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Role of Herbs and Medicinal Spices as Modulators of Gut Microbiota

Yordan Martínez and Dairon Más

Abstract

Currently, herbs, medicinal spices, green medicine, or traditional Chinese medicine has gained many followers in the world, especially as a way of life and as an alternative to the indiscriminate use of synthetic medicines such as antibiotics. These natural products are rich in secondary metabolites or phytochemicals, which are chemical compounds of relatively complex structures and restricted distribution; these compounds have defensive functions against insects, bacteria, fungi, parasites, and viruses. Likewise, several studies have shown their effectiveness in the prevention and treatment of several diseases such as cancer, autoimmune diseases, gastrointestinal diseases, diabetes, neurodegenerative diseases, Crohn's disease, and human immunodeficiency virus (HIV), among others. In addition, this review addresses the mechanisms of action of the herbs and medicinal spices on intestinal microbiota, increasing competitive exclusion in the intestinal membrane and inhibiting bacterial translocation and damage to the intestinal barrier.

Keywords: beneficial, diet, gut microbiota, health, phytochemical compound

1. Introduction

Through history, the individual and collective experiences of a population have been systematized and transformed as part of their popular culture, their means of action, and their wisdom. Popular customs based on empirical bases have found justification with the development of science and technology, after having been used for a long time. In this sense, due to advances in the areas of knowledge, especially medicine, genetics, immunology, and molecular biology, it is obvious to seek explanations and incontestable facts that justify the use of some popular practices that may be useful in the treatment of different health problems. These practices are phytochemical compounds, which have been the subject of deep research around the world [1].

The phytochemicals have been used for over 60,000 years to prevent or cure diseases that affect humans [2]. It is estimated that about 260,000 species of plants are known today, of which 10% can be considered as medicinal, with many phytochemical properties. According to the classification of medical treatments of phytotherapy, in modern and past times, many regions are favored by the proportion of phytochemical compounds, which can vary appreciably to the established percentage, since the totality of the vegetal flora is not known [3].

Despite the agro-industrial development of humanity and the strong influence of the large pharmaceutical industries, phytochemical compounds are the first sources for medical treatment in many countries, due to its effectiveness against different pathologies, low production cost, and slight residual effect [4–6]. Its use is strengthened and expanded more and more, appearing in new and novel active principles, both for human and veterinary use. It is estimated that between 75 and 80% of the world population used phytochemical compounds one way or another, China and India being the countries that used the natural products of plant origin the most, as part of their cultural roots. These beneficial phytobiotics are used mainly as food or part of the food, although they are also used as pharmaceutical preparations. In these countries, traditional medicine is used daily as a lifestyle to prevent, cure, and/or alleviate diseases. In this sense, natural compounds have been used to treat diseases that damage the nervous, cardiovascular, respiratory, gastrointestinal, renal, metabolic, immune, and musculoskeletal systems, besides preventing or curing metabolic disorders of the main biomolecules of the organism [7, 8].

Plants are natural laboratories where a large amount of chemical substances are biosynthesized, and in fact, they are considered the most important source of chemical compounds that exists. A large percentage of the active ingredients included are called “phytochemical compounds or secondary metabolites,” which are chemical compounds of relatively complex structures and restricted distribution; among these metabolites, those with defensive functions against insects, bacteria, and fungi, among others, as alkaloids, non-protein amino acids, steroids, phenols, flavonoids, glycosides, coumarins, quinones, tannins, and terpenoids, are common. There is great variation in the concentration of these phytochemicals in the plant, and there is no maximum production pattern nor special storage organs; however, it is common that the highest concentrations of these types of compounds are in flowers, leaves, and seeds [9, 10].

Currently, research on natural products is focused on the discovery of new active ingredients with beneficial properties against several systemic and infectious diseases in humans and animals [11]. It has been proven that synthetic substances sometimes have more harmful side effects than the diseases they treat; some synthetic antioxidant compounds cause toxic and mutagenic effects [12]. Thus, several authors indicate the need to reuse natural preparations as alternatives to the indiscriminate use of antibiotics and their microbial resistance [13, 14]. However, it is currently unclear how phytochemical compounds have a high compatibility with the human organism [14], because these have no enzymatic affinity and are poorly absorbed by the intestinal lumen.

