistance and can also lower the incident of hypertensive conditions that are closely related to diabetes. It has also been found that *Bifidobacterium spp* delivers pharmaco nutritional support in treating insulin resistance (Cani and Delzenne, 2011).

Hypertension

The incidence of increased blood cholesterol has been increased in adults, children and adolescence. Most important causes of hypertension are lipid abnormality, hypercholesterolemia and obesity (Yekeen *et al.*, 2003). Mann and Spoerry were among the first to illustrate that lactobacillus-fermented milk has hypocholestrolemic effects (Mann and Spoerry, 1974). New researches have shown that not only the Lactobacilli exhibit hypocholesterolemic effects, but Bifidobacteria could also cause a significant reduction in serum cholesterol when cholesterol is elevated. As we know that most of the cholesterol is synthesized and absorbed in intestine, therefore intestinal micro flora has shown to effect cholesterol level in blood. Studies have shown that probiotics have been proved beneficial in lowering hypertension by decreasing blood cholesterol level and increasing resistance of LDL to oxidation (Goel *et al.*,

2006). A group of scientist (Kieling *et al.*, 2002) performed a randomized, crossover, and placebo-controlled design trial consisting 29 women to test the hypocholesterolemic effect of yoghurt containing *L.* acidophilus and *B. longum*. This cross over study was performed to 21 weeks duration and involved the administration of 300g/day yogurt. The result of the study showed that HDL increased significantly. Another placebo-controlled experiment was performed to study the effects of a probiotic containing food on blood cholesterol levels in 20 young Swiss mice (Sindhu and Khetarpaul, 2003). The results showed that the food sample of *L. casei* and *Saccharomyces boulardii* cause 19% decrease in total serum cholesterol, while LDL cholesterol levels was decreased by 37% after the 42 day feeding trial. There are different biochemical factors which regulate blood pressure. Most important factor is rennin-angiotensin system (RAS) which regulate blood pressure (FitzGerald, 2004). Angiotensin converting enzyme (ACE) regulates this pathway. There are some probiotics which upon fermentation produces proteinases capable of producing ACE inhibitory peptides. And thus regulate blood pressure (Yamamoto and Takano, 1999). Several studies have demonstrated that *Lactobacillus helveticus* are involved in producing antihypertensive peptides which are ACE inhibitory tripeptides Val-Pro-Pro (VPP) and Ile-Pro-Pro (IPP) from milk protein casein (Korhonen, 2009).

Urogenital heath care

Urinogenital infections (Rahman and Qadir, 2011; Yousuf *et al.*, 2012)) proved to be one of the most common diseases which women are facing today. Globally, an estimated 1 billion women have bladder or vaginal infections each year (Reid *et al.*, 2004)**.** UTI such as bacterial veginosis can lead to increased risk of preterm delivery (Flynn *et al.*, 1999). Mostly oral and vaginal sex play an important role in causing vaginitis and UTI, but these can also caused by a change in person's own microorganism. This change occurs due to change in vaginal environmental in which lactobacilli decrease in concentrations or are absent and are subsituted by pathogenic Gram-positive cocci, Gram-negative rods, or yeast. Many researches are carried out to find the different between normal and abnormal micro flora (Bruce *et al.*, 1973; Stamey and Sexton, 1975; Wilson, 2004; Schwebke *et al.*, 1999). Research on the vaginal micro flora during the whole menstrual cycle has proved that only 22% women maintain a lactobacilli-rich flora (Daus and Hafez, 1975) and it is also clear that epithelial cell receptivity to lactobacilli attachment enhances at peak estrogen levels midcycle (Chan *et al.*, 1984), it is still not found what factors cause such a dramatic alteration in the flora.

Lactose intolerance

Lactose intolerance means the inability of adults to digest lactose due to lack of lactose metabolizing enzyme lactase. Mostly peoples deficit in lactase generally tolerate lactose better from yogurt than from milk. Reason for this is that it has been assumed that bacterial micro flora in the small intestine enhances lactose digestion (Shah, 2000 and Farnworth, 2008) possibly by increasing contact between lactose and lactase.

Crohn's disease and ulcerative colitis

Crohn's disease (CD) and ulcerative colitis (UC) are the chronic diseases of GIT with more or less common symptoms. Both are collectively called inflammatory bowl disease (IBD). In ulcerative colitis only mucosa and sub mucosa of colon are inflamed. In case of Crohn's disease, the mucosa, submucosa and serosa are inflamed and the inflammation can spread to whole GIT. Crohn's disease is associated with diarrhea, wait loss and abdominal pain while Ulcerative colitis has the symptoms of diarrhea and bleeding (Jonkers and Stockbrügger 2003). Exact cause of Inflammatory bowl disease in not known. Probiotics are used in the treatment of inflammatory bowl disease considering that bacteria are involved in the etiology of the disease. Different studies show beneficial effect of probiotic in the treatment of inflammatory bowl disease in animal models (Gionchetti *et al.*, 2002).

Clinical placebo controlled studies also shows that Probiotics cause improvement in the condition of IBD (Jonkers and Stockbrügger 2003).

