IP Restore

Scobiotic™ for Gastrointestinal Repair

Aust L 333743

bioclinic® naturals

Active Ingredients

Each capsule contains:

	0.67 billion CFU		8.33 mg
	0.67 billion CFU	Equiv. chromium	16.66 micrograms
	83.33 mg		10.42 mg
	16.67 mg	Equiv. molybdenum	20.83 micrograms
	66.67 mg		33.30 mg
	50 mg	Equiv. dry flower and fruit	333 mg
	50 mg		16.67 mg
	16.67 mg		16.67 mg
	47.62 mg		44.44 mg
Equiv. fresh *Saccharomyces cerevisiae*	232 mg		33.33 mg

CFU = colony forming units

Recommended Dosage

Adults: 1 capsule 3 times daily or as directed by a health care practitioner.

Uses

- Unique Scobiotic™, syntrophic mixed culture of bacteria, fungi and yeasts that targets the underlying causes and associated symptoms of impaired gastrointestinal permeability.
- Prebiotics specific for promoting healthy *bifidobacteria* and *lactobacilli* balance.
- Soothes, repairs and strengthens the gastrointestinal epithelial lining and promotes beneficial bacterial adherence to the intestinal mucosa.

Other Uses

- To improve intestinal inflammation and digestive symptoms.
- Promotes intestinal immune system activity.
- Enhances general gastrointestinal health and wellbeing.

Side Effects

The long history of safe use of probiotics and a significant body of evidence confirms that oral ingestion of probiotic microorganisms is generally considered to be safe.[1,2] Documented side effects attributed to probiotic use are relatively mild and include flatulence and bloating, and far less commonly, nausea, vomiting, diarrhea, spasms, taste disturbances, skin rashes and acne.[3]

There are very few reported adverse effects associated with molybdenum supplementation at recommended doses. The risk of toxicity with oral intake of high chromium yeast is considered to be low, with the rare incidence of adverse effects reported including irritability, insomnia and gastrointestinal upsets.[1,5,6]

Doses of up to 14 g/day of glutamine have been used safely by healthy humans, with uncommon adverse effects including mild gastrointestinal complaints.[1] *Cichorium intybus* ingestion has also been associated with infrequent occurrence of minor gastrointestinal effects.

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There are no side effects documented with the oral ingestion of *Iberis amara, Ganoderma lucidum, Polyporus umbellatus, Grifola frondosa, Cordyceps sinensis, Lentinula edodes, Cichorium intybus* and *Saccharomyces boulardii/cerevisiae.*

Cautions

Not to be used in children under 2 years of age without medical advice. If you are pregnant or breastfeeding, talk to your health care practitioner before taking this product. If symptoms persist, worsen, or become more frequent, talk to your health care practitioner. Do not take while on warfarin therapy without medical advice. Caution is advised with use of *Saccharomyces cerevisiae* by immunocompromised and critically ill individuals. Contains yeast.

Interactions

Concomitant use of probiotics with antibiotic medications can adversely influence the gastrointestinal microbiome and probiotic colonisation capacity.[1,2] As chromium may decrease dosage requirements for hypoglycaemic medications, caution is advised with concomitant use and dosages adjusted accordingly. Chromium may theoretically potentiate the therapeutic effects of lipid lowering medications.[1] Animal data has demonstrated that high molybdenum doses inhibit acetaminophen metabolism, however the clinical relevance in doses used by humans is unconfirmed.[4]

Contraindications

- Probiotics and prebiotics are contraindicated in individuals with hypersensitivities to probiotics or components.[1]
- Glutamine is contraindicated in individuals with hypersensitivity to glutamine, with hepatic disease or in any condition associated with increased risk of accumulation of nitrogen waste in the blood.[1]

Mechanism of Action

PROBIOTICS:

- support and stabilise gut barrier function and permeability by:
  - improving intestinal integrity.[1]
  - upregulating tight junction proteins (claudin-1, occludin, zonulin).[2,7,8]
  - modulating tight junction and adhesion protein synthesis and degradation genes.[9]
  - supporting tight junction protein abundance.[9]
  - modulating genes involved in shifting mucosal cellular energy supply from oxidative phosphorylation towards glutamine synthesis.[9]
  - improving paracellular permeability.[10]
  - promoting mucous secretion.[2,8]
  - inhibiting epithelial cell apoptosis.[11]
  - increasing butyrate levels.[2,11]
  - modulation of the microbiome.[2]
  - promoting synthesis of exopolysaccharides which support binding to intestinal mucous and protect epithelial cells.[12]
- inhibit pathogen-mediated infection by:
  - fortifying intestinal epithelial resistance to pathogens.[9]
  - reducing adherence of pathogenic bacteria.[13]
  - competing for nutrients and binding sites.[14]
  - secreting antimicrobial substances (organic acids, bacteriocins, hydrogen peroxide).[8,14]
  - reducing gut pH.[14]
- reduce intestinal inflammation by:
  - reducing oxidative stress.[15]
  - inhibiting penetration of inflammatory compounds (e.g. lipopolysaccharides and cytotoxins).[16,17]

GANODERMA LUCIDUM

- supports and maintains intestinal barrier health, integrity and function.[24-26]
- regulates intestinal immunity.[24]
- improves concentrations of intestinal SIgA.[24]
- acts as a prebiotic to beneficially modulate gastrointestinal microbiota.[24-26]

POLYPORUS UMBELLATUS:

