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Botanicals in human nutrition: focus on bioactive food-derived compounds on gut microbiota in gastrointestinal inflammatory diseases

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ABSTRACT

The interest of botanicals in human nutrition is a growing and promising field. However, these substances are still neglected or poorly understood in clinical practice. Since they are metabolized by the gut microbiota, the rationale for their effectiveness could rely not only on their nutritional properties but also on their prebiotic effects. By the way, an interesting field of research is the gastrointestinal tract. We conducted a literature review investigating the role of several nutraceuticals in chronic gut inflammatory and irritable diseases. We carry out a research on Pubmed – using MeSH terms – on the role of nutraceuticals such as *Punica granatum* (pomegranate), *Ribes nigrum* (blackcurrant), *Vaccinium myrtillus* (blueberry), *Vaccinium macrocarpon* (cranberry), *Olea europea*, *Aronia melanocarpa* (chokeberry), and inulin. We found preclinical and clinical studies confirming a striking potential role of these nutraceuticals in reducing gut inflammation in such conditions through gut eubiosis restoration. However, their effects could not be easily reached only by the food source assumption due to the large food amount needed to reach their therapeutic dosages. Thus, it appears useful to use the dry extract of fruits (or plants) in food for special medical purposes to ensure efficacy and long-term adherence to therapy. Further studies on clinical practice are warranted to confirm this preliminary evidence.

KEYWORDS

BOTANICALS
GUT MICROBIOTA
GUT INFLAMMATION
NUTRITION

INTRODUCTION

Botanicals, also known as plant-derived substances, play a significant role as nutraceuticals in human nutrition. Nutraceuticals are bioactive compounds or substances with potential health benefits beyond basic nutrition. Botanical nutraceuticals have been used for centuries in traditional medicine and are now gaining recognition for their diverse health-promoting properties[1].

The interest of botanicals in human nutrition is primarily due to their nutritional content: indeed, many botanicals are rich in essential nutrients such as vitamins, minerals, and antioxidants. For example, fruits like berries and citrus contain high levels of vitamin C, while leafy greens like spinach and kale are excellent sources of vitamins A and K. These nutrients play crucial roles in maintaining overall health and preventing nutrient deficiencies[2].

Botanicals are also abundant sources of phytochemicals, natural bioactive compounds found in plants. Phytochemicals include various groups, such as polyphenols, flavonoids, terpenes, alkaloids, and carotenoids, among others. These compounds possess antioxidant, anti-inflammatory, antimicrobial, and immune-modulating properties[3]. Many botanicals are known for their potent antioxidant and anti-inflammatory effects, helping to mitigate chronic low-grade inflammation, which is associated with several health conditions. Antioxidants help neutralize harmful free radicals, protecting cells from oxidative damage and reducing the risk of chronic diseases such as cardiovascular diseases, cancer, and neurodegenerative disorders[4].

Botanicals often contribute to a well-balanced diet, promoting overall health and well-being. For example, certain botanicals, such as *Zingiber officinalis* (ginger), *Mentha piperita* (peppermint), *Aloe vera*, and *Glycyrrhiza glabra* (licorice), have been traditionally used to support digestive health. These plants can help alleviate symptoms of indigestion, bloating, and nausea; some may even possess anti-ulcer and gastroprotective properties[5]. Several other botanicals have been studied for their potential cognitive-enhancing effects: indeed, *Ginkgo biloba* is believed to improve memory and cognitive function[6]; *Curcuma longa* (turmeric) contains curcumin, which has shown neuroprotective properties and may help with age-related cognitive decline[7]. Leaves of *Camellia sinensis*, in its unfermented form (green tea), contain catechins, which have been associated with cardiovascular health[8]. Some botanicals, like *Panax ginseng* and *Withania somnifera* (ashwagandha), are believed to have adaptogenic properties, helping the body cope with stress and improve overall vitality[9].

Many botanicals used as nutraceuticals have a long history of traditional use in various cultures. Traditional medicine systems, such as Ayurveda, Traditional Chinese Medicine, and Native American healing practices, incorporate botanicals as key components in promoting health and treating various ailments. Modern research often validates the traditional uses of these botanicals and sheds light on their mechanisms of action[10].

Recently, scientific research highlighted the role of botanicals as gut microbiota modulators. Botanicals can influence the composition and activity of the gut microbiota, which in turn can impact human health. Indeed, botanicals may have prebiotic properties, modulating microbial diversity and abundance of gut microbial species[11].

The intestinal microbiota is composed of over 100 trillion cells that have a beneficial role in maintaining physiological homeostasis. Its dysregulation, known as dysbiosis, reduces and alters the content of intestinal bacteria and can modify intestinal permeability, triggering inflammation[12]. It is, therefore, a factor that can lead to metabolic dysfunctions such as obesity, insulin resistance, and the inflammatory process of the intestinal barrier.

Some botanical compounds possess antimicrobial properties that can selectively target harmful bacteria while preserving beneficial ones[13]. On the other side, botanicals may elicit the production of bioactive metabolites by the gut microbiota: when digested by gut microbiota, certain botanical compounds can be metabolized into bioactive substances. These metabolites may have direct or indirect effects on human health. For example, the microbial metabolism of flavonoids found in fruits and vegetables can generate metabolites with antioxidant and anti-inflammatory properties[14]. This could, in turn, increase gut barrier function: the gut microbiota plays a crucial role in maintaining the integrity of the gut barrier.

Some botanicals have been shown to enhance gut barrier function by influencing the gut microbiota and reducing gut inflammation[15]. Finally, botanicals may have indirect effects on gut-brain axis. Emerging research suggests that the gut microbiota can influence brain function and mental health. Some botanicals, including polyphenol-rich foods like green tea and berries, may positively impact the gut-brain axis by modulating the gut microbiota composition and function[16].

Nowadays, botanicals are available in various forms, including capsules, tablets, extracts, teas, and powders. Nutraceutical formulations provide standardized doses of botanical extracts or active compounds, ensuring consistent and reliable intake. These formulations are often used to target specific health concerns, such as immune support, cognitive function, joint health, and energy enhancement.

As the public interest in botanicals is growing, it is fundamental for healthcare professionals to deeply understand their role to integrate them in modern medicine. This work aimed to outline the "state of the art" relating to the use of botanicals in gut microbiota modulation regarding gastrointestinal inflammatory disorders.

Materials and Methods

We focused on some of the most active botanicals on gut health, such as *Punica granatum*, *Ribes nigrum*, *Vaccinium myrtillus*, *Vaccinium macrocarpon, Olea europea*, *Aronia melanocarpa* and inulin. Due to their antioxidant and anti-inflammatory properties, we investigated their role on inflammatory or irritable gastrointestinal syndromes.

A bibliographic search was carried out in PUBMED and MEDLINE. The search strategy did not consider any time limit. Articles in English, Spanish, French, or Italian have been considered. The following search strategy was used: inflammatory bowel disease (IBD) OR irritable bowel syndrome (IBS) AND microbiota OR gut microbiota AND *Punica granatum*[mh OR *Ribes nigrum* OR *Vaccinium myrtillus*[mh] OR *Vaccinium macrocarpon* OR *Olea europea*[mh] OR *Aronia melanocarpa*[mh] OR inulin[mh].

Additional studies were retrieved manually by searching through the references of the articles selected from the online search.

Results

We have reported the main characteristics and effects of the aforementioned botanical compounds in Table 1. Then, we analyzed their specific role in the following paragraphs.

***Punica granatum* (pomegranate)**

Punica granatum L. (PG) is a medicinal plant native to the Mediterranean regions[17] belonging to the genus *Punica* and the Lythraceae family. The plant is cultivated all over the world, where it has been used for generations to treat various diseases. Scientific evidence shows that the beneficial properties attributed to the consumption of pomegranate are useful for the prevention of various conditions, such as obesity, diabetes, and the improvement of the intestinal microbiota[18].

The benefits of pomegranate are mainly attributed to the presence of ellagitannins, particularly punicalagins and ellagic acid: polyphenolic compounds whose metabolism by the microbiota produces compounds known as microbial or post-biotic metabolites with recognized biological activity, including urolithins[19]. In turn, urolithins are metabolized in the large intestine by intestinal bacteria. These metabolites have specific effects on our bodies and may explain people's different responses to polyphenol consumption.

