

Polybac 8™

General Description

A broad-spectrum multi-strain probiotic supplement for the maintenance of a robust intestinal milieu – to help fortify natural resistance.

Product Features and Highlights

Polybac 8™ combines a select group of highly important probiotic microorganisms. These include both human resident strains, and transient strains. These microorganisms are bio-synergistic and create a stable, rapid growing matrix of beneficial bacteria.

POLYBAC 8™ is the most reliable probiotic combination for immediate bowel recolonisation during antibiotics.

Active Ingredients

Each 5mL level medicinal spoonful / capsule (equiv. 3 grams) of Polybac 8™ contains:

<i>Lactobacillus rhamnosus</i>	9.0 billion organisms
<i>Lactobacillus acidophilus</i>	7.5 billion organisms
<i>Lactobacillus plantarum</i>	7.5 billion organisms
<i>Lactobacillus casei</i>	7.5 billion organisms
<i>Bifidobacterium lactis</i>	4.5 billion organisms
<i>Bifidobacterium longum</i>	4.5 billion organisms
<i>Lactobacillus salivarius</i>	3.0 billion organisms
<i>Streptococcus thermophilus</i>	1.5 billion organisms

Dosage

Powder

Dissolve in water, 1 level 5ml medicinal spoonful (equiv. 3g). Take 30 minutes before a meal once daily or as directed by your healthcare practitioner.

Capsules*

Take one capsule daily or as directed.

Children

Infants up to the age of 2 years: an 8th to ¼ of a metric teaspoon (frequency of dose will depend on the condition and individual health needs of the child).

Children 2 years and over: ½ of a metric teaspoon daily or as advised.

* POLYBAC 8™ Capsules are not suitable for ingestion by children.

Description

Dietary supplement. Broad-spectrum multi strain probiotic. Low allergy exipients. Free from added salt, yeasts, gluten, wheat, dairy products, preservatives, artificial colours and flavors.

Potential Uses

When appropriately prescribed, the active ingredients in Polybac 8™ may assist patients suffering from the following conditions. Note that this statement does not imply or make a claim for a cure for these disorders. The use of Polybac 8™ powder should be based on published and relevant scientific and clinical data for each condition.

Polybac 8™

- Relief or treatment of diarrhoea.
- Relief of the symptoms/pain/discomfort of gastritis.
- For the symptomatic relief of medically diagnosed irritable bowel syndrome
- Aids digestion.
- Helps maintain healthy digestive function.
- Aids, assists or helps in the maintenance or improvement of general well-being.
- Aids or assists in the relief of flatulence.
- Relief of indigestion.
- Restore bowel microflora after antibiotics, while using the contraceptive pill, or to assist when the diet is inadequate.
- Relieves bloating.
- Can increase tolerance in food-sensitive individuals.
- Can stimulate digestion.

General Information

The human organism is highly dependent on bacteria for its health and survival. The number of bacteria in the human body is astounding. In total, a healthy adult can carry individual bacteria that have been estimated in multiples of 10²⁴ in the gastrointestinal tract alone. (Heumer and Callam 2000) Collectively they operate as a highly organised entity similar to a body organ, although each individual bacterium is much smaller than a human cell.

The resident human micro-flora consists of many different species, some of which are implanted at birth, and others that are acquired during the later stages of life. The birth canal is rich in the Lactobacillus species, and another important species Bifido bacteria are introduced soon after, protecting the newborn and discouraging pathogens, which could otherwise cause disease.

It is now widely accepted that the indigenous or commensal bacteria that inhabit the gastrointestinal environment (and other niches in the human body) play a powerful role in human immunity. When, to borrow a phrase from scientist James Lovelock, “we threaten the integrity of our exquisitely engineered internal homeostasis,” the susceptibility to disease is increased. (Lovelock 1985)

The human body can be seen as a dynamic self-regulating organism, whose health (homeostasis) is dependent on the maintenance of a balanced internal ecosystem. The maintenance of this ecosystem, and subsequent immunity, is carried out by the symbiotic relationship between our cells (epithelium) and the resident microbiota. (Madara 2004)