- supports intestinal microbiome health.[27]
- immune-enhancing activity.[27,28]
- anti-inflammatory activity.[28]

GRIFOLA FRONDOSA:

- regulates intestinal microflora.[29]
- promotes abundance of short-chain fatty acid-producing microbiota.[30]
- immune-modulatory activity.[31-33]
- antibacterial and antiviral activity.[34]

CORDYCEPS SINENSIS:

- bifidogenic activity.[35]
- protects gut barrier by:
    - supporting integrity and upregulating of intestinal mucosal tight junction protein expression (occludin, claudin-1, zonula occludins).[36,37]
    - restoring activity of intestinal enzymes.[37]
    - promoting mucins expression.[37]
- promotes colonic SIgA secretion-induced anti-inflammatory activity.[38]
- immune modulatory activity.[36,39]

LENTINULA EDODES:

- supports healthy intestinal mucosal barrier and immune function.[40,41]
- promotes SIgA production.[40]
- downregulates intestinal inflammation (decreases macrophage inflammatory protein-1α/chemokine C-C ligand 3 (MIP-1α/CCL3) level and tumor necrosis factor (TNF-α) and increases interleukin 4 and 8 (IL-4 and IL-8) levels).[40,42,43]
- increases species abundance of gut microbiome.[44]
- supports digestion and metabolism as a digestive substrate.[44]
- antioxidant activity.[40]

SACCHAROMYCES BOULARDII/ CEREVISIAE:

- supports intestinal barrier function.[47]
- decreases blood and tissue pro-inflammatory cytokine levels (IL-8, TNF-α).[13]
- gastrointestinal mucosa anti-inflammatory activity.[48-53]
- modulates intestinal immune responses.[48-53]
- modulates intestinal microflora concentrations and activity.[48-53]
- supports short-chain fatty acid synthesis activity of probiotics.[47]

HIGH CHROMIUM YEAST:

- anti-inflammatory activity.[4]
- immune-modulatory effects.[1]
- nutritional support.[1]

HIGH MOLYBDENUM YEAST:

- nutritional support.[4]

GLUTAMINE:

- protects and supports intestinal mucosal cell structural strength, repair and activity by improving permeability and tight junction protein expression.[1,18,19]
- supports gastrointestinal immune defences via:
    - maintenance of gut-associated lymphoid tissue.[1]
    - synthesis of secretory IgA.[1]
    - maintaining gastrointestinal integrity.[1]
    - preventing intestinal adhesion and translocation of pathogenic microbes and toxins.[1]
- protects against oxidation-induced gastrointestinal barrier function as a glutathione precursor.[1]
- supports intestinal motility.[19]
- anti-inflammatory activity.[18]
- supports survival of probiotics.[20]

CICHORIUM INTYBUS:

- stimulates growth and activity of beneficial bacteria.[21-23]
- anti-inflammatory activity.[21-23]
- gastroprotective effects.[21-23]
- antimicrobial activity.[21-23]

ARTHROSPIRA PLATENSIS:

- strong antioxidant activity by increasing total antioxidant capacity, scavenging free radicals and oxidative stress markers including malondialdehyde, superoxide dismutase, catalase, reduced glutathione and glutathione peroxidase.[45,46]
- antimicrobial activity against gram-negative and -positive bacteria including *Escherichia coli*.[46]
- regulates inflammatory cytokines (TNF-α, IL-1β, IL-2, IL-4, IL-6, IL-10) and signaling pathways (ERK1/2, JNK, MAPK p38, IκB kinase).[45,46]
- promotes growth of beneficial gastrointestinal bacteria.[45]

IBERIS AMARA:

- anti-inflammatory.[54]
- antioxidant.[54,55]

Pharmaceutical Commentary

The gastrointestinal mucosal epithelium is a single layer of cells connected by intercellular junctions that is vital for regulating intestinal digestion, absorption and neuroendocrine processes to enable optimal gastrointestinal health and function.[56] This semi-permeable barrier is also integral for protecting against the absorption of potentially harmful antigens from the intestinal lumen, thereby regulating immune balance and tolerance and local and systemic inflammation.[57]

The intercellular junctions that connect these epithelial cells are called tight junctions (TJs), comprised of proteins including occludin, claudins, junctional adhesion molecules, ZO-1, ZO-2, ZO3, 7H6, symplekin and cingulin.[56] The assembly or structure of these proteins (i.e. the opening and closing mechanisms) determine the size of the molecules that can be absorbed through the intestines. These TJs have a dynamic nature, in that their structure and therefore function can be altered by a range of endogenous and exogenous stimuli including dietary intake (e.g. chemical and processed foods and preservatives), increased age, stress, inflammation, metabolic glucose imbalances, infections (e.g. parasites, bacteria, mould and viruses), medications (e.g. antibiotics, non-steroidal anti-inflammatories and chemotherapy), heavy metal toxicity, strenuous exercise, bacterial endotoxins and dysbiosis. Consequently, TJ dysfunction is a key underlying process causing impaired intestinal permeability.[56,58-60]

Damage to this paracellular intestinal pathway causes intestinal hyperpermeability, therefore allowing substances including food components/antigens, toxins, microbes or lipopolysaccharides to pass through the intestinal mucosal layer, initiating an immune response, inflammation and dysbiosis. This immune and inflammatory response further exacerbates intestinal barrier damage and hyperpermeability, causing disordered gastrointestinal function and impaired absorption and metabolism of nutrients.[9,58-60]