Intestinal microbiota plays an important role in maintaining intestinal integrity and function; a loss in microbial balance causes severe damage at the local and systemic level [15–17]. It is important to note that the microbiota in the first years of life of children is unstable, dominated mainly by *Clostridium leptum* and *Clostridium coccoides* species [18]. The phyla *Firmicutes*, *Bacteroidetes*, and *Actinobacteria* are dominant in the microbiota of healthy adults [19]. *Actinobacteria*, especially *Bifidobacteriaceae*, are found in small concentrations compared to the species belonging to the phylum *Firmicutes* and *Bacteroidetes*; however, they are very important as modulators of intestinal barrier function [20]. The phytochemical compounds may favor the growth of specific beneficial bacteria in the intestine under health or host disease conditions [21, 22].

Many investigations have focused on demonstrating the antimicrobial effect of phytochemical compounds; however, there are contradictions in the mechanism of action of the active principles. These phytochemicals compounds could have bacteriostatic or bactericidal action as well as inhibit the adhesion of pathogenic bacteria to the intestinal and urinary mucosa. Every day the use of phytochemicals

to reduce the pathogenic effect of intestinal bacteria is more frequent, due to the increase of antimicrobial resistance to antibiotics [23, 24]. Therefore, the aim of this review is to summarize the role of herbs and medicinal spices like modulators of gut microbiota.

2. What are the phytochemical compounds?

Phytochemicals are chemical compounds synthesized by plants that fulfill nonessential functions, so that their absence is not fatal for it, since they do not intervene in the primary metabolism. These compounds intervene in the ecological interactions between the plant and its environment [25]. They also differ from the primary metabolites in that each of them has a restricted distribution in the plant kingdom, sometimes to only one species or a group of them, so many of them are useful in *Systematic Botany* [10]. For many years, the adaptive value of the most secondary metabolites was unknown. Many times, they were described as final products of metabolic processes, without a specific function, or directly as waste products of plants. In general, in the past they have received little attention by biologists and botanists, so many of the functions of secondary metabolites are still unknown [26].

The study of these substances was initiated by organic chemists of the nineteenth century and the beginning of the twentieth century, who were interested in these substances due to their importance as medicinal drugs, poisons, flavorings, glues, oils, waxes, and other materials used in the industry [27]. In fact, the study of phytochemicals stimulated the development of separation techniques, spectroscopy to elucidate their structure, and synthesis methodologies that today contribute to the development of contemporary organic chemistry [28].

In addition, the content of the active principles of a plant can vary significantly due to differences from one locality to another and, even within the same locality due to several agrochemical properties of the land, the season and variations for temperature, precipitation, pollution, lunar cycle, or other factors [5]. The plants have characteristics that allow them to influence through their components not only by direct contact but also remotely by means of emanations. There are plants that through the emanations of their active ingredients can eliminate the spores of fungi, protozoa, and malignant bacteria [2, 10]. The recognition of biological properties of many phytochemical compounds has encouraged the development of this field, for example, in the search for new drugs, antibiotics, insecticides, and herbicides. Moreover, the growing appreciation of the highly diverse biological effects of these compounds has led to the reevaluation of the different roles they have in plants, especially in the context of ecological interactions [10].

Phytochemicals can be divided into three large groups, based on their biosynthetic origins: phenolic compounds, terpenoids, and nitrogen compounds or alkaloids. They can also be divided according to their biosynthetic pathway and chemical structure: terpenoids, alkaloids, betalains, glucosinolates, cyanogenic glycosides, polyacetylenes, anthocyanins, and other flavonoids [26].

Currently, many synthetic drugs produced by the pharmaceutical industry have very harmful side effects and are not effective in alleviating or reducing the symptoms of many diseases such as cancer, HIV, Alzheimer's, and other chronic diseases. Therefore, modern medicines where phytochemicals are included as an alternative source may meet the therapeutic requirements of patients. In this sense, there is high availability of these natural products from plant sources that act as potent curative medicines [29]. Phytochemicals including polyphenols, flavonoids, and others have the potential to provide a defense against oxidative damage. Plant extracts and

phytoconstituents are found to be effective as radical scavengers and inhibitors of lipid peroxidation [30, 31]. A wide range of antioxidants from both natural and synthetic origin to treat various human diseases has been proposed [32].