The beneficial effects of probiotics can be achieved through a variety of mechanisms including regulation of cytokine production, enhancement of IgA secretion, and production of antibacterial substances. They also enhance the tight junction of the intestinal barrier — to protect against intercellular bacterial invasion, and compete with pathogenic microorganisms for enterocyte adherence. A recent study examined the basic molecular mechanisms of probiotics in regulating intestinal epithelial health and found that one probiotic, *Lactobacillus rhamnosus* GG, promoted the survival of intestinal epithelial cells. (Forchielli and Walker)

Adherence to intestinal epithelial cells is considered to be a valuable property since probiotic strains which can become established, even temporarily, are likely to have a competitive advantage and a greater or more prolonged probiotic effect. (Alander et al)

Probiotic strains of high adherence capacity have been demonstrated to enhance the immunoglobulin A response to rotavirus. Combination of specific probiotic strains may enhance adherence in a synergistic manner. (Juntunen M, Kirjavainen PV, Ouwehand AC, Salminen SJ, Isolauri E.)

Oral introduction of probiotics may halt the vicious circle in inflammation. The probiotic performance manifests itself in normalisation of the increased intestinal permeability and altered gut microecology, improvement of the intestine’s immunological barrier functions, and alleviation of the intestinal inflammatory response. (Isolauri et al)

Tolerance to food antigens

Recent studies using cultures containing probiotics strains similar to those found in Polybac 8™ have shown that polypeptides, such as gliadin in wheat, are less reactive when modified by these live cultures. If we extrapolate from these investigations, the general agreement would be that whole grains and foods that contain enzyme inhibitors, are more tolerable and assimilable, when the microecology of the human gut is fortified with supplemental live probiotics.

Recent research has shown us that these probiotic microorganisms in vitro degrade potentially toxic components of foods, such as oxalates, found in vegetables and chocolate

as well as the trypsin inhibitors found in Brassicas and legumes. When commensal bacterial colonies thrive in the human gut, our ability to digest foods and absorb essential nutrients (and degrade harmful compounds) is increased accordingly.

When humans stop producing lactase, animal milk becomes increasingly problematic as a food. Fermentation processes using probiotics cultures, such as those found in yogurt, kefir etc, help break down dairy proteins, making them more assimilable and easier to digest. Probiotic species such as *L. acidophilus*, *L. casei* and *B. lactis* help improve digestion and reduce the symptoms of food intolerances.

Resident and transient microorganisms

Probiotic microorganisms can be classified as either resident or transient. Resident strains are those commonly found in the human digestive tract throughout the course of one’s lifetime. Transient bacteria are present in food and the outer environment and can take residence in the colon to varying degrees at different times. Just as there is a symbiosis with the host, so too there is a symbiosis between transient and resident microflora. Transient strains pass through the system and do not re-establish themselves. Certain transient strains have shown excellent potential for fighting infection, but may not be present in significant numbers to have a viable effect. Some strains may display an affinity for the human gastrointestinal environment, at different stages of life. For this reason multi-strain formulations with both resident and transient microorganisms are often recommended. Resident strains include *Lactobacillus acidophilus*, *Lactobacillus salivarius*, *Bifidobacteria bifidum*, *Bifidobacteria infantis*, *Bifidobacteria longum*, *Streptococcus faecalis*, and *Streptococcus faecium*. Transient Strains include *Lactobacillus casei*, *Lactobacillus bulgarius*, *Lactobacillus yoghurti*, *Lactobacillus brevis*, *Lactobacillus kefir*, *Lactobacillus delbrueckii*, *Lactobacillus plantarum*, *Streptococcus lactis*, and *Streptococcus thermophilus*.

Probiotic microorganisms in fermented food

Prior to the development of probiotics supplements, as we know them, fermented foods provided beneficial microorganisms to help colonize the bowel and improve the assimilation and absorption of nutrients. It is not surprising that many of the microorganisms found in traditional fermented foods and beverages are now being isolated and used as therapeutic probiotics supplements. *Lactobacillus Plantarum* and *Lactobacillus Casei* are frequently identified in fermented foods, such as traditional soy products, sauerkraut and sourdough breads. (Chaoui et al 2003) Other probiotic species have been identified, such as *Bifidobacterium lactis*, which is used in yogurts and other traditional fermented beverages such as amasi found in Africa. A traditional Hawaiian food: Poi is another example. Poi is a “pasty starch made from the cooked, mashed corm of the taro plant (*Colocasia esculenta* L. 2005).”