A significant range of gastrointestinal and systemic symptoms and conditions are associated with impaired intestinal hyperpermeability, including many digestive symptoms, reduced nutrient absorption, impaired immunity, Crohn's and coeliac disease, autoimmune issues, non-alcoholic fatty liver, polycystic ovary syndrome, irritable bowel syndrome, food allergies or hypersensitivity and reduced capacity for cognitive and physical performance.[57,60]

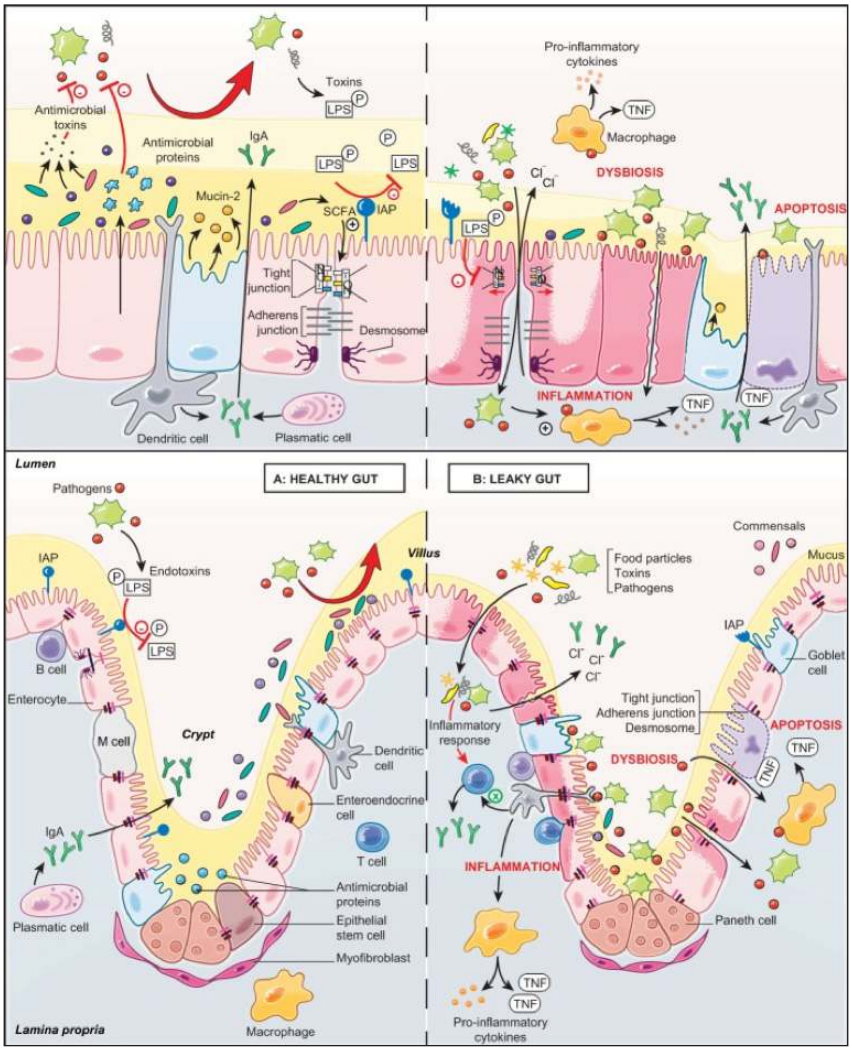

FIGURE 1: Role of the intestinal barrier components in a healthy gut and a leaky gut. Notes: The top panels show the components of the intestinal barrier: the microbiota (pale yellow), mucus (dark yellow), the epithelial layer (pink) and the immune layer (gray). The bottom panels show the intestinal barrier on the crypt–villus axis. (A) The healthy gut is characterized by an intact intestinal barrier. Commensal bacteria secrete antimicrobial toxins, which protect against pathogenic invasion and SCFAs produced by bacterial fermentation and participate in the formation of tight junctions. The epithelial cells secrete a variety of endogenous molecules, such as antimicrobial proteins and mucins (mucin-2), which make up the mucus layer, and IAPs, which protect the tissue against luminal toxins. The epithelial cells also mediate selective permeability by the apical junctional complex formed by tight and adherens junctions and desmosomes. The immune components include plasmatic cells, which secrete IgA, and the dendritic cells, which sense the luminal environment. (B) The leaky gut is characterised by a damaged intestinal barrier. Microbial dysbiosis leads to the interaction of luminal pathogens with intestinal epithelial cells via the bacterial lipid structures. Attachment of pathogens to the epithelial surface impairs the apical junctional complex and increases the intestinal permeability. As a consequence, food particles, toxins and pathogens penetrate into the tissue and provoke an inflammatory response, resulting in cell apoptosis. Increased intestinal permeability also increases the secretion of electrolytes and ions into the lumen, resulting in diarrhea. Abbreviations: IAP, intestinal alkaline phosphatase; LPS, lipopolysaccharide; M cell, microfold cell; SCFA, short-chain fatty acid.[73]

The intestinal microbiome plays a key role in mediating and enhancing intestinal barrier integrity and function by regulating mucous composition, influencing TJ expression, structure and function, modulating oxidative stress, immune responses, inflammation, vagal signaling, metabolism of food components and provision of nutrients (e.g. vitamin K, biotin, cobalamin, riboflavin).[56,57,61,62] Consequently, healthy levels of beneficial microflora are essential for promoting and maintaining the integrity of the gastrointestinal epithelial lining and improving impaired gastrointestinal permeability.