Colon cancer

Management of cancer is one of the hot issues in these days (Ilayas and Qadir, 2010; Tabasum and Qadir, 2010; Bokhari *et al.,* 2012; Farooqi *et al.,* 2013; Saleem *et al.,* 2013). In laboratory experimentation, some stains of LAB (*Lactobacillus delbrueckii subsp. bulgaricus*) have shown anti-mutagenic effects because they have ability to bind with heterocyclic amines which are carcinogenic (Wollowski *et al.*, 2001). Animal studies proved beneficial effects of LAB against colon cancer of rodents. Human trials also suggest that some types of LAB are anti-carcinogenic due to ability to decrease the activity of enzyme called β glucuronidase (Brady *et al.*, 2000) (which can generate cancer producing substances in the digestive system). The incidence of colon cancer in people consuming dairy product has been low compared to others during population studies. But there is still lot more to do to confirm this effect.

Inflammation

Some strains of LAB may decrease the inflammation by modulating inflammatory and hypersensitivity responses. This effect is thought to be caused by regulation of inflammatory mediator called cytokines (Reid *et al.*, 2003).

Immune function and infections

Some strains of LAB may decrease pathogen growth by means of competitive inhibition (i.e., by competing for

growth) and thus these may support normal immune functions. They also improve normal immune system by increasing the concentration IgA-producing Plasma cells, improving phagocytosis as well as increasing the concentration of T lymphocytes and Natural Killer cells (Reid *et al.*, 2003), (Ouwehand *et al.*, 2002). These probiotcis are thought to decrease dental caries and respiratory tract infection. *Lactobacillus salivarius* is found to protect the mice from infections caused by *Listeria monocytogenes* by producing a chemical called bacteriocin (Corr *et al.*, 2007). Some strains of probiotics are useful in treating retrovirus infection (Trois *et al.*, 2007) and sexually transmitted infections (Bolton *et al.*, 2008) but no products are approved by FDA for such indications.

Peptic ulcer

Some strains of LAB may control Helicobacter pylori infections (cause of peptic ulcers) in adults when given concomitantly with standard medical treatments. But here also there is no product approved by FDA for this purpose.

Atopic diseases

Atopic dermatitis is the first symptom of atopic disease and it is a chronic skin condition associated with inflammation and pruritis (Simpson, 2010), eczematous papules, itch and plaques. It is one of the most prevalent skin diseases. 20% children and 1-3% adults are affected by atopic dermatitis. Atopic dermatitis tends to run in family. There is a high risk of developing atopic disease in children whose mother is atopic. It is found that probiotics play a major role in reducing occurrence of atopic diseases. The risk of occurrence of eczema during first 2 years of infant life was reduced significantly in those whose mother received probiotics as compared to those whose mother takes placebo (Rautava *et al*., 2002).

Liver diseases

The liver and gut has an important relation in a sense that the blood is carried form gut to the portal system. Liver functions are stimulated by intestinal blood content. Similarly bile secretion produced by liver affects gut performance. It is found that any change in the normal composition of gut micro flora alter liver function and can lead to initiation and progression of liver diseases (Cesaro *et al*., 2011). Many complications (Hepatic encephalopathy, cirrhosis, spontaneous bacterial peritonitis) are associated with overgrowth of harmful bacteria, changed intestinal permeability and improper immune function. Probiotics are useful in the treatment of chronic liver diseases as they block entry of microorganisms to blood flow and ultimately to liver by increasing the strength of intestinal barrier (Cesaro *et al.*, 2011). Another mechanism involves the regulation of gut micro flora (Sheth and Garcia, 2008) and regulation of immune functions (Jonkers and Stockbrügger, 2007). These also reduce the development of Hepatic encephalopathy and also support other medication for the treatment of Hepatic encephalopathy (Hopkins, 2003).

Food allergy

Food allergy is caused by the antigens present in food and is associated with inflammation of intestine. Probiotic are helpful in reducing the symptoms of food allergy as they enhance gut defence by two mechanisms (non-immunologic and immunologic). First is carried out by normalizing the gut microflora and decreasing membrane permeability. Second mechanism involves the enhancement of immunological defense system of host by boosting the IgA action. This leads to enhanced degradation of food antigens and food allergy is reduced (Kirjavainen *et al.*, 2001).

Upper respiratory tract infection

Upper respiratory tract infection includes laryngitis, tracheal inflammation and common cold and these are associated with symptoms like fever, headache, and pain and cough (Hao *et al*., 2011). Most of the upper respiratory tract infections (URTs) are caused by viruses and these resolve in 3 to 7 days. To treat the symptoms like headache, pain and fever, analgesics and antipyretics are used most frequently. Fermented food containing probiotics like Lactic acid bacteria and bifidobacteria are found to reduce the episode of URTs. Probiotics are also found to decrease the risk and incidence of respiratory tract infection (RTIs) in the children having age of 3-5 years (Ouwehand *et al*., 2008). These probiotics are also found to decrease the symptoms of pain, cough, and runny nose.