Originating in Asia, this root crop is now found primarily in tropical and subtropical regions and was a major dietary staple

in the Pacific islands. The predominant bacteria in poi are *Lactococcus lactis* (95%).
(Brown AC, Valiere A. 2005)

Further afield; there have even been studies conducted which have analyzed the micro-organisms used in Pulque, a mildly alcoholic nutrient rich beverage made from a Mexican desert cactus, which identifies the *Lactobacillus* species as a dominant active biological agent. (Escalante et al 2004)

Fermented foods can certainly provide beneficial microorganisms for intestinal health, although they may not be present in significant numbers to correct long-standing conditions where the gut flora has been damaged by drugs and antibiotics.

Broad spectrum probiotic formulations can help “jump start the system in those with serious digestive problems as they will quickly populate the gut with beneficial organisms.” (Rubin and Brasco 2003)

Probiotics Using Multiple Species

Whilst each probiotic strain will have its own specific health benefits, no probiotic will elicit all health benefits of the genera and its subspecies. In many conditions, blends of multiple bacterial species may be the better option than probiotics containing one or two bacterial strains. Complementary microorganisms, create a stable, faster growing matrix of beneficial bacteria.’ (Heumer and Challam)

Nutrition Care’s Polybac 8™ is a broad-spectrum probiotic supplement that combines eight important strains of live microflora. These strains are highly viable and display significant activity to provide a balanced intestinal milieu. This synergistic combination helps build and support our gut-mediated defense mechanisms. Epithelial cell signaling and integrity are maintained, helping to arrest many conditions that have altered intestinal balance as an underlying feature.

Various toxins including antibiotics and other drugs, chemicals like chlorine and fluoride in our water, food additives, preservatives, and stimulants like coffee, can also alter the delicate balance of the human intestinal ecosystem.

Lactobacillus genus and subspecies

Members of the genus *Lactobacillus* constitute an extremely diverse and important group of organisms, of which some are members of the colonic microflora. For some time *L. Acidophilus* has been considered the most important of the gastrointestinal lactobacilli. Then back in 1980, the group of organisms known as *L. Acidophilus* was shown to be highly heterogeneous. In addition to the species comprising the *L.acidophilus* group, it was then found that other species such as *L.salvarius*, *L.casei* and *L.plantarum* were also found in the GI tracts of humans. (Tannock 1999).

Lactobacillus acidophilus

In a recent double blind placebo controlled study in 30 patients receiving antibiotic therapy for helicobacter pylori infection it was demonstrated that *L.Acidophilus* (and *B.longum*) ‘modulate the response of the intestinal microflora to the effects of antibiotic therapy.’ (Madden et al 2005)

Another study conducted in 2003 found that “The results of growth, lactic acid production and mixed cultures with *E. coli* strongly suggest that *L. acidophilus*, alone or combined with other strains of lactobacilli, can be used in probiotic products to prevent infections of the urogenital tract.” (Juarez et al 2003)

In vitro studies have shown that *L. Acidophilus* (and *S.thermophilus*) reduced epithelial damage due to invasion by enteropathogens, which has significance for the use of probiotics in Inflammatory Bowel Disease. (S Resta-Lenert, KE Barret). It displays excellent resistance to and inhibition of *S.aureus*.

Antibiotic Resistance <i>Lactobacillus acidophilus</i>			
Amoxicillin	S	Kanamycin	R
Ampicillin	S	Neomycin	R
Ceftazidime	I	Nitrofurantoin	R
Chloramphenicol	I	Penicillin G	S
Ciprofloxacin	R	Polymixin B	R
Clindamycin	I	Rifampicin	S
Dicloxacilin	S	Streptomycin	R
Erythromycin	S	Sulfamethoxazole	R
Gentamicin	R	Tetracycline	R
Imipenem	R	Trimethoprim	R
Cloxacillin	S	Vancomycin	S

S = Susceptible I= Intermediate
R = Resistant

Lactobacillus rhamnosus*

Fundamentally *Lactobacillus rhamnosus* is identified as a probiotic species, which characteristically ferments the monosaccharide rhamnose. This activity also differentiates it from other species. It is an extremely important resident bacterial strain.

It has been widely studied and is important for a range of conditions and has many important actions. Adherence to intestinal epithelial cells is considered to be a valuable property since probiotic strains which can become established, even temporarily, are likely to have a competitive advantage and a greater or more prolonged probiotic effect. Modulation of the intestinal permeability has been reported for *L.rhamnosus*.