Other metabolites have wide medicinal properties, such as sterols used as part of hormones and vitamins; triterpenes have anthelmintic, antiseptic, expectorant, antibacterial, and diuretic activity. Simple phenols have antifungal activity. The tannins (condensed tannins) have astringent, antiseptic, antibacterial, and antifungal properties. The coumarins are used in medicine for their anticoagulant and antibacterial action. The flavonoid glycosides (anthocyanins and quercetins) are attributed effects on the blood supply of the bronchi and bronchodilation. Quinones (specifically naphthoquinones) are characterized by their antibacterial and antifungal action. Cardiotonic glycosides stimulate cardiac function. The alkaloids stimulate the central nervous system and have an anesthetic effect. Saponins are precursors of steroidal hormones and corticosteroids and have emulsifying and hemolyzing functions [4–6, 33].

3. Role of the phytochemical compounds to modulate gut microbiota

The gut microbiota begins to mature from the second year of life and has various roles such as nutrient absorption and food fermentation [34], proper modulation of the immune system to the gastrointestinal tract (GIT) of the host [35], and the physiological mechanisms against pathogens [36]. In adults, the most prevalent phyla representatives are *Bacteroidetes* and *Firmicutes*, *Clostridium leptum* and *Clostridium coccoides* being the dominant groups and *Lactobacillus* the subdominant in *Firmicutes* phyla [18, 19], a gut microbiota that is highly stable [37]. It is estimated that the gastrointestinal tract inhabits 500–1000 different microbial species, with the highest concentrations in the colon (up to 10^{12} cells per gram of feces); also, the presence of *E. coli* (in 7.7 log₁₀ CFU/g) is considered a subdominant population in adults and dominant species in infants [38].

The bacterial population of the *Bifidobacterium* genus are minor constituents of the gut microbiota, whose concentration is eight to ten times lower than the two main phyla [39]. *Bifidobacterium* spp. enhance the barrier function of the gut epithelium and gut health; however, a decrease of the population of this bacterial genus causes chronic low-grade inflammation with lipopolysaccharide (LPS) (endotoxemia), related to multiple abnormal processes in the organism [40, 41]. Also, the composition of the microbiota in elderly individuals is affected by a significant reduction of *Bacteroidetes* and *Bifidobacterium*, also accompanied by a decrease in *Lactobacilli* [42] and their positive effects on the health of the host. Likewise, several authors have highlighted the variations between the number of facultative anaerobes in adults and the elderly [43, 44].

Many bacterial species are commensal flora in the intestine, and others are highly pathogenic such as *Helicobacter pylori*, *Salmonella enterica*, *Salmonella* Enteritidis, *Salmonella* Heidelberg, *Salmonella* Typhimurium, *Shigella dysenteriae*, *Clostridium difficile*, *Klebsiella* spp., *Enterobacter* spp., *Vibrio* spp., *Yersinia pestis*, *Proteus* spp., *Bacillus cereus*, *Campylobacter coli*, *Campylobacter jejuni*, and enterotoxigenic *Escherichia coli*, which cause gastrointestinal diseases with different pathogenesis according to age, gut health, chronic diseases, and immune diseases, among other triggers. Gut disturbances in the microbiota may cause dysbiosis and bacterial translocation, mediated by lipopolysaccharide binding to Toll-like receptor 4 (TLR4) and the transcription factor nuclear factor NFκB as an inflammatory response. These mechanisms origin damage in gut barrier integrity and immune system of this organ [29, 45–49] (Table 1).