In a study conducted by Cortés-Martìn et al[14] in patients affected by metabolic syndrome, it was found that supplementing the diet with functional PG-based foods can promote the growth of specific strains of the gut microbiota that are closely related to the type of therapy followed by the patient, suggesting that PG metabolites may enforce drug effectiveness.

A recent study in patients affected by IBS demonstrated a significant beneficial effect on sleep quality and intestinal symptoms after supplementation with 180mg/day of ellagic acid[20].

Another study by Lì et al[21] showed that consumption of 1g of PG extract promotes urolithin production. Authors highlighted PG's positive influence on weight and insulin resistance due to its ability to vary the ratio of Firmicutes to Bacteroidetes, also increasing *Akkermansia* abundance.

A study by Henning et al[22] came to the same conclusion, showing that microbial variation in the presence of PG extract, due to its effect on microbial metabolism, is essential for promoting the growth of beneficial bacterial strains such as *Akkermansia*.

In a study based on the fermentation culture of stool samples, it was shown that the addition of PG extract increases the amount of both *Bifidobacterium* spp. and *Lactobacillus-Enterobacterium* microbial strains[23]. Studies in rats have shown that the use of a PG decoction (300 mg/kg), thus rich in polysaccharide components and especially ellegitannins, can prevent the development of colitis-related abdominal pain.

In conclusion, in patients affected by inflammatory intestinal conditions, the supplementation of ellagitannins through a dry PG extract, could promote the growth of beneficial probiotic strains for the acquisition of a physiological state of well-being since, through nutrition, it would be impossible to achieve the necessary dose.

***Ribes nigrum* (blackcurrant)**

Ribes nigrum (RN) L., commonly known as blackcurrant, is a plant belonging to the Grossulariaceae family, native to Europe and Asian Russia. Anthocyanins are the active ingredients of blackcurrant which is characterized by a higher concentration than the other species of currant.

Anthocyanins are polyphenols widely found in fruits and vegetables that act as soluble pigments. Although in nature exist over 600 anthocyanidins,

Table 1. Botanical compounds and their main characteristics.

Botanicals	**Nutritional contents (fruit)**	**Bioactive compounds (mainly in dry extracts)**	**Known mechanisms of action**	**Microbiota modulation**	**Post-biotic metabolites**	**Healthy properties**	**Clinical areas of intervention**
Punica granatum (pomegranate)	Mainly carbohydrates (including fibers), Vitamin C, K, Folate, Potassium, Calcium, Iron, Magnesium, Phosphorus.	Ellagitannins (punicalgins, ellagic acid)	↓ ROS ↓ NF-kB ↓ Inflammatory cytokines (IL-1β, IL-6, TNF-α) ↑ Anti-inflammatory cytokines (IL-10)	↑ *Bifidobacterium* ↑ *Lactobacillus* ↑ *Enterobacterium Akkermansia* ↓ Firmicutes/ Bacteroidetes ratio	Urolithins	Anti-inflammatory -- Influence on weight and insulin resistance	• Obesity • Diabetes • Insulin-resistance • IBS
Ribes nigrum (blackcurrant)	Mainly carbohydrates (including fibers), Vitamin C, Vitamin A, Vitamin K, Vitamin E, Potassium, Calcium, Iron, Magnesium, Phosphorus	Anthocyanins and proanthocyanidins	↓ COX-LOX ↓ NF-kB ↓ Inflammatory cytokines (IL-1β, IL-6, TNF-α) ↑ Anti-inflammatory cytokines (IL-10)	↑ *Bifidobacterium* ↑ *Lactobacillus* ↓ *Bacteroides* ↓ *Clostridia*	Phenolic metabolites and conjugated compounds	Antioxidant -- Anti-inflammatory -- Weight loss -- Glucose metabolism improvement	• Diabetes • Obesity • Cancer • IBD
Vaccinium myrtillus L. (blueberry)	Mainly carbohydrates (including fibers), Vitamin C, Vitamin, Vitamin K, Vitamin E, Potassium Calcium, Iron, Magnesium, Phosphorus	Anthocyanins, flavonols, tannins, and resveratrol	↓ ROS ↓ Intestinal inflammation (↓ cytokine secretion, and apoptosis)	↑ *Bifidobacterium* ↑ *Lactobacillus*	Conjugated phenolic compounds, urolithins	Anti-inflammatory -- Intestinal inflammation improvement -- Neuroprotective	• IBD • Traveler's diarrhea
Vaccinium macrocarpon (cranberry)	Mainly carbohydrates (including fibers), Vitamin C, Vitamin E, Vitamin K, Potassium, Calcium, Iron, Magnesium, Phosphorus	Proanthocyanidins, phenols, anthocyanidins and ellagitannins	↓ COX-LOX ↓ NF-kB ↓ Inflammatory cytokines (IL-1β, IL-6, TNF-α) ↑ Anti-inflammatory cytokines (IL-10)	↑ Growth of commensal bacteria (including those of the *Akkermansia* genus ↓ Uropathogenic strains	Phenolic metabolites, polyphenol-derived metabolites, SCFAs	Antioxidant -- Anti-inflammatory -- Prevention of UTI	• UTI • LUTS • IBS
Olea europea (olives and leaves)	Monounsaturated fats (olives); less amount of oleuropein, polyphenols, flavonoids	Oleuropein, polyphenols, flavonoids (leaves)	↓ ROS ↓ LDL ↓ Intestinal permeability	↑ *Bifidobacterium* ↓ *E. coli* and other pathogenic bacteria ↓ Firmicutes/ Bacteroidetes ratio	Secoiridoids and oleuropein derivatives, phenolic metabolites	Antioxidant -- Anti-inflammatory -- Neuroprotective	• Metabolic syndrome • Intestinal permeability and inflammation
Aronia melanocarpa (chokeberry)	Mainly carbohydrates (including fibers), Vitamin C, Vitamin K, Vitamin E, Potassium, Calcium, Iron, Magnesium, Phosphorus	Anthocyanins, Flavonoids, Proanthocyanidin, phenolic acids.	↓ Inflammatory cytokines ↑ Intestinal barrier integrity	↑ *Bacteroides* ↑ *Bifidobacterium* ↑ *Blautia* ↑ *Faecalibacterium* ↑ *Akkermansia* ↓ *Prevotella* ↓ *Megamonas* ↓ *Escherichia* ↓ *Shigella*	Phenolic compounds, urolithins	Anti-inflammatory -- Antioxidant	• Intestinal inflammation • IBD
Inulin	Prebiotic fiber	Prebiotic fiber	↑ Gut mucus production ↑ Gut barrier integrity	↑ *Bifidobacterium* ↑ *Lactobacillus* ↑ *Atopobium* ↑ *Enterococcus* ↓ *Desulfovibrio* ↓ *Lachnospira* ↓ *Oscillospira* ↓ *Cellulomonas*	SCFAs, gases (H_2 and CO_2), Lactic acid	Prebiotic -- Gut mucosal inflammation improvement	• Intestinal permeability and inflammation • IBD