The beneficial effects of *Lactobacillus rhamnosus* include, the prevention of antibiotic-associated diarrhoea, treatment and prevention of rotavirus diarrhoea, treatment of relapsing *Clostridium difficile* diarrhoea, prevention of acute diarrhoea, and enhancement of intestinal immunity. (Reid, Jass et al)

*Antibiotic resistance data currently unavailable

Lactobacillus plantarum

As the name implies, *Lactobacillus plantarum* appears in many fermented foods and beverages of plant origin. It is also an important species of commensal bacteria in the human gut. *L. plantarum* is the prominent species in many food cultures, such as sourdough bread starters, sauerkraut and other fermentable liquid mediums. Its presence helps to modify foods for peak nutrient absorption and bioactivity. It helps to eliminate the protein wastes from food before they reach the bloodstream. *L. plantarum* helps modify the anti-nutrient components (phytates) of whole grain flours used in bread making. The presence of *L. plantarum* in the human gastrointestinal system would tend to have similar activity and enhance peak nutrient uptake from foods, whilst avoiding micronutrient (Mg, Zn) loss, associated with phytate binding. This also applies to soy foods, which naturally have a high phytic acid content, rendered inactive by fermentation in the presence of bacteria such as *L. plantarum*.

As part of the intestinal micro-ecology, *L. plantarum* may compensate for a lack of pancreatic enzymes necessary for hydrolysis of otherwise indigestible compounds present in soy. *L. plantarum* has demonstrated high adhesion activity to intestinal epithelial tissue, enhancing gut mediated immune activity. (Mikrobiol Z. 2004). It is a species with a high survival count when subjected to fluxes in acidity (bile and gastric acid exposure) and temperature variants. In vitro studies have also shown that *L. plantarum* is resistant to antibiotics, and shows great potential in fortifying natural resistance.

Antibiotic Resistance <i>Lactobacillus plantarum</i>			
Amoxicillin	S	Kanamycin	R
Ampicillin	S	Neomycin	R
Ceftazidime	R	Nitrofurantoin	R
Chloramphenicol	R	Penicillin G	R
Ciprofloxacin	R	Polymixin B	R
Clindamycin	R	Rifampicin	S
Dicloxacilin	R	Streptomycin	R
Erythromycin	I	Sulfamethoxazole	R
Gentamicin	R	Tetracycline	R
Imipenem	R	Trimethoprim	R
Cloxacillin	R	Vancomycin	R

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Lactobacillus casei

L. casei is one of the hardiest and most prolific lactobacillus strains. Its presence in the gastro intestinal tract also leads to the improved digestion and assimilation of dairy based foods. It also helps digest many dietary carbohydrates. *L. casei* is also resistant to antibiotics; in a recent study it was shown that *L. casei* was more resistant to all the testing antibiotics than the other strains. These results would suggest that *L. casei* is an important species in the prevention of antibiotic associated diarrhoea in children. (Chou et al 2004) *L. casei* has also been recently identified as a useful strain to increase immune competence in people over 50. (Parra et al J Nutr Health

Ageing 2004) *L. casei* has been identified as a reductant in T cell mediated skin inflammation. (Chapat et al 2004)

Antibiotic Resistance <i>Lactobacillus casei</i>			
Amoxicillin	S	Kanamycin	R
Ampicillin	S	Neomycin	R
Ceftazidime	R	Nitrofurantoin	R
Chloramphenicol	R	Penicillin G	S
Ciprofloxacin	R	Polymixin B	R
Clindamycin	I	Rifampicin	S
Dicloxacilin	S	Streptomycin	R
Erythromycin	I	Sulfamethoxazole	R
Gentamicin	R	Tetracycline	R
Imipenem	R	Trimethoprim	R
Cloxacillin	I	Vancomycin	R

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Lactobacillus salivarius

Lactobacillus salivarius has been identified as a factor in the inhibition of inflammatory bowel disease and ulcerative colitis. (Ott et al 2005). In one study it was stated: 'there is considerable evidence to indicate that the components of the resident colonic micro flora can play an important role in initiation of the disease.' (Bullock NR, Booth JC, Gibson GR 2004). *L. salivarius* is also a reasonably potent inhibitor of golden staph (*Staphylococcus aureus*). As identified in human breast milk, *L. salivarius* (and other strains present in Polybac 8™) are effective against *Staphylococcus aureus*, known as a causative agent of maternal breast infections and neonatal infections. (Heikkila MP, Saris PE. 2003)