The syntrophic combination of probiotics with prebiotic fungi and yeasts in IP Restore provide a significant range of therapeutic mechanisms that support gastrointestinal permeability, integrity and beneficial microflora balance.

Lactobacillus gasseri supports and protects intestinal barrier function by inhibiting small bowel, cytokine-induced permeability, inhibiting inflammation and reducing penetration of inflammatory compounds. This species also increases IgA production in the small intestinal Peyer's patch, lamina propria and B-cells, has significant antimicrobial activity against gram-positive and gram-negative bacteria, adheres to intestinal tissue, as well as promoting faecal lactobacilli concentrations.[6,16,17,63]

Lactobacillus plantarum reinforces the intestinal barrier and reduces permeability by protecting intestinal morphology, influencing TJ transcription, pathway, protein expression, organisation and abundance. Additionally, it upregulates intestinal mucin production and shifts mucosal cell energy supply from oxidative phosphorylation to glutamine by modulating the transcription of glutamine biosynthesis pathways.[9,11] This strain also promotes and protects intestinal barrier integrity and health by preventing the adherence of pathogens to the intestinal mucosa and modulating the lactobacilli microbiota composition.[11,26]

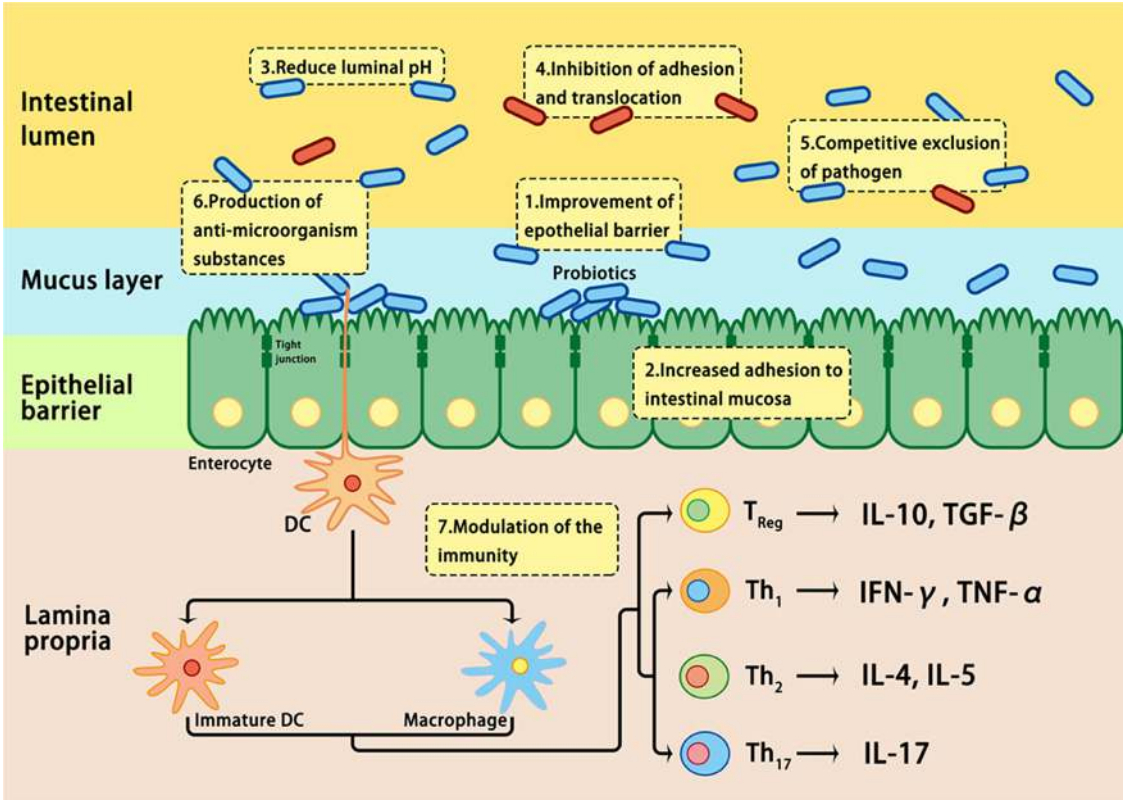

FIGURE 2: Mechanisms involved in probiotic-induced protection against intestinal dysbiosis. Probiotics suppress pathogens through various actions, including lowering luminal pH, production of antimicrobial proteins, inhibition of adhesion and translocation of flora, competitive exclusion of pathogens, improvement of epithelial barrier, enhancement of adhesion of commensal bacteria to the intestinal mucosa, and modulation of gastrointestinal mucosal immune system.[74]

The fungi and yeast prebiotics also exhibit a broad range of mechanisms that support gastrointestinal barrier integrity and function.