Abbreviations: IBS, irritable bowel syndrome; COX, cyclooxygenase; LOX, lipoxygenase; IBD, inflammatory bowel disease; ROS, reactive oxygen species; SCFAs, short chain fatty acids; UTI, urinary tract infection; LUTS, lower urinary tract symptoms; LDL, low-density lipoprotein

known as aglycones, as of now, only 17 of them have been identified[24]. Through biochemical reactions, anthocyanidins produce anthocyanins, pigments that have shown several beneficial properties for health. Among them, the main ones have antioxidant and anti-inflammatory properties, playing a major role in the prevention of diseases such as diabetes, obesity, cancer, and IBD[25].
Anthocyanins also promote weight loss by reducing the inflammatory state and increasing energy consumption. Moreover, numerous *in vivo* and *in vitro* studies support the beneficial effects of anthocyanidin's supplementation in different chronic inflammatory diseases, including IBD[26-28].
Current literature highlighted that most food anthocyanins are not fully absorbed in the upper intestine but reach the gut microbiota, where they are metabolized and absorbed. This, in turn, promotes the colonization of bacteria containing enzymes necessary to break down anthocyanins[29]. In their study, Molan and co-authors[30] showed that dietary supplementation with RN extract, a plant rich in anthocyanins, has several benefits for the intestinal microbiota. Specifically, this plant can both promote the growth of beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus*, and reduce the level of other bacteria, such as *Bacteroides* and *Clostridia*.
Polyphenols, including anthocyanins, can act as prebiotics[31] by promoting the growth of health-beneficial bacteria. At the same time, they can also show antimicrobial effects against pathogenic bacteria[32]. The interaction between polyphenols and gut microbiota is essential for their bioavailability and activity, influencing also their effects on the host's health[33]. Esposito et al[34] showed that supplementation with 1% of RN extract (with 32% of anthocyanins) in a diet reduces body weight gain and improves glucose metabolism in mice with intact gut microbiome. RN also, enhance the bacteria's effects such as the prevention of inflammatory and tumor diseases, the vitamin synthesis and the strengthening of the immune system[30].
All these findings suggest that food for special medical purposes, based on RN, could promote the survival, colonization, and activity of beneficial bacteria in the gastrointestinal tract. The supplementation of berries in food for special medical purposes is particularly effective because it allows for a balanced and constant intake of both polyphenols and fibers, which cannot be easily guaranteed by separately eating different foods.

***Vaccinium myrtillus* L. (blueberry)**
V. myrtillus (VM) L., is a dwarf shrub known as blueberry and European blueberry. The shrub is native to northern Europe and North America but has also been reported in Asia[35]. The blueberry fruit is blue/black, spheroidal, and has a diameter of about 5-9 mm. Fruits are commonly referred to as "superfoods" or "functional foods", due to the presence of many health-beneficial compounds[36]. These fruits contain sugars, vitamins, and pectin, as well as a variety of healthy compounds, including anthocyanins, flavonols, tannins, and resveratrol[36]. Blueberries naturally contain high levels of polyphenols, made up of 50-80% anthocyanins[37] and 10% tannins. *In vitro* studies suggest that the use of a dry blueberry extract reduces inflammatory gene expression[38]. Thus, the supplementation of dry extracts of VM may be desirable as a complementary therapy for inflammatory bowel diseases since it provides a concentrated source of beneficial compounds and a rapid release into the gastrointestinal tract[39,40]. Tannins have anti-inflammatory, astringent, and neuroprotective properties[41], with the ability to improve the symptoms of Crohn's disease[42] and traveler's diarrhea[43]. Indeed, phenols have shown anti-inflammatory properties, being able to reduce intestinal inflammation in acute and chronic colitis, with a consequent decrease in histological scores, cytokine secretion, and apoptosis in colon epithelial cells[44,45].
Other studies demonstrated the benefits of blueberry in the treatment of ulcerative colitis, a disease characterized by an overabundance of neutrophils and macrophages that can lead to the excessive production of reactive oxygen species (ROS) in inflamed points[46]. Blueberry extract has the ability to neutralize ROS[47]. In patients with ulcerative colitis, integrating blueberries into their diet has shown significant improvements in symptoms and biological parameters, such as reduced levels of fecal calprotectin[39,48]. Literature reports that it is necessary to ingest large quantities of blueberries to experience health benefits. However, the treatment is usually carried out for a short time due to the patient refusing long-term therapies. These studies have highlighted the need to use a dry extract instead of dry blueberry fruits to ensure long-term adherence to therapy for chronic states such as ulcerative colitis. The intake of dry blueberry extract has been shown to guarantee a rapid release of anthocyanins in the gastrointestinal tract and improve disease activity in patients with mild to moderate ulcerative colitis[46]. The bioavailability of anthocyanins in the gastrointestinal tract is affected by environmental conditions and administration techniques. Recent studies highlighted how encapsulation techniques modulate the release

of anthocyanins to determine the double amount of anthocyanins available after 150 minutes[49].

In conclusion, blueberries are a fruit full of beneficial compounds for human health and rich in anthocyanins, which offer anti-inflammatory and antioxidant properties. The administration of anthocyanins through a dry blueberry extract is more feasible for patients since it would be impossible to assimilate the correct amount through nutrition. However, further clinical studies are needed to assess the therapeutic effect of integrating blueberries into the diet of patients with inflammatory bowel conditions.

Vaccinium macrocarpon* (cranberry*)

Studies indicate a close association between IBS and lower urinary tract symptoms (LUTS) in both men and women[15]. Indeed, conditions such as IBS, or IBD in general, may disrupt both the intestinal biome and the brain-gut axis resulting in an increased incidence of urinary tract infections[50].

The biological mechanisms of the correlation between IBS and LUTS[51-53] are not yet fully understood, but what seems certain is the involvement of the inflammatory state and alterations in the microbiota.

The *V. macrocarpon* (VM) Ait., also known as cranberry, and its protoanthocyanidins (PACs) are traditionally used in this context. It is mainly cultivated in various parts of North America and Europe. Its composition varies depending on the cultivar, climate, harvest time and storage conditions.

Blueberries contain mainly glucose (58% to 65.9% of monosaccharides), fructose, and a wide range of water-soluble and fat-soluble vitamins. Other important constituents are phenols, flavonoids, anthocyanidins and ellagitannins, which play a key role in the treatment of LUTS[54]. Whereas, its antioxidant properties are mainly derived from its vitamin C, E and K content[55].

Recent studies have disproved the theory that flavonoids such as PACs could be directly responsible for the prevention of urinary tract infections: it has been shown that PACs are only minimally absorbed and metabolized, but are extensively catabolized by the colonic microbiota to form various metabolites. Studies have shown that the gut microbiota is essential in regulating homeostasis[56]. It was therefore concluded that cranberry flavonoids and phenolic acids possess the ability to modulate the composition of the gut microbiota by preventing dysbiosis through their prebiotic action: they promote the growth of commensal bacteria (including those of the *Akkermansia* genus[57]) and hinder that of uropathogenic strains[58].

Based on this evidence, dry cranberry extract titrated in PACs can be considered in the context of a specific diet and prevent LUTS, especially in conditions such as IBS. Daily intake of dry cranberry extract also allows for standardization of PACs amounts with a consequent beneficial effect on the gut microbiota.

Olea europea

Olives, the fruits of *Olea europea* (OE) L., are highly considered for their high nutritional value derived from their high proportion of unsaturated fatty acids, tocopherols, phytosterols, squalene, and phenolic compounds. The last mentioned are especially recognized for their ability to reduce free radicals. The literature recognizes the essential role of extra virgin olive oil (EVOO) intake in decreasing oxidized low-density lipoprotein (LDL)[59] and markers of inflammation, thereby improving endothelial function[60,61]. The European Safety Authority has also released a health claim on the effectiveness of the oil's phenols (5 mg/day of active ingredient per 20 g of EVOO) in reducing the risk of developing cardiovascular disease[62].

The beneficial effects of olive oil intake are given by its high content of the secoiridoid oleuropein, its main phenolic compound. This element is mainly present in unprocessed olive fruit and leaves, reaching up to 140mg/g of dry matter in young olives and 60-90 mg/g of dry matter in leaves[60,63]. However, recent studies pointed out that its concentrations may fluctuate depending on cultivar, production area, and production conditions[64].

In 2020, Hermans et al demonstrated the beneficial effects of dietary supplementation with OE dry extract capsules titrated in oleuropein (50 mg/capsule) and hydroxytyrosol (10 mg/capsule)[65]. Data shows that this supplementation decreases the oxidative stress responsible for the parameters monitored in metabolic syndrome. In addition to their antioxidant function, phenolic compounds can positively impact the intestinal microbiota as through a prebiotic activity, they stimulate greater intestinal bacterial biodiversity by improving the *Firmicutes/Bacteroidetes* ratio, the imbalance of which generates dysbiosis[66]. If, on the one hand, the gut microbiota balance is essential for maintaining overall health, on the other hand, its imbalance causes increased intestinal permeability, an increase in the circulation of lipopolysaccharides (LPS), leading to endotoxemia.