Phytochemical compounds	Sources	Part used	Model experiment	Outcomes	References
<i>Polyphenols</i>					
Phenolic acids, stilbenoids, flavonols, dihydroflavonols, and anthocyanins	<i>Vitis vinifera</i>	Fruits	Humans	↑ <i>Enterococcus</i> spp., <i>Prevotella</i> spp., <i>Bifidobacterium</i> spp., <i>B. uniformis</i> , <i>E. lento</i> , <i>B. coccoides</i> , <i>E. rectale</i>	[50]
Chlorogenic acid-polyphenols	Green coffee	Bean	High fat-fed mice	↑ <i>Bacteroides</i> , <i>Bifidobacterium</i> , <i>Lactobacillus</i> , <i>Ruminococcaceae</i> ↓ <i>Desulfovibrionaceae</i> , <i>Lachnospiraceae</i> , <i>Erysipelotrichaceae</i>	[51]
Phenolic compounds	<i>Allium sativum</i>	Whole plant	In vitro	↓ <i>S. epidermidis</i> , <i>K. pneumoniae</i>	[52]
Tannins	<i>Moringa oleifera</i>	Leaves	Mice	↓ <i>Clostridium leptum</i> , ↑ <i>Bacteroides</i>	[47–49, 53]
Anthocyanidins and flavonoids	<i>Punica granatum</i>	Fruits	Mice and high fat-fed mice	↑ <i>Lactobacillus</i> spp., <i>Bifidobacterium</i> ↓ <i>E. coli</i> , <i>Salmonella</i> spp.	[21, 22, 54–56]
Anthocyanidins	<i>Rubus fruticosus</i> and <i>Rubus occidentalis</i>	Fruits	In vitro	↓ <i>H. pylori</i> , <i>S. epidermis</i> , <i>K. pneumoniae</i> , <i>S. epidermis</i> , <i>K. pneumoniae</i> , <i>E. coli</i> , <i>Salmonella</i> spp.	[57–59]
Anthocyanidins	<i>Antirrhinum majus</i>	Flowers	High fat-fed mice	↑ <i>Bifidobacterium</i> spp., <i>Lactobacillus</i> spp.	[22, 25]
Syringe, p-coumaric, 4-hydroxybenzoic, and vanillic	<i>Larix laricina</i>	Needles	Mice	↑ <i>Bifidobacterium</i> , <i>Enterococcus</i> , <i>Eggerthella lenta</i>	[60]
Catechins, flavan-3-ols, and monomeric flavan-3-ol-rich	Green tea	Leaves	Humans	↓ <i>S. mutans</i> , <i>Shigella</i> , <i>V. cholerae</i> , <i>C. histolyticum</i> , <i>C. coccoides</i> - <i>E. rectale</i> ↑ <i>Lactobacillus</i> spp.	[59, 61, 62]
Procyanidins, catechin and epicatechin	<i>Pyrus malus</i>	Fruits	Mice	↑ <i>Bifidobacterium</i> spp.	[63]
Gallic acids	<i>Phyllanthus niruri</i> and <i>Moringa oleifera</i>	Leaves	Mice	↓ <i>E. coli</i> , <i>P. aeruginosa</i>	[64, 65]
<i>Coumarins</i>					
Coumarins	<i>Anacardium occidentale</i>	Leaves	In vitro	↓ <i>Staphylococcus aureus</i>	[66]
6',7'-dihydroxy-bergamottin, officinalin, stenocarpin isobutyrate, officinalin isobutyrate, 8-methoxypeucedanin, and peucedanin	<i>Peucedanum luxurians</i>	Fruits	In vitro	↓ <i>E. coli</i> , ↓ <i>Salmonella</i> spp.	[67]

Phytochemical compounds	Sources	Part used	Model experiment	Outcomes	References
Coumarin-1,2,3-triazole conjugate and 3-heteroarylazo 4-hydroxy	Synthesized		In vitro	↓ <i>E. faecalis</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>B. subtilis</i> , <i>P. aeruginosa</i>	[49, 68, 69]
Triterpenes					
Terpineol	<i>Cinnamomum verum</i>	Whole plant	In vitro	↓ <i>H. pylori</i>	[24]
Petalostemumol	<i>Dalea purpurea</i> and <i>Vitis vinifera</i>	Flowers	In vitro	↓ <i>B. subtilis</i> , <i>S. aureus</i> , <i>Candida albicans</i>	[47, 70]
1α, 3β, 23-trihydroxyolean-12-in-29-oic acid	<i>Combretum imberbe</i>	Cortex	In vitro	↓ <i>M. fortuitum</i> , <i>S. aureus</i>	[71]
23-hydroxyursolic acid, hederagenin, 3-O-α-L-arabinopyranosyl-echinocystic acid, 3-O-α-L-arabinopyranosyl-oleanolic acid, and 3-O-α-L-arabinopyranosyl-ursolic acid	<i>Cussonia bancoensis</i>	Stem bark	In vitro	↓ <i>S. aureus</i> , <i>S. pyogenes</i> , <i>E. faecalis</i> , <i>S. Typhi</i> , <i>C. albicans</i>	[72]
Alkaloids					
4-methoxy-1-methyl-quinolin-2- (1H) -one	<i>Pleurothyrium cinereum</i> , <i>Esenbeckia alata</i> and <i>Raputia heptaphylla</i>	Leaves	In vitro	↓ <i>E. faecalis</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>S. Typhimurium</i>	
Sanguinarine, chelerythrine, protopine and allocryptopine and phenolics, gallic, protocathechuic, p-hydroxybenzoic, m-hydroxybenzoic, gentisic, p-coumaric, caffeic, ferulic, and sinapic acids	<i>Macleaya cordata</i>	Roots and leaves	In vitro	↓ <i>S. aureus</i> , <i>E. coli</i> , <i>Salmonella</i> spp.	[73, 74]
Sanguinarine and dihydrosanguinarine	<i>Argemone mexicana</i>	Seeds and leaves	In vitro	↓ <i>E. coli</i> , <i>P. aeruginosa</i>	[75]

