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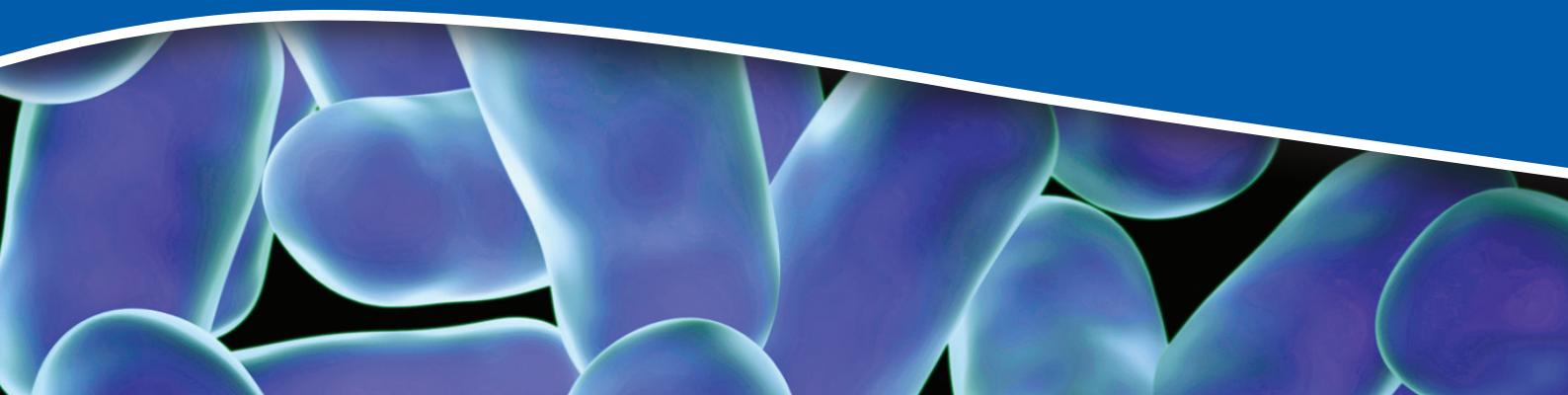


The human gut is host to a highly complex ecosystem of micro-organisms, the functions and interactions of which are largely still unknown. It is estimated that between 20-40% of observed colonic microflora are unculturable and therefore unidentified [1], in older subjects this unculturable percentage rises to nearer 80% [2]. Given that the gut flora alone comprises an astonishing 95% of the total number of cells in the human body – 100,000 billion organisms [3], it is hardly surprising that there is much yet to learn about this vast microbial ecosystem.

Whilst much yet remains undiscovered, we do have a developing understanding of some of the main bacteria existing in both the large and small intestine and, crucially, indications of how normal flora may become out of balance and the subsequent implications for health. There is a growing body of evidence that probiotic supplementation may be therapeutically helpful in some specific conditions. This paper explores the evidence behind probiotic use and provides guidelines for most effective clinical benefit.

FUNCTIONS OF MICROFLORA

The gut microflora play a vital role in health, particularly in the areas of nutrition and metabolism, immune function and protection. Healthy microflora is essential for:

- Normal physiological function of the intestinal mucosa including motility, secretion and absorption.
- Maintenance of appropriate gut pH.
- Digestive function through enzyme activity i.e. breakdown of lactose.
- Modulation of immune function – can elicit immune responses as well as producing antimicrobial substances to protect against microbial pathogens.
- Stimulation, maturation and balancing of immune system at birth & continued 'priming' of the immune system throughout life.
- Synthesis of vitamins (such as folic acid, biotin, riboflavin & vitamin K).
- Production of amino acids – ability to recycle urea into sufficient amino acids to meet around 10% of the body's overall requirements.
- Synthesis of short chain fatty acids to provide fuel for the epithelial cells as well as to the whole body.
- Detoxification and transformation of many substances that could be potentially damaging to the body – e.g. deconjugation of bile salts.