Reiishi *(Ganoderma lucidum)* supports and maintains intestinal barrier health, integrity and function and has significant prebiotic activity. Reiishi also promotes intestinal bifidobacteria and lactobacilli composition, and has immune-modulatory effects by stimulating SIgA synthesis.[24-27,64] Maitake *(Grifola frondosa)*, Caterpillar mushroom *(Cordyceps sinensis)* and zhu ling *(Polyporus umbellatus)* also have immune-modulatory effects and promote healthy intestinal microbiome balance.[27, 31,32,34] Shiitake (*Lentinula edodes)* supports healthy intestinal mucosal barrier and immune function, increases intestinal SIgA production, downregulates intestinal inflammation, supports healthy microbial populations via prebiotic activity and supports digestion.[40-44,65]

Chicory provides prebiotic, anti-inflammatory, anti-microbial and antioxidant support to the gastrointestinal tract, and increases colonic absorption of dietary minerals (calcium and magnesium).[21,22,66,67]

Saccharomyces cerevisiae and *Saccharomyces boulardii* protect epithelial barrier function via a number of mechanisms, including inhibition of pathogenic adhesion and colonisation of the intestinal mucosa, modulation of intestinal microflora and metabolic activity, and trophic, immune (i.e. promoting SIgA synthesis) and anti-inflammatory effects on the intestinal mucosa. *Saccharomyces boulardii* is particularly known to inhibit the adhesion of *Candida albicans* and therefore its colonisation.[48-53]
As an essential energy source for intestinal epithelial cells, glutamine protects and supports intestinal mucosal strength, repair and activity by influencing TJ protein expression and as a glutathione precursor, supports intestinal immune defences, promotes naïve T-cells towards T-regulatory cells differentiation, along with anti-inflammatory activity and supporting the survival of probiotics. Glutamine also increases intestinal SIgA concentrations, beneficially modulates the intestinal microbiome composition and inhibits bacterial translocation from the intestinal lumen.[18-20,68]

As a nutrient-dense source of protein, essential fatty acids, vitamins, minerals and phytonutrients, spirulina *(Arthrospira platensis)* provides nutrients for the maintenance of GIT health and for depletion of nutrients associated with suboptimal gastrointestinal barrier function. Other mechanisms that promote a beneficial effect on the gastrointestinal tract include via antioxidant, anti-inflammatory, antimicrobial, antiviral and probiotic-supporting activity.[45,46,69]

Chromium and molybdenum provide nutritional support, with chromium also having immune-modulatory and anti-inflammatory effects.[1,4]

Along with its long history of use in traditional European medicine for gastrointestinal issues, bitter candytuft *(Iberis amara)* has demonstrated significant anti-inflammatory, antioxidant and antimicrobial activity to support small intestinal health and function. It also has a tonifying effect on stomach and small intestine smooth muscle and inhibits colonic, serosal, afferent, nerve fibre sensitivity to chemical and mechanical stimuli.[70-72]

Intestinal Permeability

A systematic review assessed the association between intestinal hyperpermeability and disease states. An analysis of 48 clinical trials found that intestinal permeability is strongly associated with autoimmune (25-87.5% prevalence) and liver conditions (17-65%), and also correlated with food allergies/hypersensitivities (18.4% vs 8.3, $p<0.05$).), irritable bowel syndrome (35.6% vs 18.6% healthy controls, $p=0.007$) and polycystic ovary syndrome. Disease severity and the experience and severity of clinical symptoms in menstrual disorders and food allergy/hypersensitivity was found to directly correlate with intestinal permeability. It was also found that the severity of intestinal permeability was likely to be exacerbated by inflammation, dysbiosis and impaired glucose metabolism.