Oral health

Ptobiotics reside in oral cavity in a very less numbers, comprising only 1% of total micro biota of oral cavity (Haukioja, 2010). Probiotic species present in sliva includes *L. paracasei, L. plantarum,* L. *salivarius*, and *L. rhamnosus* (Haukioja, 2010; Ahrne *et al*., 1998). Bifidobacterial species which are found to be residing in oral cavity are *B. bifidum, B. dentium,* and *B. longum* (Haukioja, 2010). Probiotics enhance dental care by 3 possible mechanisms which include modulation of immune response, Normalization of oral microflora and metabolic effects (Parvez *et al*., 2006). Probiotics improve oral health by inhibiting incidence of following diseases.

Dental caries

One of the major causes of dental caries is mutant *streptococci*. It is suggested that the products containing probiotics when used, can decrease the number of mutant strain of *streptococci* (Nase *et al*., 2001; Cildir *et al*., 2009; Haukioja, 2010). In these studies it is found that consumption of food containing probiotics also enhances the level of slivary probiotics (Ahola *et al*., 2002; Montalto *et al*., 2006).

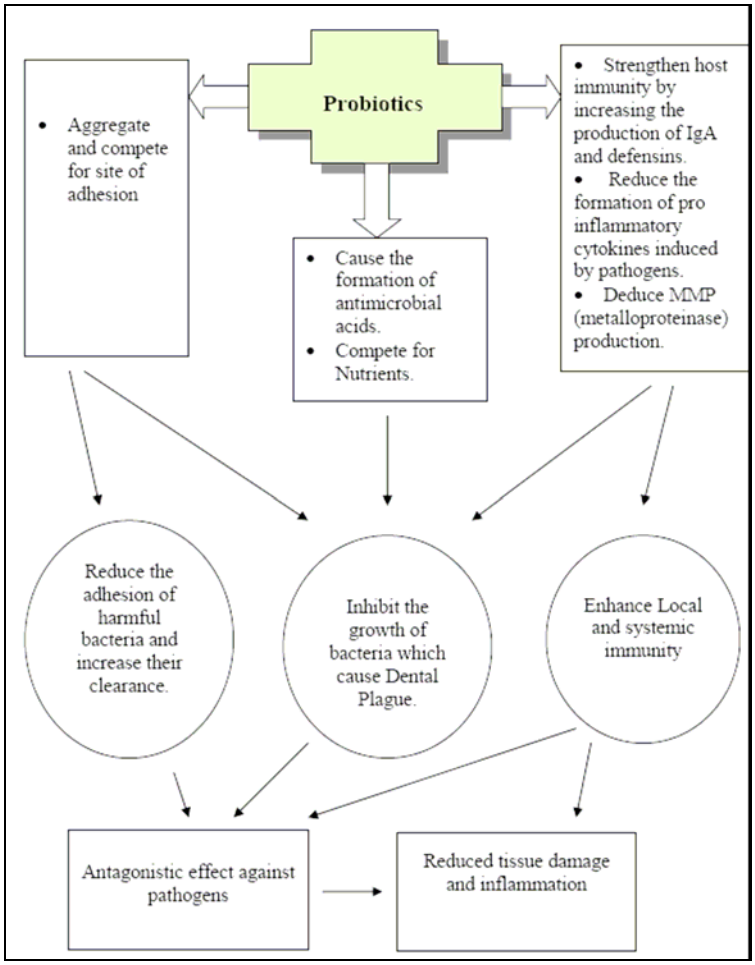

Fig. 2: Shows the mechanism by which probiotics improve oral health (Haukioja 2010)

Periodontal diseases

Periodental disease is an inflammatory disease which effect one or more periodontal tissues like alveolar bone, periodontal ligament, cementum, and gingiva. It is discovered that culture supernatant of *L. acidophilus*, when used in persons suffering from periodontal diseases (gingivitis, periodontitis and pregnancy gingivitis), treats most of the periodontal diseases. The probiotic species treating gingivitis include *L. brevis*, *L. casei, L. salivarius,* reuteri strains, *Bacillus subtilis, L. reuteri* and *L. brevis* (Krasse *et al*., 2006; Della *et al*., 2007; Twetman *et al*., 2009). *L. brevis* was found to contain anti inflammatory activity and it also inhibit MMP (collaginase) activity (Della *et al*., 2007). *B. subtilis* showed encouraging result in periodontitis by decreasing the number of pathogens in periodontal tissues (Tsubura *et al*., 2009).

Halitosis

Helitosis is the unpleasant odour exhaled in breathing. It itself is not a disease but is caused by some other diseases like periodontitis. Probiotics can be used in both gut and mouth mediated halitosis (Delanghe *et al*., 1997).

Oral candidiasis

Some strains of probiotics (*L. rhamnosus* strain, and *Propionibacterium freudenreichii*) are effective in reducing the candida yeast count (Haukioja, 2010).

Viral infections

Probiotcis are useful against many viral diseases. It is also obvious that probiotics do not show antiviral effect by direct action on viruses but do so by the mechanism of immunostimulation (De Vrese and Schrezenmeir, 2002). Those probiotics which show immunostimulation also exhibit potential antiviral effect. Thermophilus species have some antiinfluezal effect. These species also show anti herpetic effect when administered to guinea-pigs (Liaskovs *et al*., 2007). Antiviral activity of different probiotics against different viral infection is demonstrated in table 1.