LPS is an endotoxin present in gram-negative bacteria related to the activation of the Toll-like receptor 4 (TLR4). LPS regulates the secretion of pro-inflammatory cytokines both local and into the bloodstream. This variation may depend on dietary factors (such as consumption of saturated fat) which stimulate TLR4 receptors, inducing endotoxemia and inflammation[67].

The polyphenolic compound of OE has the ability to affect the microbial balance both by enhancing probiotic strains belonging to the *Bifidobacterium* genus, and by inhibiting the growth of pathogenic bacteria such as *E. coli* and reducing intestinal permeability[67,68].

***Aronia melanocarpa* (chokeberry)**

Aronia melanocarpa (AM, Michx.) Elliott is one of the most functional berries, usually used in the preparation of juices and jams. It is relevant from an ethnopharmacological point of view for the richness of biologically active molecules – antioxidants and polyphenols- with pharmaceutical and physiological effects.

According to a study conducted by Valcheva-Kuzmanova et al, fruit juice from AM, administered to rats with trinitrobenzene sulfonic-induced colitis for 14 days (three doses 2.5, 5, and 10 ml/kg), had an effect comparable to sulfalazine treatment (400 mg/kg) by improving local macroscopic and microscopic signs of colitis and preventing the colon increase of reactive substance concentrations (to thiobarbituric acid)[69].

More recently, Li et al evaluated the effects of the ethanolic extract in an intestinal disease model of mice with Dextran Sulfate Sodium (DSS)-induced inflammation. The extract was administered orally for 21 days. The results show that it exerts a prebiotic activity able to reverse the effects of intestinal dysbiosis by promoting the production of short-chain cecal fatty acids effective in inhibiting the pro-inflammatory pathway established in IBD. This activity has the secondary effect of improving clinical symptoms and regulating histopathological parameters, pro- and anti-inflammatory cytokines and oxidative stress factors, as well as mRNA and protein expression of transcription factors involved in maintaining intestinal barrier integrity[70].

To support prebiotic action, other literature data indicate that dietary supplementation with fruits are able to "suitably nourish" the microbiota by favoring beneficial species belonging to the genera *Bacteroides*, *Prevotella*, *Akkermansia*[71-73]. Yu et al[74] showed *in vitro* that anthocyanins from AM significantly increase the relative richness of *Bacteroides*, promoting the growth of *Bifidobacterium*, *Blautia*, *Faecalibacterium*, and inhibiting the growth of *Prevotella*, *Megamonas*, *Escherichia*/*Shigella*, etc. Liu et al[75] demonstrated that polyphenols are the nutritional components to the gut microbiota. Finally, Valdez JC. and colleagues demonstrated that AM also exerts its efficacy by increasing barrier function and attenuating the characteristic baseline reduction of transepithelial electrical resistance observed in response to the establishment of a pro-inflammatory framework in Caco-2 cells[76]. Because of the above, consumption of aronia berries, which are high in polyphenols, would be desirable in the diet of an IBD patient.

However, AM is mainly used to produce juices, purees, jams, jellies, wine and food coloring. The fruit is highly valued for its supply of antioxidants, particularly polyphenols, phenolic acids (neochlorogenic and chlorogenic acids) and flavonoids (anthocyanins, proanthocyanidins, flavanols and flavonols). The presence of tannins in the berry outlines its astringent characteristics, which makes it unsuitable for the consumption of fresh fruit[77] in the diet of the IBD patient, who presents a clinical picture characterized by alternating frequent diarrhea and prolonged constipation.

In addition, evidence shows that polyphenol content is subject to essential variations[78-80]. It has been estimated that the optimal storage temperature for the product is 3°C, but after only six months of storage, the content of total polyphenols decreases by 30%[81].

In conclusion, the limitations imposed by the shelf life and the quality reproducibility factors drastically invalidate the use of fresh food by making it difficult for the IBD patient to take consistent and effective doses of polyphenols. Therefore, introducing foods for special medical purposes based on the dry extract of AM titrated in polyphenols (specifically proanthocyanidins belonging to the flavonoids class) makes it possible to ensure quality food for the IBD patient.

Inulin

Inulin is a fructose-containing polymer that is part of a class of compounds called fructans. Fructans (e.g., inulin, oligofructose) can be extracted from plants, produced by hydrolysis of inulin, or enzymatically synthesized from sucrose (e.g., fructooligosaccharide, FOS). It was first isolated in 1804 from the roots of *Inula heleniumda* and named inulin in 1817. Fructans are found extensively in nature as reserve carbohydrates in more than 30,000 plants, such as chicory, Jerusalem artichoke, and dahlia. The *Cichorium intybus* (chicory) or Jerusalem artichoke tubers are important sources of inulin[82,83] used for industrial production. Chain length and molecular branching affect the quality and functionality of inulin.

Scientific literature has highlighted the role of prebiotics, such as inulin, in promoting gut flora activity. Intake of inulin can improve calcium absorption, lipid metabolism, constipation, and intestinal barrier function[82]. In a recent review, Costa et al[84] documented that ingestion of FOS and inulin in children and adolescents can improve the absorption of nutrients, such as minerals and vitamins, that may be useful in the treatment or prophylaxis of certain diseases. Indeed, it is known that the gut bacteria

promoted by these prebiotics, in addition to short-chain fatty acids, also produce vitamins (B3, B5, B6, B12, biotin, tetrahydrofolate, and vitamin K) and promote mineral absorption.
Inulin is a promising prebiotic useful in numerous medical conditions, including IBD. The recommended daily consumption of inulin generally does not exceed 25~35 g[85]. Inulin is generally recognized as safe and can be easily taken, so it can be incorporated into the diet of patients with IBD to regulate intestinal flora and promote the growth of commensal bacteria. In fact, bacteria promote saccharolysis of inulin in the large intestine, which supports the growth of bifidobacteria and lactobacilli.
In a recent review, Vinelli et al[86] summarize trials conducted by incorporating inulin into the diets of adults, showing that the introduction of amounts of inulin between 7 and 22.4 g/day for several weeks modulates the gut microbiota. In particular, an excellent bifidogenic effect detected using several molecular investigation techniques (16S rRNA gene amplicon sequencing, qPCR and FISH) is reported. These changes involve, for example, an increase in *Atopobium* and *Lactobacillus-Enterococcus* as well as a decrease in *Bacteroides-Prevotella*. Supplementation of 7.5 g/day of inulin obtained from *Agave spp*[87] significantly reduced the relative abundance of the sulfidogenic pathobiont *Desulfovibrio*, along with *Lachnobacterium* and *Ruminococcus*. Similarly, another study[88], finds a decrease in *Lachnospira* and *Oscillospira*, and a significant increase of *Nesterenkonia*, *Brevibacterium*, and *Cellulomonas*. Finally, supplementation of 20 g/day of inulin from *C. intybus* increases total anaerobes and *Lactobacillus spp*. and reduces enterobacteria, along with ammonia levels[89]. Promoting the growth of lactic acid-producing bacteria prevents the reproduction of endogenous and/or exogenous microorganisms underlying disease progression by showing a positive effect on gut barrier function.
The use of inulin with its prebiotic activity reduces mucosal inflammation in IBD subjects and in all subjects with persistent gastrointestinal disorders[82]. Inulin has a neutral taste and can be used as a substitute for sucrose, and it has a sweetness level of about 10 percent compared to the latter[90]. This represents an advantage that makes it suitable for all patients. Therefore, the introduction of inulin in a food for special medical purposes could overcome limitations in the intake of plant foods in IBD patients. Moreover, if formulated with other extracts titrated in polyphenols it may protect them in the gastric passage until they reach the intestinal districts, where they will exert their prebiotic actions[91]. For these reasons, inulin extracted from plant sources is advantageous over the intake of related foods.