References

1. Braun L, Cohen M. Herbs & natural supplements: an evidence-based guide volume 2, 4th edn. Elsevier: Sydney. 2015.
2. Suez J, Zmora N, Segal E, Elinav E. The pros, cons and many unknowns of probiotics. Nat Med 2019 May; 716-729.
3. Sotoudegan F, Daniali M, Hassani S, Nikfar S, Abdollahi M. Reappraisal of probiotics safety in human. Food Chem Toxicol 2019; doi: 10.1016/j.fct.2019.04.032.
4. Higdon J. Linus Pauling Institute Micronutrient Information Centre. Oregan State University. Accessed 23 December 2019 from https://lpi.oregonstate.edu/
5. Jach ME, Serefko A. Chapter 9 – nutritional yeast biomass: characterisation and application. Diet, Microbiome and Health 2018; 237-270.
6. Kawano M, Miyoshi M, Ogawa A, Sakai F, Kadooka Y. Lactobacillus gasseri SBT2055 inhibits adipose tissue inflammation and permeability in mice fed a high-fat diet. J Nutr Sci 2016; 5: e23.
7. Ruiz L, Delgado S, Ruas-Madiedo P, Sanchez B, Margolles A. Bifidobacteria and their molecular communication with the immune system. Front Microbiol 2017; 8: 2345.
8. Zhang Z, Lv J, Pan L, Zhang Y. Roles and applications of probiotic lactobacillus strains. Appl Microbiol Biotechn 2018; doi:10.1007/200253-018-9217-9.
9. Mujagic Z, de Vos P, Boekschoten MV, Govers C, Pieters HJHM, de Wit NJW, Bron PA, Masclee AAM, Troost FJ. The effects of Lactobacillus plantarum on small intestinal barrier function and mucosal gene transcription: a randomised double-blind placebo controlled trial. Sci Rep 2017; 7: 40128.
10. Han X, Lee A, Huang S, Gao J, Spence JR, Owyang C. Lactobacillus rhamnosus GG prevents epithelial barrier dysfunction induced by interferon gamma and faecal supernatants from irritable bowel syndrome patients in human intestinal enteroids and colonoids. Gut microbes 2019; 10.
11. Seddik HA, Bendali F, Gancel F, Fliss I, Spano G, Drider D. Lactobacillus plantarum and its probiotic and food potentialities. Probiotics and Antimicrobial proteins 2017; 9 (2): 111-122. doi: 10.1007/s12602-017-9264-z.
12. Klopper KB, Deane SM, Dicks LMT. Aciduric strains of Lactobacillus reuteri and L. rhamnosus isolated from human faeces, have strong adhesion and aggregation properties. Probiotics Antimicrob Proteins 2018 Mar; 10 (1): 89-97.
13. Distrutti E, Monaldi L, Ricci P, Fiorucci S. Gut microbiota role in irritable bowel syndrome: new therapeutic strategies. World J Gastroenterol 2016 Feb 21; 22 (7): 2219-2241.
14. Di Cerbo A, Palmieri B, Aponte M, Morales-Medina JC, Iannitti T. Mechanisms and effectiveness of lactobacilli. J Clin Pathol 2016 Mar; 69 (3): 187-203.
15. Nath A, Haktanirlar G, Varga A, Molnar MA, Albert K, Galambos I, Koris A, Vatai G. Biological activities of lactose-derived prebiotics and symbiotic with probiotics on gastrointestinal system. Medicina (Kaunas) 2018 May; 54 (2): 18.
16. Di Luccia B, Mazzoli A, Cancelliere R, Crescenzo R, Ferrandino I, Monaco A et al. Lactobacillus gasseri SF1183 protects the intestinal epithelium and prevents colitis symptoms in vivo. J Funct Foods 2018; 42: 195-202.
17. Suzuki T, Masui A, Nakamura J, Shiozawa H, Aoki J, Tsuda S et al. Yoghurt containing Lactobacillus gasseri mitigates aspirin-induced small bowel injuries: a prospective, randomised, double-blind, placebo-controlled trial. Digestion 2017; 95: 49-54.
18. He F, Wu C, Li P, Li N, Zhang D, Zhu Q, Ren W, Peng Y. Functions and signalling pathways of amino acids in intestinal inflammation. BioMed Res Inter 2018; Vol 2018, Article ID 9171905.
19. Tome D. The roles of dietary glutamate in the intestine. Ann Nutr Metab 2018; 73 (suppl 5): 15-20.
20. Bhat AR, Irorere VU, Bartlett T, Hill D, Kedia G, Charalampopoulos D, Nualkaekul S, Radecka I. Improving survival of probiotic bacteria using bacterial poly-gamma-glutamic acid. Int J Food Microbiol 2015; 196: 24-31.
21. Al-Snafi AE. Medical importance of Cichorium intybus – a review. IOSR Journal of Pharmacy. 2016 Mar; 6 (3): 41-56.
22. Saeed M, El-Hack MEA, Alagawany, Arain MA, Arif M, Mirza MA, Naveed M, Chao S et al. Chicory (Cichorium intybus) herb: chemical composition, pharmacology, nutritional and healthical applications. Int J Pharmacol 2017; 13 (4): 351-360.