Harmful effects of probiotics

Normally probiotics are considered as non-harmful bacteria that exert health benefit to the host. This is true in most cases. *Lactobecillus* are used for a long times due to

Table 1: Shows different infections mediated by different virus and the effect of different species of probiotics against these infections.

Study	Probiotic spp	Result	References
Antirotaviral effect in Mice	*B. breve*	*B. breve* showed antirotaviral activity by increasing production of IgA. It showed anti-influenzal effect by increasing IgG.	Yasui *et al*., 1999 Liaskovs *et al*., 2007
Oral polio vaccination	*L. rhamnosus* *L. paracasei*	Both showed anti polio effect due to increased IgG, IgA, and neutralizing antibodies.	De Vrese *et al*., 2001
Hepatitis A, B vaccination	*L. acidophilus* *B. bifidum*	Against Hepatitis A , B	De Vrese and Schrezenmeir, 2000
Anti herpes effect in Guinea pig	*Thermophilus spp*	*Thermophilus* showed anti herpetic effect.	Liaskovs *et al*., 2007
Treamtent of RTI in childrens	*L. rhamnosus*	Significant reduction in infection.	Hatakka *et al*., 2001
Listeria monocytogenes infection in mice	*L. salivarius*	Protection of mice from infection by producing a chemical called bacteriocin.	Corr *et al*., 2007
Effect of probiotics in Rotavirus mediated gastroenteritis in children	*Bifidobacterium lactis* *Saccharomyces boulardii*	Useful in antirotaviral therapy	Erdogan *et al*., 2012
Effect of probiotcis in HIV/AIDs infection	Yogurt bacteria	Probiotics increase CD4 count in blood and also reduce diarrhea incidence in HIV infected patients	Irvine *et al*., 2010

Table 2: Shows the risks of different species of probiotics

Probiotic spp	Health Risk	References
Sacharomyces bulardi, Bfidobacteria	Bacteraemia, Meningitis	De Vrese and Schrezenmeir, 2002
Bfidobacteria , Lactobecillus	Abdominal abscess	Brook and Friezer, 1993
L. rhamnosis	Liver abscess	Rautio *et al*., 1999
L. casei	Pneumonia and sepsis	Rogasi *et al*., 1998

their safety. Probiotics which are mostly considered as safe are *Lactococcus* and *Lactobacillus. Enterococcus*, *Streptococcus* and *Lactobacillus* contain some opportunistic bacteria (Salminen *et al*., 1998). Probiotics are also grouped into two classes based on their risk to health. Risk group 1(No risk) consists of *Lactobecillus* and *Bfidobacteria.* Risk group 2 (small risk) contains *L. rhamnosus* and *Bfidobacterium dentium* (De Vrese and Schrezenmeir, 2002). Harmful effects of different bacteria are shown in the table 2.

In addition most species are resistant to most of the antibiotics. This resistance is normally non transmissible. So there is no safety concern regarding the use of those bacteria having intrinsic resistance. But it may be possible that resistance may be transmissible as present in plasmid mediated resistance (Salminen *et al*., 1998). For example *Enterococci* have resistance against glycopeptides antibiotic (vancomycin and teicoplanin) and can transmit this resistance to other bacteria. Vancomycin is a last drug of choice in multi drug resistant pathogen. When these get resistance against vancomycin from *Enterococci* then it will be very difficult to treat them (Salminen *et al*., 1998). Pharmaceutical companies should keep in mind the potential of health risk of probiotics before adding these into particular products. Before launching any probiotic product, the safety profile of that particular probiotic species should be assessed to avoid incidence of any unexpected harmful effect.

REFERENCES

Ahmad M, Mahmood Q, Gulzar K, Akhtar MS, Saleem M and Qadir MI (2012). Antihyperlipidaemic and hepatoprotective activity of *Dodonaea viscosa* leaves extracts in alloxan-induced diabetic rabbits (*Oryctolagus cuniculus*). *Pak. Vet. J.*, **32**(1): 50-54.

Ahola AJ, Yli-Knuuttila H, Suomalainen T, Poussa T, Ahlstrom A and Meurman JH (2002). Short-term consumption of probiotic-containing cheese and its effect on dental caries risk factors. *Arch. Oral. Biol.*, **47**: 799-804

Ahrné S, Nobaek S, Jeppsson B, Adlerberth I, Wold AE and Molin G (1998). The normal Lactobacillus flora of

healthy human rectal and oral mucosa. *J. Appl. Microbiol.,* **85**: 88-94

Ali M, Qadir MI, Saleem M, Janbaz KH, Gul H, Hussain L, Ahmad B (2013) Hepatoprotective potential of *Convolvulus arvensis* against paracetamol-induced hepatotoxicity. *Bangladesh J. Pharmacol.*, **8**: 300-304.

Amin N, Qadir MI, Khan TJ, Abbas G, Ahmad B, Janbaz KH and Ali M (2012). Antibacterial activity of Vacuum liquid chromatography (VLC) isolated fractions of chloroform extracts of seeds of *Achyranthes aspera*. *J. Chem. Soc. Pak.,* **34**(3): 589-592.