PROBIOTICS

Probiotics are defined by the World Health Organisation as 'living microoganisms which when administered in adequate amounts confer a health benefit on the host.' [4] The health benefits of probiotics can be attributed to their ability to assist the microflora in some way, either to re-establish itself following imbalance or to up regulate the vital metabolic functions of the bacteria as outlined above. Of the thousands of potential probiotic bacteria, it is important to differentiate which may be the most clinically effective and safe. There have been various criteria proposed by researchers, which may be considered important in the selection of probiotic strains including:

- Organisms should be non-pathogenic and of human origin.
- Organisms should be able to maintain viability during manufacturing processes and delivery mechanisms into the body.
- Organisms must remain viable during transit through the acidic conditions of the stomach.
- Organisms must also be bile tolerant.
- Organisms must have the ability to adhere to the gut epithelial tissue.
- Organisms must be genetically stable.
- Organisms should have the ability to produce antimicrobial substances and inhibit known pathogens.
- Organisms should have a positive effect on the immune system and certain metabolic pathways.
- Organisms should have a proven clinical research track record.

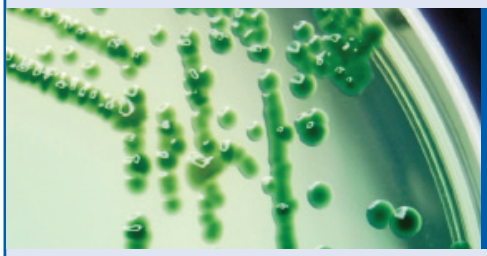
It is important to emphasise that, simply because a diversity of organisms exist in the gut, it does not necessarily follow that supplementation of multiple strains will result in a health benefit. What is critical is that the specific combination has demonstrable effects. Only a few select cultures identified in the gut have actually been proven to be beneficial and can therefore be justifiably called 'probiotics'. Of the potentially beneficial bacteria, the lactic acid bacteria (including *Lactobacilli* and *Bifidobacteria*) have proven health benefits to the host, and they have the most potential to fulfil all the criteria outlined above and as such are regarded as the most appropriate choice for probiotics.

CLINICAL APPLICATIONS OF PROBIOTICS

Antibiotic Therapy

Administration of antimicrobial agents, such as antibiotics, disturb the ecological balance between the host and normal microflora [5]. Disturbance of the microflora can result in secondary complications such as diarrhoea, gastritis or fungal infection [6].

Administration of a range of antibiotics such as penicillin, clindamycin, vancomycin and tetracycline can result in proliferation of *Candida albicans* in the intestine [7] [8]. In a significant proportion of people this overgrowth progresses to a stage of mucosal colonisation, triggering an inflammatory response. One study showed that administration of antibiotics caused intestinal overgrowth of yeasts in 50% of subjects, with a 33% incidence of mucosal surface colonisation. In up to 15% of subjects, this appeared to be persistent indicating continued mucosal colonisation and possibly continuous/intermittent low level inflammatory response [9]. These potential side effects have significant implications for patient comfort, compliance, speed of recovery and longer-term health.



'it does not necessarily follow that supplementation of multiple strains will result in a health benefit. What is critical is that the specific combination has demonstrable effects.'

- The results of a meta-analysis of studies suggests a strong benefit of probiotic administration in relation to antibiotic associated diarrhoea [10].

- At least two trials have shown that supplementation with probiotics following antibiotic use prevents multiplication of *Candida albicans*. [9] [11].

- The latter trial was a randomised double-blind placebo-controlled trial and also demonstrated significant competitive inhibition of *Clostridium difficile* in hospitalised patients given a proprietary high strength blend of *Lactobacillus acidophilus* and *Bifidobacterium bifidum*. 67% of control patients developed diarrhoea as opposed to 18% of the probiotic treated patients [9].