CONCLUSIONS

This review provides evidence-based information for the use of botanicals in human nutrition as key modulators of the gut microbiota promoting gut homeostasis. Several studies are conducted in vitro or animal models due to a pathogenetic model; however, there are also many human studies, both in healthy volunteers and patients. Evidence suggests a rationale to use such substances as contributors to inflammatory and irritable bowel conditions in the clinical practice, in a multimodal therapeutic approach.
Gut chronic inflammatory conditions are associated with intestinal mucosa barrier dysfunction and a consequent increase in permeability[92]. This process originates from the disruption of the mucosal cell tight junctions triggered by oxidative stress, and inflammatory mediators such as cytokines, and results in bacterial LPS translocation across the intestinal barrier[93,94]. Consequently, antigenic determinants derived from food or intestinal bacteria cause an intestinal immune response and tissue damage[95]. It can be deduced that oxidative stress, which occurs following the release of ROS by immune system cells, plays a role in the pathogenesis. In this inflammatory condition, the colon is infiltrated by neutrophils that produce superoxide and other strong oxidants that can accelerate disease progression[96].
The scientific interest in botanicals as nutraceuticals is a promising growing field. Researchers continue to investigate their potential health benefits, mechanisms of action, optimal dosages, and safety profiles.
Nowadays, numerous studies reported that biologically active substances extracted from plants are effective in the treatment of these pathologies by reducing oxidative stress, controlling the levels of pro-inflammatory cytokines or inflammatory mediators[97,98], and modulating the microbiota to promote the growth of beneficial probiotics, related to good health, at the expense of pathogenic ones.
However, their effectiveness cannot be easily guaranteed by eating different foods separately for the large amount needed to reach their daily effective dosages. Thus, it appears useful to use dry extract of fruits (or plants) in food for special medical purposes to ensure efficacy and long-term adherence to therapy for chronic states such as inflammatory conditions.
Further studies should assess their effectiveness in humans through well-designed health and disease approaches, aiming to determine the effective schedule and periods of administration.

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References

1. Grosso G. Effects of Polyphenol-Rich Foods on Human Health. Nutrients 2018 Aug 14;10(8):1089. Doi: 10.3390/nu10081089
2. Slavin JL, Lloyd B. Health benefits of fruits and vegetables. Adv Nutr. 2012 Jul 1;3(4):506-516. Doi: 10.3945/an.112.002154.
3. Paudel KR, Patel V, Vishwas S, Gupta S, Sharma S, Chan Y, Jha NK, Shrestha J, Imran M, Panth N, Shukla SD, Jha SK, Devkota HP, Warkiani ME, Singh SK, Ali MK, Gupta G, Chellappan DK, Hansbro PM, Dua K. Nutraceuticals and COVID-19: A mechanistic approach toward attenuating the disease complications. J Food Biochem. 2022 Dec;46(12):e14445. Doi: 10.1111/jfbc.14445.
4. Alharbi KS, Javed Shaikh MA, Imam SS, Alshehri S, Ghoneim MM, Almalki WH, Singh SK, Kumar D, Kumar AP, Dua K, Chellappan DK, Paudel KR, Gupta G. Role of Flavonoids in Management of Various Biological Targets in Alzheimer's Disease: Evidence from Preclinical to Clinical Studies. Curr Med Chem. 2023;30(18):2061-2074. Doi: 10.2174/0929867330666221122115212.
5. Micklefield GH, Redeker Y, Meister V, Jung O, Greving I, May B. Effects of ginger on gastroduodenal motility. Int J Clin Pharmacol Ther. 1999 Jul;37(7):341-346. PMID: 10442508.
6. Mahadevan S, Park Y. Multifaceted therapeutic benefits of Ginkgo biloba L.: chemistry, efficacy, safety, and uses. J Food Sci. 2008 Jan;73(1):R14-19. Doi: 10.1111/j.1750-3841.2007.00597.x.
7. Kocaadam B, Şanlier N. Curcumin, an active component of turmeric (Curcuma longa), and its effects on health. Crit Rev Food Sci Nutr. 2017 Sep 2;57(13):2889-2895. Doi: 10.1080/10408398.2015.1077195.
8. Chacko SM, Thambi PT, Kuttan R, Nishigaki I. Beneficial effects of green tea: a literature review. Chin Med. 2010 Apr 6;5:13. Doi: 10.1186/1749-8546-5-13.
9. Panossian A, Wagner H. Stimulating effect of adaptogens: an overview with particular reference to their efficacy following single dose administration. Phytother Res. 2005 Oct;19(10):819-838. Doi: 10.1002/ptr.1751.
10. Graziose R, Lila MA, Raskin I. Merging traditional Chinese medicine with modern drug discovery technologies to find novel drugs and functional foods. Curr Drug Discov Technol. 2010 Mar;7(1):2-12. Doi: 10.2174/157016310791162767.
11. Mills S, Stanton C, Lane JA, Smith GJ, Ross RP. Precision Nutrition and the Microbiome, Part I: Current State of the Science. Nutrients. 2019 Apr 24;11(4):923. Doi: 10.3390/nu11040923.
12. Deiana M, Serra G, Corona G. Modulation of intestinal epithelium homeostasis by extra virgin olive oil phenolic compounds. Food Funct. 2018 Aug 15;9(8):4085-4099. Doi: 10.1039/c8fo00354h.
13. Borges A, Abreu AC, Ferreira C, Saavedra MJ, Simões LC, Simões M. Antibacterial activity and mode of action of selected glucosinolate hydrolysis products against bacterial pathogens. J Food Sci Technol. 2015 Aug;52(8):4737-4748. Doi: 10.1007/s13197-014-1533-1.
14. Cortés-Martín A, Iglesias-Aguirre CE, Meoro A, Selma MV, Espín JC. Pharmacological Therapy Determines the Gut Microbiota Modulation by a Pomegranate Extract Nutraceutical in Metabolic Syndrome: A Randomized Clinical Trial. Mol Nutr Food Res. 2021 Mar;65(6):e2001048. Doi: 10.1002/mnfr.202001048.
15. Li Z, Huang W, Wang X, Zhang Y. The relationship between lower urinary tract symptoms and irritable bowel syndrome: a meta-analysis of cross-sectional studies. Minerva Urol Nefrol. 2018 Aug;70(4):386-392. Doi: 10.23736/S0393-2249.18.03044-8.
16. Gareau MG. Microbiota-gut-brain axis and cognitive function. Adv Exp Med Biol. 2010;671:229-234. Doi: 10.1007/978-1-4939-0897-4_16
17. Puneeth HR, Chandra SSP. A review on potential therapeutic properties of Pomegranate (Punica granatum L.). Plant Science Today. 2020;7(1):9-16. Doi: 10.14719/pst.2020.7.1.619
18. Maphetu N, Unuofin JO, Masuku NP, Olisah C, Lebelo SL. Medicinal uses, pharmacological activities, phytochemistry, and the molecular mechanisms of Punica granatum L. (pomegranate) plant extracts: A review. Biomed Pharmacother. 2022 Sep;153:113256. Doi: 10.1016/j.biopha.2022.113256.
19. García-Villalba R, Tomás-Barberán FA, Iglesias-Aguirre CE, Giménez-Bastida JA, González-Sarrías A, Selma MV, Espín JC. Ellagitannins, urolithins, and neuroprotection: Human evidence and the possible link to the gut microbiota. Mol Aspects Med. 2023 Feb;89:101109. Doi: 10.1016/j.mam.2022.101109.
20. Mirzaie Z, Bastani A, Hesami S, Pouryousefi E, Kavianpour M, Haghighian HK. Improving Effect of Ellagic Acid on Sleep Quality and Gastrointestinal Symptoms in Patient With Irritable Bowel Syndrome: Randomized Double-Blind Clinical Trial. Turk J Gastroenterol. 2021 Nov;32(11):937-944. Doi: 10.5152/tjg.2021.20344.
21. Li Z, Henning SM, Lee RP, Lu QY, Summanen PH, Thames G, Corbett K, Downes J, Tseng CH, Finegold SM, Heber D. Pomegranate extract induces ellagitannin metabolite formation and changes stool microbiota in healthy volunteers. Food Funct. 2015 Aug;6(8):2487-24795. Doi: 10.1039/c5fo00669d.