Asif MA and Qadir MI (2011). Molecular approaches for development of malarial vaccines. *Rev. Pharmacol.,* **4**: 276-278.

Bokhari TH, Hina S, Ahmad M, Iqbal M, Shafiq M, Arshad MN, Asghar MN, Aslam M, Qadir MI (2012) Concentration of 188Re-Perrhenate for Therapeutic Radiopharmaceuticals. *J. Chem. Soc. Pak.,* **35**: 147-150.

Bolton, Michael, Straten VD, Ariane Cohen and Craig R (2008). Probiotics: Potential to Prevent HIV and Sexually Transmitted Infections in Women. *Sexually Transmitted Diseases,* **35**: 214-225.

Brady LJ, Gallaher DD and Busta FF (2000). The role of probiotic cultures in the prevention of colon cancer. *J. Nutr.,* **130**: 410-414.

Brook I and Frazier EH (1993). Significant recovery of non spurulating anerobic rods from clinical specimens, Clinical infectious diseases, **16**: 476-480.

Bruce AW, Chadwick P, Hassan A and van Cott GF (1973). Recurrent urethritis in women. *Can. Med. Assoc. J.,* **108**: 973-976.

Calcinaro F, Dionisi S, Marinaro M, Candeloro P, Bonato V, Marzotti S, Corneli RB, Ferretti E, Gulino A, Grasso F, De Simone C, Di Mario U, Falorni A, Boirivant M and Dotta F (2005). Oral probiotic administration induces interleukin-10 production and prevents spontaneous autoimmune diabetes in the non-obese diabetic mouse. *Diabetologia,* **48**: 1565-1575.

Cani PD and Delzenne NM (2011). The gut microbiome as therapeutic target. *Pharmacol. Ther.*, **130**: 202-212.

Cesaroa C, Tisoa A, Pretea AD, Cariellob R, Tuccilloa C, Cotticellia G, Blancoa CDV and Loguercioa C (2011). Gut microbiota and probiotics in chronic liver diseases. *Digest. Liver Dis.,* **43**: 431-438.

Chan RC, Bruce AW and Reid G (1984). Adherence of cervical, vaginal and distal urethral normal microbial flora to human uroepithelial cells and the inhibition of adherence of gram-negative uropathogens by competitive exclusion. *J. Urol.,* **131**: 596-601.

Cildir SK, Germec D, Sandalli N, Ozdemir FI, Arun T and Twetman S (2009), Reduction of salivary mutans *streptococci* in orthodontic patients during daily consumption of yoghurt containing probiotic bacteria, *Eur. J. Orthod.,* **31**: 407-4011.

Corr SC, Li Y, Riedel CU, O'Toole PW, Hill C and Gahan CGM (2007). Bacteriocin production as a mechanism for the antiinfective activity of *Lactobacillus salivarius* UCC118. *Proc. Natl. Acad. Sci. USA,* **104**: 7617-7621

Daus AD and Hafez ES (1975). *Candida albicans* in women. *Nurs. Res.,* **24**: 430-433.

De Vrese and Schrezenmeir (2000), Effect of probiotics on a defined immunologic challenge with Hepatitis A and B vaccine. Annual Report, p.57.

De Vrese M and Schrezenmeir J (2002), Probiotics and non-intestinal infectious condiditons, *Br. J. Nutr,* **88**: 59-66.

De Vrese M, Rautenberg p, Lauce C, Koopmans M, Herremans T and Schrezenmeir J (2001). Effect of probiotics on immune response to polio vaccination, proceding of German Nutrition Society, 3, 7.

Degnan FH (2008). The US Food and Drug Administration and Probiotics: Regulatory Categorization. *Clin. Infect. Dis.,* **46:** 133-136.

Delanghe G, Ghyselen J, van Steenberghe D and Feenstra L (1997), Multidisciplinary breath-odour clinic. *The Lancet,* **350**:187-187.

Della Riccia DN, Bizzini F, Perilli MG, Polimeni A, Trinchieri V and Amicosante G (2007). Anti-inflammatory effects of Lactobacillus brevis (CD2) on periodontal disease. *Oral Dis.,***13**: 376-385

Ehsan O, Qadir MI, Malik SA, Abbassi WS and Ahmad B (2012) Efficacy of nanogold-insulin as a hypoglycemic agent. *J. Chem. Soc. Pak.,* **34**(2): 365-370.

Erdoğan O, Tanyeri B, Torun E, Gönüllü E, Arslan H, Erenberk U and Oktem F (2012). The comparison of the efficacy of two different probiotics in rotavirus gastroenteritis in children. *J. Trop. Med.,* **2012**: 1-5.

Farnworth ER (2008). The evidence to support health claims for probiotic. *J. Nutr.,* **138**: 1250-1254.

Farooqi AA, Butt G, Yousaf G, Qadir MI, Shaukat U, Mansoor Q, Awan M, Bhatti S, Begum A (2013) Making personalized prostate cancer medicine a reality: Challenges and opportunities in the re-establishment of gold standards. *Pak. J. Pharm. Sci.*, **26**: 831-840.

