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REVIEW ARTICLE

Current View on How Human Gut Microbiota Mediate Metabolic and Pharmacological Activity of *Panax ginseng*. A Scoping Review

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Abstract: *Panax ginseng* is one of the most important remedies in ancient Eastern medicine. In the modern Western world, its reputation started to grow towards the end of the XIX century, but the rather approximate understanding of action mechanisms did not provide sufficient information for an appropriate use. Nowadays, *Panax ginseng* is frequently used in some pathological conditions, but the comprehension of its potential beneficial effects is still incomplete. The purpose of this study is to highlight the most recent knowledge on mechanisms and effects of ginseng active ingredients on the intestinal microbiota. The human microbiota takes part in the immune and metabolic balance and serves as the most important regulator for the control of local pathogens. This delicate role requires a complex interaction and reflects the interconnection with the brain- and the liver-axes. Thus, by exerting their beneficial effects through the intestinal microbiota, the active ingredients of *Panax ginseng* (glycosides and their metabolites) might help to ameliorate both specific intestinal conditions as well as the whole organism's homeostasis.

Keywords: Gut microbiota, *Panax ginseng*, ginseng glycosides, ginseng metabolites, immunity, probiotics.

1. INTRODUCTION

Ginseng is one of the most famous herbs worldwide, and no other plant has been regarded with such awe and amazement by the East Asian population. The name ginseng has a Chinese origin, whose meaning ("human root") refers to the characteristic bifurcated shape of the root that resembles human legs. In 1843, the Russian botanist Carl Anton von Meyer, considering its many therapeutic properties, named it *Panax ginseng* (from the Greek term panacea, the medicine that cures everything, with an anthropomorphic root aspect) [1, 2]. In the modern Western countries, the medicinal uses of ginseng root are based on their 'traditional use'. This means that, even in the absence of sufficient evidence from clinical trials, the plausible effectiveness of this herbal product is established from its safe and long-standing (for at least 30 years) use. A current overview is available at (https://www.ema.europa.eu/en/medicines/herbal/ginseng-radix#overview-section).

However, similar to drugs, the pharmacological effects of ginseng may depend on its absorption, distribution, metabolism, and excretion (ADME), and several recent studies have recognized the central role of gut microbiota on the biochemical transformation of ginseng in its active metabolites. This further reinforces the need for investigation clarifying the influence of gut microbiota composition on ginseng activities, in the attempt to obtain the most favorable effects and avoid undesirable consequences when administered in humans.

1.1. The Genus *Panax*

Genus *Ginseng* belongs to the Araliaceae plants family and has many species of the Genus *Panax* such as *P. trifolius*, *P. notoginseng, P. quinquefolius, P. ginseng, P. pseudoginseng*, *P. zingiberensis, P. stipuleanatus, P. japonicus, P. japonicus var. angustifolius, P. japonicus var. major,* and *P. japonicus var. bipinnatifidus.* Ginseng plant is a leafy perennial with very slow growth. It consists of shiny red berries and well-formed green leaves which are positioned circulating around the stem but only the root is the one that holds all the beneficial properties. Its root is distant and flexible, and it has two thick legs from which many small rhizomes slip through and in its upper part is the "throat" which is a small rhizome. The color of the root can be light yellow, brown, or white and its taste is slightly bitter with some aromatic traits. Ginseng root ripens after the fourth year and can live for more than hundreds of years, so as it grows, each

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year, to penetrate deep into the soil, it leaves a wrinkle in the "neck", from which the age of the plant can be assumed [3, 4]. Ginseng thrives in the pristine mountain forests of the Far Eastern in northern temperate zone and is grown primarily in Korea, China, Japan, the Americas, and Russia (Siberia). Cultivated oriental ginseng has two varieties, white and red. The one that circulates throughout Europe is of Korean origin and is mainly of the red variety and is considered more effective than the Chinese one [1] (Also see https://www.ncbi.nlm.nih.gov/books/NBK501922/ for more information). The most interesting one is the wild ginseng variety, such as that from Korea, Manchuria and nearby territories. The used species are two. The first includes the Asian ginseng (*Panax ginseng*), which embraces the Korean (red variety) and Chinese (white variety); both tend to become extinct in their natural environment but are still actively cultivated. The second species is represented by the American ginseng (*P. quinquefolium*), which is harvested and cultivated for commercial use. Ginseng is characterized by the presence of ginsenosides, which represent its active ingredients. *Panax ginseng*, however, should not be confused with Siberian ginseng (*Eleutherococcus senticosus*), since this last contains eleutherosides instead of ginsenosides and (despite being an excellent adaptogen remedy) cannot be considered true Ginseng. In the 20th century, when it became possible to analyze and document its effects with scientific methods, ginseng was finally recognized as a medicinal plant. Additional studies have been recently implemented by research on plants focusing on the relationship between the composition of the microbial community of the soil that grows the plant, an important factor accounting for high-quality production for rusty roots. It has been reported that, among the harmful microbial genera found in the soil, bacteria such as *Acrophialophora* and *Doratomyces* can be found in the rhizosphere of *P. ginseng*; similarly, pathogenic fungi such as *Cylindrocarpon, Alternaria* and *Fusarium* can be associated with the onset of rusty root symptoms [5, 6].