- A further randomised placebo-controlled double-blind trial demonstrated significant reduction of opportunistic pathogen

re-growth following use of antibiotics. Specifically there was statistically significant reduction of *Staphylococci, Enterococci* and *Enterobacteria* (coliforms) in patients given a proprietary high strength blend of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* after antibiotic dosage. The effect was more profound if the probiotics were given both with and following antibiotics [12].

'there was statistically significant reduction of Staphylococci, Enterococci and Enterobacteria (coliforms) in patients given a proprietary high strength blend of Lactobacillus acidophilus and Bifidobacterium bifidum after antibiotic dosage.'

- A further well-designed study showed reduction in antibiotic associated diarrhoea for patients given a probiotic drink consisting of *Lactobacillus casei, Lactobacillus bulgaricus* and *Streptococcus thermophilus* [13].

Antibiotic Resistance

A related area of growing concern is that of antibiotic resistance [1]. Bacteria have life cycles of minutes as opposed to years and as such have an extraordinary ability to evolve and adapt to changes in their environment [14]. In a world where only the fittest survive, those bacteria that have developed antibiotic resistance will predominate. Antibiotic resistance is particularly apparent in hospital environments where bacteria are constantly exposed to a wide cross section of different antibiotics, potentially leading to the emergence of ever more virulent hospital borne infections. One possible solution to antibiotic resistance may be the use of probiotics themselves.

- Certain probiotic bacteria have been shown to produce potent antimicrobial peptides called bacteriocins, which specifically target the invading pathogen (15). Whilst traditional antibiotics usually exert their action by a specific mode of action, bacteriocins have diverse multiple modes of actions, significantly reducing the risk of resistance development. [16].

- A trial using a high strength blend of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* demonstrated greater than 70% reduction in antibiotic resistance in coliforms and *Enterococci* [17].

Vaginal Thrush

There is good evidence for the use of *Lactobacillus* species such as *acidophilus* and *gasseri* in prevention of *candidal* vaginitis [18].

- In one study such bacteria were shown to protect the vaginal epithelium through improving barrier function and increasing interference with pathogens. [18b].

- In another trial, women who were HIV-positive and predisposed to vaginal *Candida* infection, received either *Lactobacillus acidophilus* vaginal suppositories, an antifungal drug, or placebo for 21 months. Compared to those receiving placebo, women receiving *Lactobacillus acidophilus* suppositories had only half the risk of experiencing an episode of *Candida* vaginitis [19].

Travellers' Diarrhoea

A meta-analysis of 34 masked, randomised placebo controlled trials showed that *Lactobacillus acidophilus* reduced the risk of acute travellers' diarrhoea [20].

H.Pylori Infection

Lactobacilli, particularly *Lactobacillus acidophilus* have been shown to inhibit *H. pylori* in vitro by pH reduction and several studies show promise in vivo alongside traditional antibiotic therapies [21] [22].

- In one study printed in the American Journal of Gastroenterology, only *Lactobacillus salivarius* was able to produce high amounts of lactic acid and completely inhibit the growth of *H.pylori* in a mixed culture [23].

- A study on children who had previous *H.pylori* infections, indicates that probiotics may be of benefit for the prevention of re-infection by inhibiting adhesion of *H.pylori* to gastric epithelial cells [24].

Irritable Bowel Syndrome

It has been suggested that one causative factor for IBS may be colonic mal-fermentation due to an imbalance of gut flora. In the past there have been mixed results in probiotic intervention trials, possibly due to insufficient duration or potency of the products used. However recent high quality studies are showing very positive results.

- One study was a double-blind, randomised, placebo-controlled trial conducted at the University of Sheffield using a proprietary high strength blend of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* & *lactis*. Subjects showed a significant improvement in the symptom severity score including quality of life, pain and satisfaction with bowel habit [25].

- A further recent trial explored the effect of *Bifidobacterium lactis* on abdominal distension - an extremely common feature of IBS. Using an objective technique for measuring abdominal girth, probiotic treatment significantly reduced distension as well as other symptoms when compared to placebo [26].