Antibiotic Resistance <i>Lactobacillus salivarius</i>			
Amoxicillin	S	Kanamycin	R
Ampicillin	S	Neomycin	R
Ceftazidime	R	Nitrofurantoin	R
Chloramphenicol	R	Penicillin G	S
Ciprofloxacin	R	Polymixin B	R
Clindamycin	S	Rifampicin	S
Dicloxacilin	R	Streptomycin	R
Erythromycin	I	Sulfamethoxazole	R
Gentamicin	R	Tetracycline	R
Imipenem	R	Trimethoprim	R
Cloxacillin	S	Vancomycin	R

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Streptococcus thermophilus*

It was hypothesized that *S. thermophilus* would be useful in reducing the clinical symptoms in allergic patients. A recent Italian study confirmed this, showing increased immune activity in patients given supplemental probiotics that contained *S. thermophilus*. It has also been demonstrated that *S. thermophilus* 'releases metabolites exerting an anti-TNF- α effect capable of crossing the intestinal barrier.'

These results underline the beneficial effect of commensal bacteria in intestinal homeostasis and may explain the role of some probiotic bacteria in alleviating digestive inflammation. (Menard et al 2004) This species has also been used in fermented infant formulas, and is useful in the reduction of severity in infant diarrhoea. (Thibault et al 2004)

* Antibiotic resistance data currently unavailable

Bifidobacteria Benefits

Bifidobacteria dominate the flora of the large intestine. They ferment several sugars, especially lactose and its components glucose and galactose. However, while Lactobacilli ferment those sugars exclusively into lactic acid (homofermentative) or into lactic acid and other products including gas (heterofermentative), bifidobacteria ferment sugars into acetic and lactic acids in the proportion of 3:1 and do not produce gas. This metabolic pathway is specific and is named the bifidus path.

The genus Bifidobacterium includes 29 closely related species. Mitsuoka has found that the species of bifidobacteria which are most prevalent in the colon of newborn infants are *Bifidobacterium breve*, *B.parvulorum*, *B.bifidum*, *B.longum* and *B.adolescentis*.

Bifidobacteria lower the pH of faeces and keep putrefactive bacteria in check. In the presence of the bifidus factors, they produce L (+) Lactic, acetic and traces of formic acids which lower the pH from 7.0 to 5.0, thus inhibiting pathogenic strains of Escherichia coli and infections produced by Clostridium difficile and Clostridium perfringens.

Bifidobacteria are sensitive to wide spectrum antibiotics and to those which are potent against gram-positive bacteria. However, they often limit their side effects, such as nausea and diarrhoea. In a well controlled experiment, Colombel and associates (1987) treated 10 volunteers with erythromycin administered orally and yoghurt containing B.longum. The stool weight and number, the presence of abdominal discomfort and the number of clostridium spores were noted. The simultaneous intake of yoghurt containing B.longum with erythromycin reduced the frequency of gastrointestinal disorders and reduced the clostridial spore count. The placebo yoghurt had no effect. Consequently, bifidobacteria longum can re-establish the normal flora.

Another study by Schell et al, established that the genome sequence of Bifidobacterium longum reflects its adaptation to the gastrointestinal tract. Bioinformatic analysis revealed several physiological traits that could partially explain the successful adaptation of this bacteria to the colon. An unexpectedly large number of the predicted proteins appeared to be specialized for catabolism of a variety of oligosaccharides. This ability to scavenge from a large variety of nutrients likely contributes to the competitiveness and persistence of bifidobacteria in the colon.

Reports on research with mice has shown that Bifidobacterium longum exerts marked inhibitory effects on ulcerative colitis and protects a host from invasion of the intestinal mucosa by

dietary antigens that have escaped enzymatic digestion in the intestine.

Bifidobacterium lactis*

B.lactis is a subspecies of B.animalis. It is not a resident strain of bacteria, such as Bifidobacterium longum. B.lactis is often used in fermented dairy products, although similar benefits can be attained using the isolated bacteria in a probiotic powder.