Table 1.
Some phytochemical compounds that modulate gut microbiota.

Currently, many investigations focus on the search for therapeutic treatments through diet to modulate the intestinal microbiota, reducing inflammation in this organ, preventing chronic and degenerative diseases [22]. It has been shown that small concentrations of active ingredients from medicinal plants or other plant sources have microbiostatic and microbicidal activities against enteric pathogenic microbiota [76]. An increase of the competitive exclusion in the intestinal

epithelium guarantees a greater metabolization of the phytochemical compounds by the bacteria and therefore benefits the biological response of the host [54, 77]. Although the mechanisms are not well, the phytochemical compounds can reduce the proliferation of pathogenic bacteria in the GIT, affect cell reproduction, mediate microbial metabolic processes, and regulate signal translation or genetic expression with phospholipoidal cell membranes, thus increasing the permeability and loss of cellular constituents, imbalance of the enzymes to the production of cellular energy and synthesis of organelle compounds, and destruction or inactivation of genetic material [45–48, 78].

3.1 Phenolic compounds

Scientific evidences show that within the phytochemical compounds, polyphenols are the most effective antimicrobials. In this sense, the phenolic compounds such as flavonols, flavones, and flavanones, and phenolic acids are poorly metabolizable by some gut microbiota. However, species such as *E. coli*, *Bifidobacterium* spp., *Lactobacillus* spp., *Bacteroides* spp., and *Eubacterium* spp. can catabolize these phenolic compounds and its fermentation products [49]. Also, colon bacteria metabolize the polyphenolic compounds into bioactive metabolites of low molecular weight easily absorbed by the organism [68].

The relationship between the most representative phylum of the intestine, *Firmicutes/Bacteroides*, is affected by phenolic compounds of vegetable origin [70]. A study in humans indicated that the consumption of polyphenols from *Vitis vinifera* rich in phenolic acids, stilbenoids, flavonols, dihydroflavonols, and anthocyanins significantly increased the number of *Enterococcus* spp., *Prevotella* spp., *Bifidobacterium* spp., *Bacteroides uniformis*, *Eggerthella lenta*, *Blautia coccoides*, and *Eubacterium rectale*, although the population of *Lactobacillus* spp. remained unchanged [50]. Also, in rats treated with chlorogenic acid-polyphenols (rich in green coffee bean), the concentration of beneficial bacteria such as *Bacteroides*, *Bifidobacterium*, and *Lactobacillus* spp. was significantly increased, while the composition of *Ruminococcaceae*, *Desulfovibrionaceae*, *Lachnospiraceae*, and *Erysipelotrichaceae* decreased with the experimental treatment [51]. Moreover, phenolic compounds extracted from *Allium sativum* juice decrease the growth of pathogenic bacteria such as *Staphylococcus epidermidis* and *Klebsiella pneumoniae* [52]. Likewise, in rats with diets rich in tannins (rich in *Moringa oleifera*), *Clostridium leptum* decreased, while *Bacteroides* increased significantly; apparently, this diet suppressed the bacterial cell proliferation by blocking proteolytic macerating enzymes and inactivating microbial adhesins and cell envelope transport proteins [47, 48, 53].