- Whorwell et al (2006) assessed the efficacy of *Bifidobacterium infantis* in a large scale, multicentre, clinical trial on women with IBS. *B. infantis* at a dose of $1x10^8$ cfu was significantly superior to placebo for reducing abdominal pain, incomplete evacuation, straining and passage of gas [27].

Inflammatory Bowel Disease

A consistent feature in a chronic inflammatory condition such as IBD seems to be an increase in intestinal permeability, which can develop into inflammatory lesions and trigger mucosal inflammation. The mucosal barrier provides an important interface between the contents of the gut and the host's immune cells. In a healthy state, intricately evolved feedback mechanisms control gut wall responses to commensal bacteria, but during chronic inflammation immune signals are dysregulated [28].

Lactobacillus salivarius has been shown to strengthen the epithelial barrier, whilst simultaneously reducing mucosal levels of inflammatory cytokines [29] In addition it also has ability to break down incompletely digested proteins and their undesirable by-products, leading to a reduced potential for putrefaction.

A further key factor in IBD is the lack of regulation of the immune response through release of T regulatory cytokines. *Sierra et al* [30] observed that *Lactobacillus salivarius*, exhibits immunomodulatory properties that may induce the activation of both innate and specific immune responses enhancing defence against pathogens, whilst also inducing immuno-modulatory cytokines.

The Infant Microflora

Pregnancy, birth and early infancy are vital times for development of the microflora. An infant is delivered into this world sterile; the

gastrointestinal tract totally devoid of micro-organisms. Colonisation occurs rapidly, with the newborn being exposed to the mother's vaginal and faecal microflora as well as organisms from the environment [31].

- It has been shown that there are significant differences between the microflora of naturally born infants and those delivered by caesarean. Caesarean section infants have profoundly different microflora in the first months of life and abnormalities remain at 7 years and probably lifelong and these infants may be at increased risk of allergy compared to vaginal birth infants [32].

  Breast feeding can also be influential on microflora. Prebiotic and other factors in breast milk result in a predominance of *Bifidobacteria* species, with *enterobacteria* and *enterococci* present in small quantities [33].

- In a recent trial, the gut flora of breast compared to formula fed infants was still significantly different at 6 months - formula feeding leading to a persistent reduction in *Bifidobacteria* compared to breastfeeding [34].

  A further major shift in microflora occurs during weaning - other organisms start to colonise establishing a more 'adult' flora including *Lactobacilli, Bacteroides,* and *Streptococci* [35].

  At each of these key stages, probiotics may offer a benefit in helping to establish a more favourable microflora, which could then pave the way for associated health benefits throughout life.

- In terms of treatment of specific gastrointestinal conditions, one study has shown positive results using probiotics including *Bifidobacteria* in treating Necrotising Enterocolitis in low birth weight neonates [36].

Immune Priming

It is speculated that this early colonisation of the human intestine by the normal microflora is essential for the development of the human immune system - priming and enabling the immune cells to react to harmful and harmless antigens in an appropriate way. A failure to develop this symbiotic relationship may lead to a reduced immune function and/or allergy.

Allergies

Allergies such as asthma, allergic rhinitis & atopic dermatitis have seen a significant increase over the last decade, especially in children. One hypothesis for the rise in allergies is the simultaneous increase in use of antibiotics, especially in children under 2 years [43]. As further evidence for this theory, children with an atopic profile have been found to have imbalanced levels of bowel flora, notably decreased levels of *Bifidobacteria and Lactobacilli*, and increased levels of *Staphylococcus aureus* [44].

It would therefore seem that the role of probiotic bacteria in helping to modulate an appropriate immune response to potential antigens might be important potential treatment option, research is on going in this area:

- One study with children at high risk of allergy demonstrated reduction of developing atopic disease (specifically eczema) up to 2 years of age using *Lactobacillus rhamnosus* probiotics [45]. A follow up study confirmed that the reduction continued until the same children reached 4 years of age [46]. Wickens (2008) has had similar success with prevention of eczema using another strain of *Lactobacillus rhamnosus* [47].