B. lactis has been shown to be extremely useful in the metabolism and degradation of toxic food components such oxalate. (Federici et al 2004)

It has also been shown to inhibit Cox 2 expression, thus reducing the incidence and severity of gut mediated inflammatory conditions. Recent data have outlined a relationship between the composition of the intestinal micro flora and allergic inflammation, and demonstrated the competence of probiotics such as Bifidobacterium lactis, as an important treatment adjunct. This strain has very important applications in pediatric healthcare, to reduce the frequency of antibiotic use, and improve generalized resistance to infection and illness among this group.

*Antibiotic resistance data currently unavailable

Antibiotic Resistance Bifidobacterium longum			
Amoxicillin	S	Kanamycin	R
Ampicillin	S	Neomycin	R
Ceftazidime	R	Nitrofurantoin	I
Chloramphenicol	S	Penicillin G	S
Ciprofloxacin	R	Polymixin B	R
Clindamycin	S	Rifampicin	R
Cloxacillin	R	Streptomycin	R
Dicloxacillin	R	Sulfamethoxazole	R
Erythromycin	S	Tetracycline	R
Gentamicin	R	Trimethoprim	S
Imipenem	R	Vancomycin	R

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Post antibiotic re-colonisation

Re-colonisation of the intestine after antibiotics can be a considerable undertaking. These drugs can cause swift and rapid damage to the delicate micro flora, which can impair immune-signaling and gastrointestinal function. When the intestinal flora is not effectively re-colonised, ongoing health problems, such as inflammation, an increased susceptibility to infections, as well as allergies and food intolerances can occur. It is therefore important that highly viable probiotics supplements are used for re-colonisation to take place. Several species may also be necessary. It is also important to address any 'maintaining causes' such as recreational drug use and the continued ingestion of nutrient poor food and heat damaged oils, which can compromise the intestinal milieu. For recolonisation to be effective, a fairly restrictive maintenance diet may be necessary, with the avoidance of highly reactive

foods, such as sugar and alcohol, and the total avoidance of petrochemical colours and additives. When these strategies are implemented, the effectiveness of probiotics can be increased markedly.

When choosing probiotics, the main selection criteria include:

- Ability to resist degradation by bile and gastric acids
- Capable of successful implantation in the intestinal tract
- Resistant to pancreatic enzymes
- Stability of numbers and characteristics
- Colonisation potential
- Survival in situ
- The safety and efficacy of the strain must be validated by clinical trials

Mechanism of Action

Polybac 8™ is a potent bio therapeutic agent, used to maintain and restore normal intestinal flora. These bacteria are thought to exert their pharmacological effects through a variety of actions:

- Modulating the immune system, increasing the production of antibodies, mobilizing macrophages, lymphocytes and other cells of the immune response system
- Increasing mucin production in the intestine, thereby providing local protection as well as enhancing the innate immune response
- Direct adhesion to intestinal epithelial cells and production of antimicrobial substances
- Acidification of the intestinal lumen creating an unsuitable environment for pathogenic micro-organisms while allowing indigenous microflora to proliferate
- Suppressing the activity of toxic and carcinogenic amine-producing enzymes associated with other intestinal flora
- Coating the intestinal mucosa and protection against invasion of pathogenic bacteria and prevention of diseases caused by intestinal infections.
- Hydrolysis of lactose and reduction of lactose intolerance
- Supports detoxification and immune function during pregnancy, and reduces the incidence of atopy and allergy in the infant
- Inhibition of helicobacter pylori and therefore important in the prevention of peptic ulcer
- Contribution to intestinal peristalsis and elimination of harmful amines derived from amino acids
- Limiting the action of putrefactive microbes, thus controlling production of toxins and their noxious effects

Contraindications

Caution should be displayed in administering probiotics to Immunocompromised individuals and infants with short bowel syndrome. (Cannon et al 2004 and Land et al 2005)

Complementary Considerations

Avoid commonly consumed foods including white flour products, non-fermented dairy products, sugar and overly depleted, refined and packaged foods. Fast foods and deep fried foods should also be avoided when bowel recolonisation protocols are implemented.

Companion Formulae

Pancenz, Bepep, Liver Formula, Gastinal, Chaparral, Formula 33/33SE, Formula SF88, Isofem, Marine Oil – Marine Oil/EPO.

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