FitzGerald RJ, Murray BA and Walsh DJ (2004), Hypotensive peptides from milk proteins. *J. Nutr.,* **134**: 980-988.

Flynn CA, Helwig AL and Meurer LN (1999). Bacterial vaginosis in pregnancy and the risk of prematurity: A meta-analysis. *J. Fam. Pract.,* **48**: 885-892.

Furrie E (2005). Probiotics and allergy, Proceedings of the Nutrition Society, **64**: 465-469.

Gionchetti P, Amadini C, Rizzello F, Venturi A, Palmonari V, Morselli C, Romagnoli R and Campieri M (2002). Probiotics Role in inflammatory bowel disease. *Digest. Liver Dis.*, **34**: 58-62.

Goel A.K, Dilbaghi N, Kambojm DV and Singh L (2006) Probiotics: Microbial therapy for health modulation. *Defence. Sci. J.,* **56**: 513-529.

Hamilton JMT and Miller (2004). Probiotics and prebiotics in the elderly. *Postgrad Med. J.,* **80**: 447-451.

Hao Q, Lu Z, Dong BR, Huang CQ and Wu T (2011). Probiotics for preventing acute upper respiratory tract

infections, Cochrane Database of Systematic Reviews, Issue 9. Art. No: CD006895. DOI: 10.1002/ 14651858.CD006895.pub2.

Hatakka K, Savilahti E, Ponka A, Meurman JH, Poussa T, Nase L, Saxelin M and Korpela R (2001), Effect of long turm consumption of probiotics milk on infections in children's attending day care centers: Double-blinded, randomized trials. *Br. Med. J.,* **322**: 1327-1329.

Haukioja A (2010). Probiotics and oral health. *Eur. J. Dent.,* **4**: 348-355.

Hoffman FA, Heimbach JT, Sanders ME and Hibberd PL (2008). Executive Summary: Scientific and Regulatory Challenges of Development of Probiotics as Foods and Drugs. *Clin. Infect. Dis.,* **46**: 53-57.

Holzapfel WH and Schillinger U (2002). Introduction to pre and probiotics. *Food Res. Int.,* **35**: 109-116.

Hopkins J (2003), Probiotics can treat hepatic Encephalopathy. *Med. Hypotheses,* **61**: 307-313.

Hussain A, Khalid SH, Qadir MI, Massud A, Ali M, Khan IU, Saleem M, Iqbal MS, Asghar S and Gul H (2011). Water uptake and drug release behaviour of methyl methacrylate-co-itaconic acid (P/MMA/IA) Hydrogels Cross-linked with methylene bis-acrylamide. *J. Drug. Delvr. Sci. Tech.,* **21**(3): 249-255.

Ilayas M, Qadir MI (2010) Role of estrogen in breast cancer. *Rev. Pharmacol.,* **2**: 48-52.

Irvine, Stephanie L, Hummelen, Ruben, Hekmat, Sharareh, Looman WN, Caspar, Habbema, Dik JF, Reid and Gregor (2010). Probiotic yogurt consumption is associated with an increase of CD4 count among people living with HIV/AIDS. *J. Clin. Gastroenterol.,* **44**: e201-e205.

Janbaz KH, Jan A, Qadir MI, Gilani AH (2013b) Spasmolytic, bronchodilator and vasorelaxant activity of methanolic extract of *Tephrosia purpurea*. *Acta Pol. Pharm.*, **79**: 261-269.

Janbaz KH, Nizsar U, Ashraf M and Qadir MI (2012) Spasmolytic, bronchodilator and antioxidant activities of *Erythrina superosa* Roxb. *Acta Pol. Pharm.,* **69**(6): 1111-1117.

Janbaz KH, Qadir MI, Jan A, Gilani AH (2013a) Anti-diarrheal activity of methanolic extract of *Tephrosia purpurea*. *Acta Pol. Pharm.*, **79**: 345-347.

Javed F, Qadir MI, Janbaz KH and Ali M (2011). Novel drugs from marine microorganisms. *Critical Rev. Micro.*, **37**(3): 245-249.

Jonkers D and Stockbrügger R. (2007), Probiotics in gastrointestinal and liver diseases. *Aliment Pharmacol. Ther.,* **26**: 133-148.

Khalid SH, Qadir MI, Massud A, Ali M and Rasool MH (2009). Effect of degree of cross-linking on swelling and drug release behaviour of poly (methyl methacrylate-co-itaconic acid) [P(MMA/IA)] hydrogels for site specific drug delivery. *J. Drug. Delvr. Sci. Tech.,* **19**(6): 413-418.

Kieling G., Schneider J and Jahreis G (2002). Long-term consumption of fermented dairy products over 6 months increases HDL cholesterol. *Eur. J. Clin. Nutr,* **56**: 843-849.

Kirjavainen PV, Apostolou.E, Salminen SJ and Isolauri E (2001). New aspects of probiotics-a novel approach in the management of food allergy. *Allergy,* **54**: 909-915

Korhonenn H (2009), Milk-derived bioactive peptides: From science to applications. *J. Func. Foods,* **1**: 177-187

Krasse P, Carlsson B, Dahl C, Paulsson A, Nilsson A and Sinkiewicz G (2006), Decreased gum bleeding and reduced gingivitis by the probiotic Lactobacillus reuteri. *Swed Dent J.,* **30**: 55-60.