23. Thorat BS, Raut SM. Chicory the supplementary medicinal herb for human diet. J Med Plants Studies 2018; 6 (2): 49-52.
24. Jin M, Zhang H, Wang J, Shao D, Yang H, Huang Q et al. Response of intestinal metabolome to polysaccharides from mycelia of Ganoderma lucidum. International J Biol Macromol 2019; doi: 10.1016/j.ibiomac.2018.10.224.
25. Chang CJ, Lin CS, Lu CC, Martel J, Ko YF, Ojcius DM et al. Ganoderma lucidum reduces obesity in mice my modulating the composition of the gut microbiota. Nature Communications 2015; 6: 7489.
26. Wang Y, Huang X, Nie S. Novel prospective of wild mushroom polysaccharides as potential prebiotics. Biology Macrofungi, Fungal Biology. Springer Nature Switzerland AG 2018.
27. Huang Q, Li L, Chen H, Liu Q, Wang Z. GPP (composition of Ganoderma lucidum polysaccharides and Polyporus umbellatus polysaccharides) enhances innate immune function in mice. Nutrients 2019; 11 (7): 1480.
28. Zhao YY. Traditional uses, phytochemistry, pharmacology, pharmacokinetics and quality control of Polyporus umbellatus (Peers.) Fries: a review. J Ethnopharmacol 2013; 149 (1): 35-48.
29. Chen Y, Liu D, Wang D, Lai S, Zhong R, Liu Y et al. Hypoglycaemic activity and gut microbiota regulation of a novel polysaccharide from Grifola frondosa in type 2 diabetic mice. Food Chem Toxicol 2019; 126; 295-302.
30. Pan YY, Zeng F, Guo WL, Li TT, Jia RB, Huang ZR et al. Effect of Grifola frondosa 95% ethanol extract on lipid metabolism and gut microbiota composition in high-fat diet-fed rats. Food Funct 2018 Dec; 9 (12): 6288-6278.
31. Jayachandran M, Xiao J, Xu B. A critical review on health promoting benefits of edible mushrooms through gut microbiota. Int J Mol Sci 2017; 18: 1934.
32. He X, Wang X, Fang J, Chang U, Ning N, Guo H, Huang L, Huang X, Zhao Z. Polysaccharides in Grifola frondosa mushroom and their health promoting properties: a review. Int J Biol Macromol 2017; 101: 910-921.
33. Nishihira J, Sato M, Tanaka A, Okamatsu M, Azuma T, Tsutsumi N, Yoneyama S. Maitake mushrooms (Grifola frondosa) enhances antibody production in response to influenza vaccination in healthy adult volunteers concurrent with alleviation of common cold symptoms. Funct Food Health Dis 2017; 7 (7): 462-482.
34. Von Ameln S, Dicks L, Prange A, Ellinger S. Dietary supplements made from mushrooms. Ernaehrungs Umschau 2018; 65 (6): 92-99.
35. Song AX, Mao YH, Siu KC, Wu JY. Bifidogenetic effects of Cordyceps sinensis fungal exopolysaccharide and konjac glucomannan after ultrasound and acid degradation. Int J Biol Macromol 2018; 111: 587-594.
36. Gu GS Ren JA, Li GW, Yuan YJ, Li N, Li JS. Cordyceps sinensis preserves intestinal mucosal barrier and may be an adjunct therapy in endotoxin-induced sepsis rat model: a pilot study. Int J Clin Exp Med 2015; 8 (5): 7333-41.
37. Ying M, Yu Q, Zheng B, Wang H, Wang J, Chen S, Gu Y, Nie S, Xie M. Cultured Cordyceps sinensis polysaccharides attenuate cyclophosphamide-induced intestinal barrier injury in mice. J Funct Foods 2019 Nov; 62: 103523.
38. Fan ST, Nie SP, Huang XJ, Wang S, Hu JL, Xie JH, Nie QX, Xie MY. Protective properties of combined fungal polysaccharides from Cordyceps sinensis and Ganoderma atrum on colon immune dysfunction. Int J Biol Macromol 2018 Jul; 114: 1049-1055.
39. Wang J, Nie S, Cui SW, Wang Z, Phillips AO, Phillips GO, Li Y, Xie M. Structural characterisation and immunostimulatory activity of a glucan from natural Cordyceps sinensis. Food Hydrocolloids 2017; 67: 139-147.
40. Finimundy TC, Dillon AJP, Henriques JAP, Ely MR. A review on general nutritional compounds and pharmacological properties of the Lentinula edodes mushroom. Food Nutr Sci 2014; 5: 1095-1105.
41. Schwartz B, Hadar Y. Possible mechanisms of action of mushroom-derived glucans on inflammatory bowel disease and associated cancer. Ann Transl Med 2014 Feb; 2 (2): 19.
42. Kupcova K, Stefanova I, Plavcova Z, Hosek J, Hrouzek P, Kubec R. Antimicrobial, cytotoxic, anti-inflammatory and antioxidant activity of culinary processed shiitake medicinal mushroom (Lentinus edodes, Agaricomycetes) and its major sulfur sensory-active compound lanthionine. Int J Med Mush 2018; 20 (2): 165-175.