Several authors have reported the modulating effect of anthocyanidins on the colonic microbiota and some inflammatory markers [21, 22, 60]. Anthocyanidins have the ability to inhibit the growth of intestinal pathogenic bacteria; apparently an interaction exists between the phenolic compounds and the local microbiota specifically (mainly *Bifidobacterium*), which increases the anti-inflammatory activity [22, 54]. The species *Lactobacillus* spp. and *Bifidobacterium* spp. maintain the stability of the enzyme activity, especially the β -glucosidase; this enzyme acts as a catalyst in the metabolic reactions of anthocyanidins; thus this phytochemical in the treatment of gut-related diseases could stimulate the growth of these beneficial bacterial species [21]. Gastric and intestinal bacteria such as *Helicobacter pylori*, *Salmonella* spp., and *Bacillus cereus* were inhibited by the anthocyanidins extracted from *Rubus fruticosus* and *Rubus occidentalis* fruits; also, this secondary metabolite has a bacteriostatic effect in vitro against *Staphylococcus epidermis*, *Klebsiella pneumoniae*, and *Escherichia coli* [57–59]. Other results showed that expression

of *Bifidobacterium* spp. and *Lactobacillus* spp. increased with the consumption of anthocyanidins (*Antirrhinum majus* flowers) rich in in maternal diets with high content of trans-fatty acids [22, 25]. Also, fecal concentration of *Bifidobacterium*, *Enterococcus*, and *Eggerthella lenta* is higher with the prolonged consumption of polyphenol-rich foods, as well as the urinary concentrations of the anthocyanin metabolites, such as syringe, p-coumaric, 4-hydroxybenzoic, and vanillic (*Larix laricina*), which have been positively correlated with bifidobacteria of the intestine [60].

Green tea has high concentrations of catechins, which belong to the group of flavonoids; these secondary metabolites have good effects against *Streptococcus mutans*, *Shigella*, and *Vibrio cholerae* proven in in vivo studies [79]. Other in vivo and in vitro studies with green tea extracts rich in flavan-3-ols and monomeric flavan-3-ol-rich rich found a modulation of the intestinal microbiota, which produced changes in beneficial bacteria such as *Lactobacillus* spp., inhibiting other groups such as *Clostridium* spp. [59, 61, 62]. On the other hand, catechins significantly inhibited the growth of *Clostridium histolyticum*, *E. coli*, and members of the *Clostridium coccoides*/*Eubacterium rectale* group, without affecting the growth of *Lactobacillus* spp. and *Bifidobacterium* spp. [62]. Also, the extract of *Punica granatum* (rich in flavonoids) increased *Bifidobacterium* spp. in the cecum of the mice with hypercholesterolemia, obesity, and inflammatory disorders induced with high-lipid diets [54]. Likewise, in other studies, the stilbenoid resveratrol, ellagitannins, and urolithin A in pomegranate (alcoholic extract) treatment are responsible for the competitive exclusion in the intestinal epithelium with a higher population of *Bifidobacterium* spp. and *Lactobacillus* spp. in mice [55, 56].

As an interesting fact, the increase of the *Clostridium coccoides*/*Eubacterium rectale* group is related to its capacity for metabolizing these flavonoid compounds. In this sense, in an experiment treatment with flavonoids such as procyanidins, catechin, and epicatechin (*Pyrus malus*), the authors found an increase in *Bifidobacterium* spp. in the colon and a decrease of the inflammation biomarkers such as prostaglandin E2, TNF- α , and leukotriene B4 [63]. Furthermore, the gallic acids (*Phyllanthus niruri* and *Moringa oleifera*) bind to bacterial dihydrofolate reductase (DHFR) enzymes, which reduces the bacterial population of *E. coli* through the inhibition of supercoiling activity and bonding of ATP and gyrase B, so that it binds to bacterial DNA, thereby modulating topoisomerase IV enzyme-mediated DNA cleavage and bacterial growth stasis [64, 65]. This means that several groups of polyphenols directly influence the intestinal bacterial population of the organism (Table 1).

3.2 Coumarins

According to the in vitro results, the family of coumarins and reducing carbohydrates abundant in the hexane, chloroform, and ethyl acetate extracts of the leaves of *Anacardium occidentale* are responsible for the antistaphylococcal activity [66]. Another in vitro study where they isolated 6',7'-dihydroxybergamottin, officinalin, stenocarpin isobutyrate, officinalin isobutyrate, 8-methoxypeucedanin, and peucedanin from *Peucedanum luxurians* fruits found a positive response by reducing all challenged Gram-negative pathogenic bacteria, such as *E. coli* and *Salmonella* spp. [67]. At present, the synthesis of some phytochemical compounds from plants and fungi is one of the very novel forms of use. Many coumarins are synthesized in the lab and used as medicines for humans and animals. In this sense, coumarin-1,2,3-triazole conjugate and 3-heteroarylazo 4-hydroxy showed bactericidal action against *Enterococcus faecalis* [80] and *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, and *Pseudomonas aeruginosa* [69], respectively (Table 1).