Larsen N, Vogensen FK, van den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, Al-Soud WA, Sørensen SJ, Hansen LH and Jakobsen M (2010). Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS ONE*, **5**: e9085.

Liaskovs'kyĭ TM, Rybalko SL, Pidhors'kyĭ VS, Kovalenko NK and Oleshchenko LT (2007). Effect of probiotic lactic acid bacteria strains on virus infection. *Mikrobiol Z.,* **69**: 55-63.

Lye HS, Kuan CY, Ewe JA, Fung WY and Liong MT (2009). The improvement of hypertension by probiotics: Effects on cholesterol, diabetes, renin and phytoestrogens. *Int. J. Mol. Sci.,* **10**: 3755-3775.

Macfarlane S, Furrie E, Cummings JH and Macfarlane GT (2004). Chemotaxonomic analysis of bacterial populations colonizing the rectal mucosa in patients with ulcerative colitis. *Clin. Infect. Dis.,* **38**: 1690-1699.

Mann G.V and Spoerry A (1974). Studies of a surfactant and cholesteremia in the Maasai. *Am. J. Clin. Nutr,* **27**: 464-469.

Masood MI, Qadir MI, Shirazi JH and Khan IU (2011). Beneficial effects of lactic acid bacteria on human beings. *Critical Rev. Micro.*, **37**(1): 91-98.

Mattila-Sandholm TSE (1998). Demonstration of safety of probiotics: A review. *Int. J. Food Microbiol.,* **44**: 93-106.

Montalto M, Vastola M, Marigo L, Covino M, Graziosetto R and Curigliano V (2004). Probiotic treatment increases salivary counts of lactobacilli: A double-blind, randomized, controlled study. *Digestion*, **69**: 53-56.

Näse L, Hatakka K, Savilahti E, Saxelin M, Ponka A and Poussa T (2001). Effect of long-term consumption of a probiotic bacterium, Lactobacillus rhamnosus GG, in milk on dental caries and caries risk in children. *Caries Res.,* **35**: 412-420.

Naz S, Qadir MI, Ali M and Janbaz KH (2012) Nanotechnology for imaging and drug delivery in cancer. *J. Chem. Soc. Pak.,* **34**(1): 107-111.

Nisa TU, Qadir MI and Malik SA (2010) Anti-diabetic activity of inorganic metals *Eugenia jambolana* Lam. (Myrtaceae) flowers. *Pharmacologyonline,* **2**: 979-985.

Ouwehand A, Leyer G and Carcano D (2008). Probiotics reduce incidence and duration of respiratory tracts infection symptoms in 3- to 5-year-old children. *Pediatrics,* **121**: 115.

Parvez S, Malik KA, Ah Kang S and Kim HY (2006). Probiotics and their fermented food products are beneficial for health. *J. Appl. Microbiol.,* **100**: 1171-1185.

Qadir MI (2009) Medicinal and cosmetological importance of *Aloe vera*. *Int. J. Nat. Ther.,* **2**: 21-26.

Qadir MI (2010) Medicinal values of ginger. *Int. J. Nat. Ther.,* **3**: 19-22.

Qadir MI (2011) Qadirvirtide. *Pak. J. Pharm. Sci.*, **24**(4): 593-595.

Qadir MI, Malik SA (2008) Plasma lipid profile in gynecologic cancers. *Europ. J. Gyne. Oncol.,* **29**:158-161.

Qadir MI, Malik SA (2010) HIV fusion inhibitors. *Rev. Med. Virol.,* **20**: 23-33.

Qadir MI, Malik SA (2011) Genetic variation in the HR region of the *env* Gene of HIV: A perspective for resistance to HIV fusion inhibitors. *AIDS Res. Hum. Retrovir.,* **27**: 57-63.

Qadir MI, Malik SA, Naveed AK and Ahmad I (2006) Plasma lipid profile in sarcoma patients. *Pak. J. Pharm. Sci.*, **19**: 155-158.

Qadir MI, Naveed AK, Ahmad I, Malik SA (2007) Plasma lipid profile in childhood non-Hodgkin lymphoma patients. *Pak. Paed. J.*, **31**: 167-70.

Qadir MI, Nisa TU and Malik SA (2009). Effect of *Eugenia jambolana* leaves extracts on blood glucose levels of experimental diabetic rabbits. *Pharmacology online,* **3**: 829-835.

Rahman H, Qadir MI (2011) AIDS. *Health Sciences: International Journal.* **1**:2-4.

Rautava S, Kalliomäki M and Isolauri E (2002). Probiotics during pregnancy and breastfeeding might confer immunomodulatory protection against atopic disease in the infant. *J. Allergy Clin. Immunol.,* **109**: 191-121.

Rautio M, Jousimies-Somer H, Kauma H, Pietarinen I, Saxelin M, Tynkkynen S and Koskela M (1999). Liver abcess due to *Lactobecillus rhamnosis* strain indistinguishable from *L. rhamnosos* strain GG. *Clin. Infect. Dis.,* **28**: 1159-1160.