43. Sakaguchi K, Shirai Y, Itoh T, Mizuno M. Lentinan exerts its anti-inflammatory activity by suppressing TNFR1 transfer to the surface of intestinal epithelial cells through dectin-1 in an in vitro and mice model. Immunome Res 2018; 14: 3.
44. Anwar H, Suchodolski JS, Ullah MI, Hussain G, Shabbir MZ, Mustafa I, Sohail MU. Shiitake culinary-medicinal mushroom, Lentinus edodes (Agaricomytes) supplementation alters gut microbiome and corrects dyslipidemia in rats. Int J Med Mush 2019; 21 (1): 79-88.
45. Finamore A, Palmery M, Bensehaila S, Pelusa I. Antioxidant, immunomodulating and microbial-modulating activities of the sustainable and eco-friendly spirulina. Oxid Med Cell Longev; 2017: 3247528.
46. Wu Q, Liu L, Miron A, Klimova B, Wan D, Kuca K. The antioxidant, immunomodulatory and anti-inflammatory activities of spirulina: an overview. Archives of Toxicol 2016; 90 (8): 1817-1840.
47. Moens F, Duysburgh C, van den Abbeele P, Morera M, Marzorati M. Lactobacillus rhamnosus GG and Saccharomyces cerevisiae boulardii exert synergistic antipathogenic activity in vitro against enterotoxigenic Escherichia coli. Beneficial microbes 2019; doi: 10.3920/BM2019.0064.
48. Pinheiro I, Robinson L, Verhelst A, Marzorati M, Winkens B, Van den Abbeele P, Possemiers S. A yeast fermentate improves gastrointestinal discomfort and constipation by modulation of the gut microbiome: results from a randomised double blind placebo controlled pilot trial. BMC Complement Altern Med 2017; 17: 441.
49. Seed PC. The human mycobiome. Cold Spring Harbour Perspectives in Medicine 2015; 5: a019810.
50. Palma ML, Zamith-Miranda D, Martins FS, Bozza FA, Nimrichter L, Montero-Lomeli M, Marques Jr ETA, Douradinha B. Probiotic Saccharomyces cerevisiae strains as biotherapeutic tools: is there room for improvement? App Microbiol Biotechnol 2015; doi: 10.1007/s00253-015-6776-x.
51. Ringot-Destrez B, D'Alessandro Z, Lacroix JM, Mercier-Bonin M, Leonard R, Robbe-Masselot C. A sensitive and rapid method to determine adhesion capacity of probiotics and pathogenic microorganisms to human gastrointestinal mucins. Microorganismsm 2018; 6: 49.
52. Terciolo C, Dapoigny M, Andre F. Beneficial effects of Saccharomyces boulardii CNCM I745 on clinical disorders associated with intestinal barrier disruption. Clin Exp Gastroenterol 2019; 12: 67-82.
53. Thijssen AY, Jonkers DMAE, Elamin E, Bast A, Arts I, Driessen A et al. Explorative study on mechanisms contributing to beneficial effect of LcS probiotic treatment in Irritable Bowel Syndrome patients. Accessed 30 November 2019 from https://cris.maastrichtuniversity.nl/portal/files/1492761/guid-50c4f4de-ae5d-404f-8685-730af34cb87d-ASSET1.0#page=62)
54. Liu X, Ou H, Xiang Z, Gregersen H. Optimisation, chemical constituents and bioactivity of essential oil from Iberis amara seeds extracted by ultrasound-assisted hydro-distillation compared to conventional techniques. J Appl Res Med Aromat Plants 2019.
55. El-Ghazaly M, El-Hazek RM, Khayyal MT. Protective effect of the herbal preparation, STW 5, against intestinal damage induced by gamma radiation in rats. Int J Radiat Biol 2015; 91 (2): 150-156.
56. Smyth MC. Intestinal permeability and autoimmune disease. Bioscience Horizons 2017; 10: doi: 10.1093/biohorizons/hzs015.
57. Karl JP, Margolis LM, Hadslien EH, Murphy NE, Castellani JW, Gundersen Y et al. Changes in intestinal microbiota composition and metabolism coincide with increased intestinal permeability in young adults under prolonged physiological stress. Am J Physiol Gastrointest Liver Physiol 2017; 312: G559-G571.
58. Del Piano M, Balzarini M, Carmagnola S, Pagliarulo M, Tari R, Nicola S, Deidda F, Pane M. Assessment of the capability of a gelling complex made of tara gum and the exopolysaccharides produced by the microorganism Streptococcus thermophilus ST10 to prospectively restore the gut physiological barrier: a pilot study. J Gastroenterol 2014 Nov-Dec; 48 (Suppl 1): S56-61.
59. Umeda N. Gut flora 'the second brain" connects Eastern and Western medicine: intestinal hyperpermeability or Qi deficiency can affect brain, mind and whole body. Longhua Chin Med 2019; 2: 6.
60. Leech B, Schlos J, Steel A. Association between increased intestinal permeability and disease: a systematic review. Adv Integr med 2019; 6: 23-34.
61. De Santis S, Cavalcanti E, Mastronardi M, Jirillo E, Chieppa M. Nutritional keys for intestinal barrier modulation. Front Immunol 2017 Dec.
62. Shin A, Preidis GA, Shulman R, Kashap P. The gut microbiome in adult and pediatric functional gastrointestinal disorders. Clinical Gastroenterology and Hepatology. 2018; doi: 10.1016/j.cgh.2018.08.054.
63. Mahboubi M. Lactobacillus gasseri as a functional food and its role in obesity. Int J Med Rev 2019 June; 6 (2): 59-64.
64. Bashir KM, Choi JS. Clinical and physiological perspectives of beta-glucans: the past, present and future. Int J Mol Sci 2017; 18: 1906.
65. Dai X, Stanilka JM, Rowe CA, Esteves EA, Nieves C, Spaiser SJ et al. Consuming Lentinula edodes (Shiitake) mushrooms daily improves human immunity: a randomised dietary intervention in healthy young adults. J Am Coll Nutr 2015; 34 (6).
66. D'evoli L, Morroni F, Lombardi-Boccia G, Lucarini M, Hrelia P, Cantelli-Forti G, Tarozzi A. Red chicory (Cichorium intybus L. cultibar) as a potential source of antioxidant anthocyanins for intestinal health. Oxid Med Cell Long 2013; Article ID 704310.
67. Riviere A, Selak M, Lantin D, Leroy F, De Vuyst L. Bifidobacteria and butyryate-producing colon bacteria: importance and strategies for their stimulation in the human gut. Front Microbiol 2016 June.
68. Ren W, Wang K, Yin J, Chen S, Liu G, Tan B, Wu G, Baz FW, Peng Y, Yin Y. Glutamine-induced secretion of intestinal secretory immunoglobulin A: a mechanistic perspective. Front Immunol 2016 Nov.
69. Beheshtipour H, Mortazavian AM, Mohammadi R, Sohrabvandi S, Khosravi-Darani K. Supplementation of Spirulina platensis and Chlorella vulgaris algae into probiotic fermented milks. Comp Rev Food Sci Saf 2013; 12: 144-154.
70. Okpanyi SN. The anti-inflammatory activity of the plant extract of Iberis amara. Planta Med 1993; 59: A665-A666.
71. Reichling J, Saller R. Iberis amara L. (bitter candytuft) – profile of a medicinal plant. Comp Nat Class Med 2002; 9 (Suppl 1): 21-33.
72. Mueller MH, Seeliger H, Hering N, Hasparek MS, Abdel AH, Kreis ME. Differential desensitisation of afferent nerve fibres by Iberis amara (STW 6) and Iberocast (STW5) in the murine colon. Am J Phytomed Clin Ther 2018; 6 (1): 4.
73. Terciolo C, Dapoigny M, Andre F. Beneficial effects of Saccharomyces boulardii CNCM I-745 on clinical disorders associated with intestinal barrier disruption. Clin Exp Gastroenterol. 2019;12:67–82.
74. Zhang, M Sun K, Wu YE et al. Interactions between Intestinal Microbiota and Host Immune Response in Inflammatory Bowel Disease. Front Immunol. 2017 Aug 14;8:942.