22. Henning SM, Summanen PH, Lee RP, Yang J, Finegold SM, Heber D, Li Z. Pomegranate ellagitannins stimulate the growth of Akkermansia muciniphila in vivo. Anaerobe. 2017 Feb;43:56-60. Doi: 10.1016/j.anaerobe.2016.12.003.
23. Bialonska D, Ramnani P, Kasimsetty SG, Muntha KR, Gibson GR, Ferreira D. The influence of pomegranate by-product and punicalagins on selected groups of human intestinal microbiota. Int J Food Microbiol. 2010 Jun 15;140(2-3):175-82. Doi: 10.1016/j.ijfoodmicro.2010.03.038.
24. Speciale A, Bashllari R, Muscarà C, Molonia MS, Saija A, Saha S, Wilde PJ, Cimino F. Anti-Inflammatory Activity of an In Vitro Digested Anthocyanin-Rich Extract on Intestinal Epithelial Cells Exposed to TNF-α. Molecules. 2022 Aug 23;27(17):5368. Doi: 10.3390/molecules27175368.
25. Ma Z, Du B, Li J, Yang Y, Zhu F. An Insight into Anti-Inflammatory Activities and Inflammation Related Diseases of Anthocyanins: A Review of Both In Vivo and In Vitro Investigations. Int J Mol Sci. 2021 Oct 14;22(20):11076. Doi: 10.3390/ijms222011076.
26. Farzaei MH, El-Senduny FF, Momtaz S, Parvizi F, Iranpanah A, Tewari D, Naseri R, Abdolghaffari AH, Rezaei N. An update on dietary consideration in inflammatory bowel disease: anthocyanins and more. Expert Rev Gastroenterol Hepatol. 2018 Oct;12(10):1007-1024. Doi: 10.1080/17474124.2018.1513322.
27. Ghattamaneni NK, Sharma A, Panchal SK, Brown L. Pelargonidin 3-glucoside-enriched strawberry attenuates symptoms of DSS-induced inflammatory bowel disease and diet-induced metabolic syndrome in rats. Eur J Nutr. 2020 Oct;59(7):2905-2918. Doi: 10.1007/s00394-019-02130-1.
28. Li S, Wang T, Wu B, Fu W, Xu B, Pamuru RR, Kennett M, Vanamala JKP, Reddivari L. Anthocyanin-containing purple potatoes ameliorate DSS-induced colitis in mice. J Nutr Biochem. 2021 Jul;93:108616. Doi: 10.1016/j.jnutbio.2021.108616.
29. Faria A, Fernandes I, Norberto S, Mateus N, Calhau C. Interplay between anthocyanins and gut microbiota. J Agric Food Chem. 2014 Jul 23;62(29):6898-902. Doi: 10.1021/jf501808a.
30. Molan AL, Liu Z, Plimmer G. Evaluation of the effect of blackcurrant products on gut microbiota and on markers of risk for colon cancer in humans. Phytother Res. 2014 Mar;28(3):416-22. Doi: 10.1002/ptr.5009.
31. Tomás-Barberán FA, Selma MV, Espín JC. Interactions of gut microbiota with dietary polyphenols and consequences to human health. Curr Opin Clin Nutr Metab Care. 2016 Nov;19(6):471-476. Doi: 10.1097/MCO.0000000000000314.
32. Etxeberria U, Fernández-Quintela A, Milagro FI, Aguirre L, Martínez JA, Portillo MP. Impact of polyphenols and polyphenol-rich dietary sources on gut microbiota composition. J Agric Food Chem. 2013 Oct 9;61(40):9517-33. Doi: 10.1021/jf402506c.
33. Ozdal T, Sela DA, Xiao J, Boyacioglu D, Chen F, Capanoglu E. The Reciprocal Interactions between Polyphenols and Gut Microbiota and Effects on Bioaccessibility. Nutrients. 2016 Feb 6;8(2):78. Doi: 10.3390/nu8020078.
34. Esposito D, Damsud T, Wilson M, Grace MH, Strauch R, Li X, Lila MA, Komarnytsky S. Black Currant Anthocyanins Attenuate Weight Gain and Improve Glucose Metabolism in Diet-Induced Obese Mice with Intact, but Not Disrupted, Gut Microbiome. J Agric Food Chem. 2015 Jul 15;63(27):6172-6180. Doi: 10.1021/acs.jafc.5b00963.
35. Zoratti L, Klemettilä H, Jaakola L. Nutritional Composition of Fruit Cultivars, 2016.
36. Vaneková Z, Rollinger JM. Bilberries: Curative and Miraculous - A Review on Bioactive Constituents and Clinical Research. Front Pharmacol. 2022 Jun 29;13:909914. Doi: 10.3389/fphar.2022.909914.
37. Määttä-Riihinen KR, Kamal-Eldin A, Mattila PH, González-Paramás AM, Törrönen AR. Distribution and contents of phenolic compounds in eighteen Scandinavian berry species. J Agric Food Chem. 2004 Jul 14;52(14):4477-4486. Doi: 10.1021/jf049595y.
38. Roth S, Spalinger MR, Gottier C, Biedermann L, Zeitz J, Lang S, Weber A, Rogler G, Scharl M. Bilberry-Derived Anthocyanins Modulate Cytokine Expression in the Intestine of Patients with Ulcerative Colitis. PLoS One. 2016 May 6;11(5):e0154817. Doi: 10.1371/journal.pone.0154817.
39. Piberger H, Oehme A, Hofmann C, Dreiseitel A, Sand PG, Obermeier F, Schoelmerich J, Schreier P, Krammer G, Rogler G. Bilberries and their anthocyanins ameliorate experimental colitis. Mol Nutr Food Res. 2011 Nov;55(11):1724-1729. Doi: 10.1002/mnfr.201100380.
40. Wu LH, Xu ZL, Dong D, He SA, Yu H. Protective Effect of Anthocyanins Extract from Blueberry on TNBS-Induced IBD Model of Mice. Evid Based Complement Alternat Med 2011: 525462. Doi: 10.1093/ecam/neq040.
41. Maugeri A, Lombardo GE, Cirmi S, Süntar I, Barreca D, Laganà G, Navarra M. Pharmacology and toxicology of tannins. Arch Toxicol. 2022 May;96(5):1257-1277. Doi: 10.1007/s00204-022-03250-0.
42. Plein K, Burkard G, Hotz J. Trattamento della diarrea cronica nella malattia di Crohn. Uno studio pilota sull'effetto clinico del tannino albuminato e del lattato di etacridina. Fortschr Med. 1993;111:114-118.