- Some progress has also been reported in positively treating existing atopic dermatitis using *Lactobacillus fermentum* [48].

- In terms of asthma, long-term consumption of yoghurt containing *Lactobacilli* and *Bifidobacteria* reduced circulating IgE levels and clinical symptoms in 3 clinical trials [49] [50] [51].

Food Sensitivities

Probiotics may be important in non-allergy related food intolerance reactions due to their ability to improve digestion, help absorption and change the immune systems response to the potential allergens [52] [53] [54].

- The probiotic *Pedicoccus pentosaceus* may also be of interest for its ability to help with full breakdown of food. Research has shown this species to be proteolytically active on gluten. [55]

'probiotics may offer a benefit in helping to establish a more favourable microflora, which could then pave the way for associated health benefits throughout life.'

- *Lactobacilli* have been found to stimulate production of regulatory T cells producing TGF-B and IL-10 and suppressing Th2 cytokines in both animal and human infants [37] [38].

- Other specific research has shown that *Lactobacillus bulgaricus* down-regulates pro-inflammatory cytokines in gut tissue samples taken from Crohn's sufferers [39] whilst *Lactobacillus rhamnosus* has been shown to be a potent stimulator of Interleukin 12, which positively enhances cell mediated immunity [40].

- In a comprehensive research review, Gill (2003) gives several examples where probiotics have been used to enhance immunity including one trial where subjects given *Lactobacillus rhamnosus* generated more phagocytically active blood leukocytes than controls [41]. This is just one example of a probiotic, which has been shown to exhibit non-specific and specific immune enhancing activity.

- Further clinical trials have demonstrated that probiotics may decrease the incidence of respiratory tract infections in children [42].

Ageing

Age-related changes in gut physiology, microflora and mucosal immune response are well established [56]. Numbers of *Bifidobacteria* in the gut decrease markedly after 55-60 years of age; therefore probiotics may have a particular relevance for preventing immune senescence and several age-related diseases in this high-risk group.

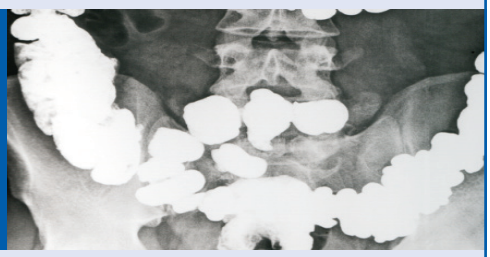
Obesity

The connection between gut flora, energy production, inflammation and obesity-related disorders is becoming increasingly recognised. Following encouraging results in animals, several short-term randomised trials have demonstrated the benefits of pre and probiotics on insulin sensitivity, inflammatory markers, post-prandial insulin release and glucose tolerance.

- In a recent Finnish randomised controlled trial, 256 women were divided into three groups during the first trimester of pregnancy. Two of the groups received dietary counselling consistent with current recommendations. One of these groups also received a daily probiotic, whilst the other group received a

placebo. The third group received placebo capsules and no counselling. Supplementation continued until the women stopped exclusive breastfeeding up to 6 months. At the end of the study, central obesity was recorded in 18% fewer women in the probiotic group than in women who received placebo and counselling. Average body fat was 28% in probiotic group versus 29-30% in other groups [57].

'It has been suggested that probiotics may modulate several major intestinal functions potentially associated with development of colon cancer.'



"Bacteria are passed from mother to child through the birth canal, as well as through breast milk and research indicates that early nutrition may influence the risk of obesity later in life. There is growing evidence that this approach might open a new angle on the fight against obesity, either through prevention or treatment" Laitinen [57].

Hyperlipidaemia

In vivo studies have shown a positive benefit of administration of pre and probiotics in improving lipid profiles, including the reduction of serum total cholesterol. The process by which probiotics exert this action is thought to involve deconjugation of bile acids. Once deconjugated, bile acids are less soluble and are absorbed by intestines for excretion in faeces. Cholesterol is used to synthesise new bile acids in a homeostatic response resulting in a lowering of total cholesterol [58].