Reid G, Jass J, Sebulsky MT and McCormick JK (2003), Potential uses of probiotics in clinical practice. *Clin. Microbiol.,* **16**: 658-672.

Roberfroid M, Gibson GR, Hoyles L, McCartney AL, Rastall R, Rowland I, Wolvers D, Watzl B, Szajewska H, Stahl B, Guarner F, Respondek F, Whelan K, Coxam V, Davicco M-J, Léotoing L, Wittrant Y, Delzenne NM, Cani PD, Neyrinck AM and Meheust A (2010). Prebiotic effects: Metabolic and health benefits. *Br. J. Nutr.,* **104**: 1-63.

Rogasi PG, Vigano S, Pecile P and Leoncini F (1998). *Lactobecillus casei* pneumonia and sepsisin patient with AIDS, Case report and review of literature. *Annali Italani de medicine interna,* **13**: 180-182.

Saleem M, Qadir MI, Perveen N, Ahmad B, Saleem U, Irshad T, Ahmad B (2013) Inhibitors of apoptotic proteins: New targets for anti-cancer therapy. *Chem. Biol. Dru. Desi.,* **82**: 243-251.

Salminen:http://www.sciencedirect.com/science/article/pii/S0168160598001287 - AFF1

Sanders ME (2008). Probiotics: Definition, sources, selection and uses. *Clin Infect Dis.,* **46**: 58-61.

Schwebke JR, Richey CM and Weiss HL (1999). Correlation of behaviours with microbiological changes in vaginal flora. *J. Infect Dis.,* **180**: 1632-1636.

Shah NP (2000). Some beneficial effects of probiotic bacteria. *Biosci. Microflora,* **19**: 99-106.

Sheth AA and Garcia-Tsao G (2008), Probiotics and liver disease. *J. Clin Gastroenterol,* **42**: 80-84.

Simpson EL (2010). Atopic dermatitis: A review of topical treatment options. *Curr. Med. Res. Opin.,* **26**: 633-640.

Sindhu SC and Khetarpaul N (2003). Effect of feeding probiotic fermented indigenous food mixture on serum cholesterol levels in mice. *Nutr. Res.,* **23**: 1071-1080.

Stamey TA and Sexton CC (1975). The role of vaginal colonization with enterobacteriaceae in recurrent urinary infections. *J. Urol.,* **113**: 214-217.

Tabasum A, Qadir MI (2010) Deficiency of vitamin K linked to cancer, osteoporosis and heart diseases. *Int. J. Pharm. Rev. Res.,* **1**: 24-32.

Troisa L, Cardosob EM and Miurac E (2007). Use of Probiotics in HIV-infected Children: A Randomized Double-blind Controlled Study. *J. Trop. Pediat.,* **54**: 19-24.

Tsubura S, Mizunuma H, Ishikawa S, Oyake I, Okabayashi M and Katoh K (2009). The effect of Bacillus subtilis mouth rinsing in patients with periodontitis. *Eur. J. Clin. Microbiol. Infect. Dis.,* **28**: 1353-1356

Tuohy K, Probert HM, Smejkal CW and Gibson GR (2003). Using probiotics and prebiotics to improve gut health. *Therapeutic Focus,* **8**: 692-700.

Twetman S, Derawi B, Keller M, Ekstrand K, Yucel-Lindberg T and Stecksen-Blicks C (2009). Short-term effect of chewing gums containing probiotic *Lactobacillus reuteri* on the levels of inflammatory mediators in gingival crevicular fluid. *Acta Odontol. Scand.,* **67**: 19-24

Wassenaar, Trudy M, Klein and Günter (2008). Safety aspects and implications of regulation of probiotic bacteria in food and food supplements. *J. Food Protect.,* **71**: 1734-1741.

Wilson J (2004). Managing recurrent bacterial vaginosis. *Sex Transm. Infect.,* **80**: 8-11.

Wollowski I, Rechkemmer G and Pool-Zobel BL (2001). Protective role of probiotics and prebiotics in colon cancer. *Am. J. Clin. Nutr.*, **73**: 451-455.

Wright and Atte v (2005). Regulating the Safety of

Probiotics: The European approach. *Curr. Pharm. Des.*, **11**: 17-23.

Yadav H, Jain S and Sinha PR (2007). Antidiabetic effect of probiotic dahi containing Lactobacillus acidophilus and Lactobacillus casei in high fructose fed rats. *Nutr,* **23**: 62-68

Yamamoto N and Takano T (1999). Antihypertensive peptides derived from milk proteins. *Nahrung,* **43**: 159-164.

Yekeen LA, Sanusi RA and Ketiku AO (2003). Prevalence of obesity and high level of cholesterol in hypertension: Analysis of data from the university college hospital, Ibadan. *Afr. J. Biomed. Res.*, **6**: 129-132.

Yousuf A, Qadir MI, Bashir A (2012) Recent advances in treatment of ovarian cancer. *Pharmacologyonline*, *Nl* **3**: 1-7.