43. Ericsson CD. Agenti non antimicrobici nella prevenzione e nel trattamento della diarrea del viaggiatore. Clino Infettare Dis. 2005; 41: S557-S563.
44. Crozier A, Jaganath IB, Clifford MN. Dietary phenolics: chemistry, bioavailability and effects on health. Nat Prod Rep 2009;26:1001-1043. Doi: 10.1039/b802662a.
45. Cardona F, Andrés-Lacueva C, Tulipani S, Tinahones FJ, Queipo-Ortuño MI. Benefits of polyphenols on gut microbiota and implications in human health. J Nutr Biochem 2013;24:1415-1422. Doi: 10.1016/j.jnutbio.2013.05.001.
46. Biedermann L, Mwinyi J, Scharl M, Frei P, Zeitz J, Kullak-Ublick GA, Vavricka SR, Fried M, Weber A, Humpf HU, Peschke S, Jetter A, Krammer G, Rogler G. Bilberry ingestion improves disease activity in mild to moderate ulcerative colitis – an open pilot study. J Crohns Colitis. 2013 May;7(4):271-279. Doi: 10.1016/j.crohns.2012.07.010.
47. Liu Z, Ren Z, Zhang J, Chuang CC, Kandaswamy E, Zhou T, Zuo L. Role of ROS and Nutritional Antioxidants in Human Diseases. Front Physiol. 2018 May 17;9:477. Doi: 10.3389/fphys.2018.00477
48. Osman N, Adawi D, Ahrné S, Jeppsson B, Molin G. Probiotics and blueberry attenuate the severity of dextran sulfate sodium (DSS)-induced colitis. Dig Dis Sci. 2008 Sep;53(9):2464-73. Doi: 10.1007/s10620-007-0174-x.
49. Oidtmann J, Schantz M, Mäder K, Baum M, Berg S, Betz M, Kulozik U, Leick S, Rehage H, Schwarz K, Richling E. Preparation and comparative release characteristics of three anthocyanin encapsulation systems. J Agric Food Chem. 2012 Jan 25;60(3):844-851. Doi: 10.1021/jf2047515.
50. Juganavar A, Joshi KS. Chronic Pelvic Pain: A Comprehensive Review. Cureus. 2022 Oct 26;14(10):e30691. Doi: 10.7759/cureus.30691.
51. Coyne KS, Sexton CC, Irwin DE, Kopp ZS, Kelleher CJ, Milsom I. The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study. BJU Int. 2008 Jun;101(11):1388-1395. Doi: 10.1111/j.1464-410X.2008.07601.x.
52. Milsom I, Kaplan SA, Coyne KS, Sexton CC, Kopp ZS. Effect of bothersome overactive bladder symptoms on health-related quality of life, anxiety, depression, and treatment seeking in the United States: results from EpiLUTS. Urology. 2012 Jul;80(1):90-96. Doi: 10.1016/j.urology.2012.04.004.
53. Zingone F, Iovino P, Santonicola A, Gallotta S, Ciacci C. High risk of lower urinary tract symptoms in patients with irritable bowel syndrome. Tech Coloproctol. 2017 Jun;21(6):433-438. Doi: 10.1007/s10151-017-1653-5.
54. Drugs and Lactation Database (LactMed®) [Internet]. Bethesda (MD): National Institute of Child Health and Human Development; 2006–. Cranberry. 2022 Apr 18. https://www.ncbi.nlm.nih.gov/books/NBK501922/
55. United States Department of Agriculture. Food Data Central. Cranberries, Raw. Available online: https://fdc.nal.usda.gov/fdc-app.html#/food-details/171722/nutrients (accessed on 27 May 2023).
56. Sekirov I, Russell SL, Antunes LC, Finlay BB. Gut microbiota in health and disease. Physiol Rev. 2010 Jul;90(3):859-904. doi: 10.1152/physrev.00045.2009.
57. Bekiares N, Krueger CG, Meudt JJ, Shanmuganayagam D, Reed JD. Effect of Sweetened Dried Cranberry Consumption on Urinary Proteome and Fecal Microbiome in Healthy Human Subjects. OMICS. 2018 Feb;22(2):145-153. Doi: 10.1089/omi.2016.0167.
58. González de Llano D, Liu H, Khoo C, Moreno-Arribas MV, Bartolomé B. Some New Findings Regarding the Antiadhesive Activity of Cranberry Phenolic Compounds and Their Microbial-Derived Metabolites against Uropathogenic Bacteria. J Agric Food Chem. 2019 Feb 27;67(8):2166-2174. Doi: 10.1021/acs.jafc.8b05625.
59. Castañer O, Fitó M, López-Sabater MC, Poulsen HE, Nyyssönen K, Schröder H, Salonen JT, De la Torre-Carbot K, Zunft HF, De la Torre R, Bäumler H, Gaddi AV, Saez GT, Tomás M, Covas MI; EUROLIVE Study Group. The effect of olive oil polyphenols on antibodies against oxidized LDL. A randomized clinical trial. Clin Nutr. 2011 Aug;30(4):490-3. Doi: 10.1016/j.clnu.2011.01.013.
60. Schwingshackl L, Lampousi AM, Portillo MP, Romaguera D, Hoffmann G, Boeing H. Olive oil in the prevention and management of type 2 diabetes mellitus: a systematic review and meta-analysis of cohort studies and intervention trials. Nutr Diabetes. 2017 Apr 10;7(4):e262. Doi: 10.1038/nutd.2017.12.
61. Davis CR, Hodgson JM, Woodman R, Bryan J, Wilson C, Murphy KJ. A Mediterranean diet lowers blood pressure and improves endothelial function: results from the MedLey randomized intervention trial. Am J Clin Nutr. 2017 Jun;105(6):1305-1313. Doi: 10.3945/ajcn.116.146803.
62. Medina-Remón A, Tresserra-Rimbau A, Pons A, Tur JA, Martorell M, Ros E, Buil-Cosiales P, Sacanella E, Covas MI, Corella D, Salas-Salvadó J, Gómez-Gracia E, Ruiz-Gutiérrez V, Ortega-Calvo M, García-Valdueza M, Arós F, Saez GT, Serra-Majem L, Pinto X, Vinyoles E, Estruch R, Lamuela-Raventos RM; PREDIMED Study Investigators. Effects of total dietary polyphenols on plasma nitric oxide and blood pressure

in a high cardiovascular risk cohort. The PREDIMED randomized trial. Nutr Metab Cardiovasc Dis. 2015 Jan;25(1):60-67. Doi: 10.1016/j.numecd.2014.09.001.
63. George ES, Marshall S, Mayr HL, Trakman GL, Tatucu-Babet OA, Lassemillante AM, Bramley A, Reddy AJ, Forsyth A, Tierney AC, Thomas CJ, Itsiopoulos C, Marx W. The effect of high-polyphenol extra virgin olive oil on cardiovascular risk factors: a systematic review and meta-analysis. Crit Rev Food Sci Nutr. 2019;59(17):2772-2795. Doi: 10.1080/10408398.2018.1470491.
64. Romani A, Mulas S, Heimler D. Polyphenols and secoiridoids in raw material (Olea europaea L. leaves) and commercial food supplements. Eur Food Res Technol. 2017;243:429-435. Doi: 10.1007/s00217-016-2756-3.
65. Hermans MP, Lempereur P, Salembier JP, Maes N, Albert A, Jansen O, Pincemail J. Supplementation Effect of a Combination of Olive (Olea europea L.) Leaf and Fruit Extracts in the Clinical Management of Hypertension and Metabolic Syndrome. Antioxidants (Basel). 2020 Sep 15;9(9):872. Doi: 10.3390/antiox9090872.
66. Telle-Hansen VH, Holven KB, Ulven SM. Impact of a Healthy Dietary Pattern on Gut Microbiota and Systemic Inflammation in Humans. Nutrients. 2018 Nov 16;10(11):1783. Doi: 10.3390/nu10111783.
67. Bailey MA, Holscher HD. Microbiome-mediated effects of the Mediterranean diet on inflammation. Adv Nutr. 2018;9:193-206. Doi: 10.1093/advances/nmy013.
68. Marcelino G, Hiane PA, Freitas KC, Santana LF, Pott A, Donadon JR, Guimarães RCA. Effects of Olive Oil and Its Minor Components on Cardiovascular Diseases, Inflammation, and Gut Microbiota. Nutrients. 2019 Aug 7;11(8):1826. Doi: 10.3390/nu11081826.
69. Valcheva-Kuzmanova S, Kuzmanov A, Kuzmanova V, Tzaneva M. Aronia melanocarpa fruit juice ameliorates the symptoms of inflammatory bowel disease in TNBS-induced colitis in rats. Food Chem Toxicol. 2018 Mar;113:33-39. Doi: 10.1016/j.fct.2018.01.011
70. Li Y, Nguepi Tsopmejio IS, Diao Z, Xiao H, Wang X, Jin Z, Song H. Aronia melanocarpa (Michx.) Elliott. attenuates dextran sulfate sodium-induced Inflammatory Bowel Disease via regulation of inflammation-related signaling pathways and modulation of the gut microbiota. J Ethnopharmacol. 2022 Jun 28;292:115190. Doi: 10.1016/j.jep.2022.115190
71. Chen C , Yang X , Liu S , Zhang M , Wang C , Xia X , Lou Y , Xu H . The effect of lipid metabolism regulator anthocyanins from Aronia melanocarpa on 3T3-L1 preadipocytes and C57BL/6 mice via activating AMPK signaling and gut microbiota. Food Funct. 2021 Jul 21;12(14):6254-6270. Doi: 10.1039/d1fo00907a.
72. Zhu Y, Zhang JY, Wei YL, Hao JY, Lei YQ, Zhao WB, Xiao YH, Sun AD. The polyphenol-rich extract from chokeberry (Aronia melanocarpa L.) modulates gut microbiota and improves lipid metabolism in diet-induced obese rats. Nutr Metab (Lond). 2020 Jul 7;17:54. Doi: 10.1186/s12986-020-00473-9.
73. Zhu Y, Wei YL, Karras I, Cai PJ, Xiao YH, Jia CL, Qian XL, Zhu SY, Zheng LJ, Hu X, Sun AD. Modulation of the gut microbiota and lipidomic profiles by black chokeberry (Aronia melanocarpa L.) polyphenols via the glycerophospholipid metabolism signaling pathway. Front Nutr. 2022 Aug 4;9:913729. Doi: 10.3389/fnut.2022.913729
74. Yu W, Gao J, Hao R, Yang J, Wei J. Effects of simulated digestion on black chokeberry (Aronia melanocarpa (Michx.) Elliot) anthocyanins and intestinal flora. J Food Sci Technol. 2021 Apr;58(4):1511-1523. Doi: 10.1007/s13197-020-04664-3.
75. Liu X, Martin DA, Valdez JC, Sudakaran S, Rey F, Bolling BW. Aronia berry polyphenols have matrix-dependent effects on the gut microbiota. Food Chem. 2021 Oct 15;359:129831. Doi: 10.1016/j.foodchem.2021.129831.
76. Valdez JC, Cho J, Bolling BW. Aronia berry inhibits disruption of Caco-2 intestinal barrier function. Arch Biochem Biophys. 2020 Jul 30;688:108409. Doi: 10.1016/j.abb.2020.108409.
77. Jurikova T, Sochor J, Rop O, Mlček J, Balla S, Szekeres L, Zitný R, Zitka O, Adam V, Kizek R. Evaluation of polyphenolic profile and nutritional value of non-traditional fruit species in the Czech Republic--a comparative study. Molecules. 2012 Jul 27;17(8):8968-81. Doi: 10.3390/molecules17088968.
78. Jakobek L, Drenjancevic M, Jukic V, Šeruga M. Phenolic acids, flavonols, anthocyanins and antiradical activity of Nero, Viking, Galicianka and wild chokeberries. Sci Horticult. 2012;147:56-63.
79. Wangensteen H, Bräunlich M, Nikolic V, Malterud KE, Slimestad R, Barsett H. Anthocyanins, proanthocyanidins and total phenolics in four cultivars of Aronia: Antioxidant and enzyme inhibitory effects. J Funct Foods 2014;7:746-752.
80. Jeppsson N, Johansson R. Changes in fruit quality in black chokeberry (Aronia melanocarpa) during maturation. J Hortic Sci Biotechnol. 2000;75:34-67.
81. Misiak M, Irzyniec Z. Effect of the temperature and storage time on polyphenol content and antioxidant properties of freeze-dried chokeberries. Zesz Nauk Pol Łód´z Chem Spoz Biotechnol. 2009;73:73-81.
82. Akram W, Garud N, Joshi R. Role of inulin as prebiotics on inflammatory bowel disease. Drug Discov Ther. 2019; 13 (1):1-8. Doi: 10.5582/ddt.2019.01000.