Other research has shown that certain strains of probiotics are able to remove cholesterol by a secondary mechanism - binding onto cellular surfaces. In a parallel 8-week study on hypercholesterolemic pigs, *Liong at al* found a combination of *Lactobacillus acidophilus*, fructooligosaccharides, insulin & mannitol decreased plasma total cholesterol, LDL cholesterol and triacylglycerols compared to control [59].

More clinical evidence is needed to strengthen these proposals and ascertain effective dosage needed to exert a hypocholesterolemic effect.

Oral Health

In the oral cavity, probiotics can create a bio-film which acts as a protective lining against oral diseases.

- *Nase et al* reported a reduced tooth decay incidence in children taking probiotic *Lactobacillus rhamnosus* enriched milk versus a control group of children taking milk without probiotic supplementation [60].
- High levels of *Lactobacillus* in the microflora have been shown to effectively reduce gingivitis causing bacteria by 82% [61].
- In an open-label pilot trial, 20 patients with genuine halitosis received oral administration of *Lactobacillus salivarius* with xylitol for 4 weeks. Oral malodor parameters significantly decreased after 2 weeks and bleeding on probing of the periodontal pocket significantly decreased at 4 weeks [62].

Urinary Tract Infections

The predominant bacteria in the urinary tract of healthy women are *Lactobacilli*. Recurrent urinary tract infections are usually caused by *E.coli* and are treated with antibiotics. Some studies have suggested probiotics as a good alternative to antibiotic therapy due to their ability to adhere to uro-epithelial cells as well as producing inhibitors of pathogenic growth. The same authors were able to show that under the right conditions, oral supplementation of *Lactobacillus acidophilus* will result in colonisation within the urinary tract [63].

Colon Cancer

There seems to be a strong relationship between colon cancer, diet and intestinal microflora. It has been suggested that probiotics may modulate several major intestinal functions potentially associated with development of colon cancer, in particular research has shown that probiotics:

- May prevent the growth of deleterious organisms, which have potential to produce carcinogenic substances.
- Help to deconjugate bile salts reducing the potentially cytotoxic effect on the gut lining.
- Can increase levels of butyric acid which is an important energy source and growth regulator of colonic cells.
- May prevent harmful enzymatic activity in the gut (β-glucoronidase, nitro-reductase).
- Can stimulate the activity of beneficial enzymes such as glutathione S transferase, which has the ability to inactivate carcinogens.
- Produce lactic acid and short chain fatty acids to protect against pathogenic overgrowth [64].

Autistic Spectrum Disorder

Children on the autistic spectrum are commonly seen to exhibit gastrointestinal abnormalities. *Melmed et al* reported in a study of 385 autistic people, that 46% experienced chronic diarrhoea, constipation or other GI symptoms [65].

- A study by D'Eufemia found that 43% of a sample of autistic children had increased intestinal permeability [66].
- GI problems were associated with high levels of *clostridium histolyticum* in patients with ASD compared with unrelated healthy children. This group of researchers speculated that there could be an overproduction of *Clostridia* related neurotoxins in an autistic gut leading to increased toxin levels in the bloodstream subsequently exerting detrimental systemic effects [67].

The use of probiotics and prebiotics in improving the integrity of the gut mucosa as well as the gut flora, has been suggested as a beneficial approach in ASD [68].

CONCLUSIONS

There is a growing body of evidence that probiotic supplementation may be helpful in a wide gamut of health conditions. Probiotics play an important role in improving abnormalities of the intestinal microflora, elaborating antibacterial molecules, enhancing mucosal barrier defenses and supporting host metabolism. Research in this exciting area is expanding by the day and will undoubtedly uncover new wisdom about these powerful allies residing within our gut.