3.3 Triterpenes

On the other hand, phytochemical compounds such as terpineol from *Cinnamomum verum* have antiulcer activity by reducing the infection by *Helicobacter pylori* in vitro [24]. The ethanol-soluble fraction of *Dalea purpurea* and *Vitis vinifera* has a terpenoid called petalostemumol, which showed excellent activity against *Bacillus subtilis*, *Staphylococcus aureus*, and *Candida albicans* and lesser activity against Gram-negative bacteria [47]. Likewise, triterpene 1 α , 3 β , and 23-trihydroxyolean-12-in-29-oic acid isolated *Combretum imberbe* which inhibited the in vitro growth of *Mycobacterium fortuitum* and *Staphylococcus aureus* [81]. In an in vitro study, triterpenes such as 23-hydroxyursolic acid, hederagenin, 3-O- α -L-arabinopyranosyl-echinocystic acid, 3-O- α -L-arabinopyranosyl-oleanolic acid, and 3-O- α -L-arabinopyranosyl-ursolic acid isolated from the stem bark of *Cussonia bancoensis* stopped the growth of *Staphylococcus aureus*, *Streptococcus pyogenes*, *Enterococcus faecalis*, *Salmonella typhi*, and *Candida albicans* [71] (**Table 1**).

3.4 Alkaloids

Other groups of phytochemicals with bactericidal or bacteriostatic importance are alkaloids. In an investigation, 4-methoxy-1-methyl-quinolin-2- (1H)—one obtained from three tropical plants such as *Pleurothyrium cinereum*, *Esenbeckia alata*, and *Raputia heptaphylla*—showed an effective reduction against *Enterococcus faecalis*, *Staphylococcus aureus*, *Escherichia coli*, and *Salmonella typhimurium* [72]. Isoquinoline alkaloids from the roots and leaves of *Macleaya cordata* such as sanguinarine, chelerythrine, their dihydro derivatives, protopine and allocryptopine and phenolics, and gallic, protocatechuic, p-hydroxybenzoic, m-hydroxybenzoic, gentisic, p-coumaric, caffeic, ferulic, and sinapic acids have antibacterial action against *Staphylococcus aureus*, *E. coli*, and *Salmonella* spp. [73, 74]. Also, the leaves and seeds of *Argemone mexicana*, another plant rich in isoquinolinic alkaloids such as sanguinarine and dihydrosanguinarine, have powerful bactericidal action in vitro against *E. coli* and *Pseudomonas aeruginosa* [75] (**Table 1**).

In general, the antimicrobial activities of several phytochemical compounds based on chemical studies, in vitro and in vivo, are known. However, due to the alimentary habit of a part of the world population, many of these medicinal compounds are not used, mainly as part of the diet, as aqueous extracts, or as alcoholic extracts, although other times they are used empirically, showing their beneficial effect. The daily use of phytochemicals in a controlled manner and according to scientific bases, both chemical and biological, could prevent or treat many ailments and diseases related to intestinal dysbiosis in humans.

4. Conclusions

This review has highlighted the role of the phytochemical compounds like modulators of gut microbiota. It was identified that alkaloids, steroids, phenols, flavonoids, glycosides, coumarins, quinones, tannins, and terpenoids are the main phytochemical compounds with biological activity. In addition, in vitro and in vivo experiments demonstrated that these beneficial chemical compounds can reduce the proliferation of pathogenic bacteria in the gastrointestinal tract through various biochemical and physiological processes that cause disturbances in the bacterial cell membrane, which causes competitive exclusion in the epithelial membrane by a greater expression of *Bifidobacterium* spp. and *Lactobacillus* spp., which reduce the appearance of dysbiosis, bacterial translocation, damage to the intestinal barrier, and gastrointestinal problems.

Conflict of interest

The authors declare no conflict of interest.

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