83. Wan X, Guo H, Liang Y, Zhou C, Liu Z, Li K, Niu F, Zhai X, Wang L. The physiological functions and pharmaceutical applications of inulin: a review. Carbohydr Polym. 2020 Oct 15;246:116589. Doi: 10.1016/j.carbpol.2020.116589
84. Costa G, Vasconcelos Q, Abreu G, Albuquerque A, Vilarejo J, Aragão G. Changes in nutrient absorption in children and adolescents caused by fructans, especially fructooligosaccharides and inulin. Arch Pediatr. 2020 Apr;27(3):166-169. Doi: 10.1016/j.arcped.2020.01.004.
85. Wan X, Guo H, Liang Y, Zhou C, Liu Z, Li K, Niu F, Zhai X, Wang L. The physiological functions and pharmaceutical applications of inulin: a review. Carbohydr Polym. 2020 Oct 15;246:116589. Doi: 10.1016/j.carbpol.2020.116589.
86. Vinelli V, Biscotti P, Martini D, Del Bo' C, Marino M, Meroño T, Nikoloudaki O, Calabrese FM, Turroni S, Taverniti V, Unión Caballero A, Andrés-Lacueva C, Porrini M, Gobbetti M, De Angelis M, Brigidi P, Pinart M, Nimptsch K, Guglielmetti S, Riso P. Effects of Dietary Fibers on Short-Chain Fatty Acids and Gut Microbiota Composition in Healthy Adults: A Systematic Review. Nutrients. 2022 Jun 21;14(13):2559. Doi: 10.3390/nu14132559.
87. Holscher HD, Bauer LL, Gourineni V, Pelkman CL, Fahey GC Jr, Swanson KS. Agave Inulin Supplementation Affects the Fecal Microbiota of Healthy Adults Participating in a Randomized, Double-Blind, Placebo-Controlled, Crossover Trial. J Nutr. 2015 Sep;145(9):2025-32. Doi: 10.3945/jn.115.217331.
88. Brandl B, Lee YM, Dunkel A, Hofmann T, Hauner H, Skurk T. Effects of Extrinsic Wheat Fiber Supplementation on Fecal Weight; A Randomized Controlled Trial. Nutrients. 2020 Jan 22;12(2):298. Doi: 10.3390/nu12020298.
89. Holscher HD, Bauer LL, Gourineni V, Pelkman CL, Fahey GC Jr, Swanson KS. Agave Inulin Supplementation Affects the Fecal Microbiota of Healthy Adults Participating in a Randomized, Double-Blind, Placebo-Controlled, Crossover Trial. J Nutr. 2015 Sep;145(9):2025-2032. Doi: 10.3945/jn.115.217331.
90. Slavin J, Feirtag J. Chicory inulin does not increase stool weight or speed up intestinal transit time in healthy male subjects. Food Funct. 2011 Jan;2(1):72-77. Doi: 10.1039/c0fo00101e.
91. Shoaib M, Shehzad A, Omar M, Rakha A, Raza H, Sharif HR, Shakeel A, Ansari A, Niazi S. Inulin: Properties, health benefits and food applications. Carbohydr Polym. 2016 Aug 20;147:444-454. Doi: 10.1016/j.carbpol.2016.04.020.
92. Paturi G, Butts CA, Monro JA, Hedderley D. Effects of Blackcurrant and Dietary Fibers on Large Intestinal Health Biomarkers in Rats. Plant Foods Hum Nutr. 2018 Mar;73(1):54-60. Doi: 10.1007/s11130-018-0652-7.
93. Amasheh S, Dullat S, Fromm M, Schulzke JD, Buhr HJ, Kroesen AJ. Inflamed pouch mucosa possesses altered tight junctions indicating recurrence of inflammatory bowel disease. Int J Colorectal Dis. 2009 Oct;24(10):1149-1156. Doi: 10.1007/s00384-009-0737-8.
94. Sheth P, Delos Santos N, Seth A, LaRusso NF, Rao RK. Lipopolysaccharide disrupts tight junctions in cholangiocyte monolayers by a c-Src-, TLR4-, and LBP-dependent mechanism. Am J Physiol Gastrointest Liver Physiol. 2007 Jul;293(1):G308-318. Doi: 10.1152/ajpgi.00582.2006.
95. Petecchia L, Sabatini F, Usai C, Caci E, Varesio L, Rossi GA. Cytokines induce tight junction disassembly in airway cells via an EGFR-dependent MAPK/ERK1/2-pathway. Lab Invest. 2012 Aug;92(8):1140-8. Doi: 10.1038/labinvest.2012.67.
96. Neurath MF, Schürmann G. Zur Immunpathogenese der chronisch entzündlichen Darmerkrankungen [Immunopathogenesis of inflammatory bowel diseases]. Chirurg. 2000 Jan;71(1):30-40. German. Doi: 10.1007/s001040050005.
97. Cooke CL, Davidge ST. Peroxynitrite increases iNOS through NF-kappaB and decreases prostacyclin synthase in endothelial cells. Am J Physiol Cell Physiol. 2002 Feb;282(2):C395-402. Doi: 10.1152/ajpcell.00295.2001. PMID: 11788351.
98. Debnath T, Kim DH, Lim BO. Natural products as a source of anti-inflammatory agents associated with inflammatory bowel disease. Molecules. 2013 Jun 19;18(6):7253-7270. Doi: 10.3390/molecules18067253.