PROBIOTICS AND THEIR USES

HEALTH CONDITION	PROBIOTIC	BENEFIT	EVIDENCE
Antibiotic associated diarrhoea	High strength *L.acidophilus* & *B.bifidum* blend	Shown to help prevent diarrhoea associated with post antibiotic C.difficile overgrowth	Cremonini F et al, 2002 Plummer S et al, 2004
Candida albicans	High strength *L.acidophilus* & *B.bifidum* blend	Shown to help prevent post antibiotic overgrowths	Plummer S et al, 2004 Elmer GW et al, 1996
Vaginal Thrush	*L.acidophilus* pessary		Williams A et al, 2000
Prevention of antibiotic resistance	High strength *L.acidophilus* & *B.bifidum* blend	Demonstrated a 70% reduction in antibiotic resistance	Plummer S et al, 2005
Travellers' diarrhoea		Take prophylactically	Sazawal S et al, 2006
H.pylori	*L.acidophilus* *L.salivarius*	Taken alongside antibiotic therapy helps prevent regrowth by preventing adhesion of H.pylori Produces sufficient lactic acid to inhibit growth & protect against infection	Canducci F et al, 2000 Hamilton-Miller JM, 2003 Lionetti E et al, 2010 Aiba Y et al, 1998
Irritable Bowel Syndrome	High strength *L.acidophilus* & *B.bifidum* blend *L.lactis* *L.infantis*	Shown to significantly improve pain and bowel habits Helps with abdominal distension Shown to help pain, straining, incomplete evacuation & bloating. Dosage of 1 x 10^8 cfu	Williams E et al, 2008 Agrawal A et al, 2008 Whorwell et al, 2006
Intestinal Bowel Disease	*L.salivarius*	Helps immune regulation (T reg) Strengthens epithelial barrier Down regulates inflammatory cytokines	O' Hara AM et al, 2006 Sierra S et al, 2010
Crohn's Disease	*L.bulgaricus* *L.rhamnosus*	Down regulates inflammatory cytokines Increases 112 & cell mediated immunity	Borruel N et al, 2002 Hessle C et al, 1999
Development of infant immunity	*B.infantis*	Most dominant Bifido organism in natural birth, breast fed infants	Rasic J, 1992
Immune support	*L.acidophilus*	Stimulates production of T-reg cells Down regulates inflammatory cytokines	Von der Weid T et al, 2001 Pessi T et al, 2001
Childhood allergies	*L.rhamnosus* *L.fermentum*	Shown to help reduce risk of developing childhood atopic disease Some success shown in treatment of existing atopic dermatitis	Kalliomaki M et al, 2001 & 2003 Wickens K et al, 2008 Weston S et al, 2005
Food sensitivities	Probitiotics *Pedicoccus pentosaceus*	May help non-allergy related food reactions by improving digestion, absorption & immune response Proteolytically active on gluten	Kirjavainen PV et al, 1999 Pelto L et al, 1998 Salimen S et al, 1996 Gerez CL et al, 2006
Age related health decline	*B.bifidum*	Shown to help prevent immune senescence & some age-related diseases	Romeo J et al, 2010
Obesity	Probiotic	Shown to help with post pregnancy weight loss. Take through pregnancy & during breast feeding	Laitinen K et al, 2009
Hyperlipidaemia	*L.acidophilus*	Shown to decrease plasma total cholesterol, LDL & triacylglycerols	Liong et al, 2007
Oral health	*L.rhamnosus* *Lactobacillus* *L.salivarius*	Reduces incidence of tooth decay in children Shown to effectively reduce gingivitis causing bacteria Shown to benefit halitosis after 2 weeks oral use Shown to benefit bleeding gums after 4 weeks oral use	Nase et al, 2001 Koll-Klais P et al, 2005 Iwamoto T et al, 2010 Iwamoto T et al, 2010
Urinary Tract infections	*L.acidophilus*	Shown to adhere to uro-epithelial cells & inhibit pathogenic growth	Zuccotti et al, 2008

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