1.2. Pharmacokinetics of the Main Bio-compounds

The active ingredients composition of ginseng root consists of active and non-active ingredients, including triterpene saponins with steroid structure (ginsenosides 1-3%), polysaccharides (sugars, starches), essential and non-essential amino acids. Other include polyphenols, sterols, fatty acids (oleic, palmitic and stearic acid), phytosterols, B vitamins (B1, B2 and B12), vitamin C, folic acid, nicotinic acid, biotin, pantothenic acid, essential oils (0.05%), and mineral salts [7]. The structural diversity of ginsenosides is mainly a consequence of the high variety of sugar chains connected to different aglycone backbones [8, 9]. In general, based on the structure of aglycone, ginsenosides can be classified into three different types, dammarane-, oleanane-, and ocotillol-types [10]. The dammarane type includes Rb1, Rb2, Rb3, Rc, Rd, Rg3, Rh2, and compound K, as well as Re, Rf, Rg1, Rg2, and Rh1 moieties. Minor ginsenosides include ocotillo-type (F11) oleanane-type (Ro) ginsenosides, and other compounds (Rh4, Rg5) [8]. The current nomenclature of ginsenosides comes from an old classification, based on their chromatographical profile (Ginsenoside Rb1, Rb2, Rc) [9]. Ginsenosides Rg2, Rg6, F4, 20(E)-F4, Rh1, Rh4, Rk3, Rg3, Rg5, Rz1, Rk1, Rg9, and Rg10 are converted from the major ginsenosides Rb1, Rb2, Rc, Rd, Rg1, and Re, and their mechanism of action appears to resemble that of steroid hormones. Ginsenoside RB1 is metabolized by the intestinal microbiota into monoglycoside M1 [20-O-beta-D-gluco pyranosil-20 (S) -protopanaxadiol] and its presence can be detected for approximately 7h in plasma and 12h in urines after administration [7, 8, 11] (Fig. **1**)

The pharmacokinetics of ginseng are complex due to the heterogeneous chemical structures of ginsenosides. In fact, ginsenosides represent the most pharmacologically important molecules and we have considered *P. ginseng* and *P. quinquefolius* as the most widespread, used and studied. After oral administration, the bioavailability of ginseng is low because absorption at the intestinal level is not complete. Saponins are metabolised by the microbiota at the intestinal level, through deglycosylation processes and their bioavailability is less than 5% due to the poor bioavailability due to the intense metabolism, their reduced permeability of the intestinal wall and the poor solubility of the deglycosylated metabolites [12]. Saponins that are derived from protopanaxadiol (Ra3, Rb1, Rd, Rg3, and Rh2) are less bioavailable than saponins that are derived from protopanaxadiol (Rg1, Re, Rh1, and R1). Specifically, the saponins Rb1 and Rd are metabolized to compounds K and Rg3 and Rg5 to compounds Rh2 and Rh3. In the protopanaxtriol group, however, Rg1 and Re are converted into Rh1 and F1. Therefore, given the different speeds of degradation, modifications of the pharmaceutical formulation, such as micronization, could increase the bioavailability of saponins derived from protopanaxadiol (micronization doubled the bioavailability of Rh2). The plasma half-life is less than 24 hours. At the hepatic level, cytochrome P45 (the CYP3A4 isoform) catalyzes the oxidative metabolism of ginsenosides [13]. Adding more sugar molecules to protopanaxadiol ginsenosides blocks access to bile transporters and consequently delays their release into the bile. Most ginsenosides and their deglycosylated metabolites are in fact excreted in the bile, via active transport. Approximately 0.2%-1.2% of ginsenosides are excreted in the urine. Finally, enterohepatic recirculation is hypothesized, because multiple peaks were detected after its oral administration [14].

1.3. Mechanism of Action and Potential Biological Activities

The so-called adaptogen activity of ginseng is related to its ability to increase physical and mental performance, with a tonic and stimulating action that helps mitigate fatigue and improve the body's resistance to stressful factors (physical and /or mental stress); protective effects against various harmful agents such as radiations, infections, and toxins have also been observed. Thus, it is used as a natural remedy for the treatment of fatigue and asthenia, even during convalescence and increases mental concentration and the body's immune defenses, supports cardiac activity and gonadotropic activity (ginseng appears to be useful in cases of erectile dysfunction); the treatment of neurodegenerative diseases and anti-wrinkle and toning cosmetic preparations (ginseng induces an improvement in subepidermal layer microcirculation and vasoprotection) (Table **1** and Fig. **2**). However, it is important to underline that ginseng cannot replace

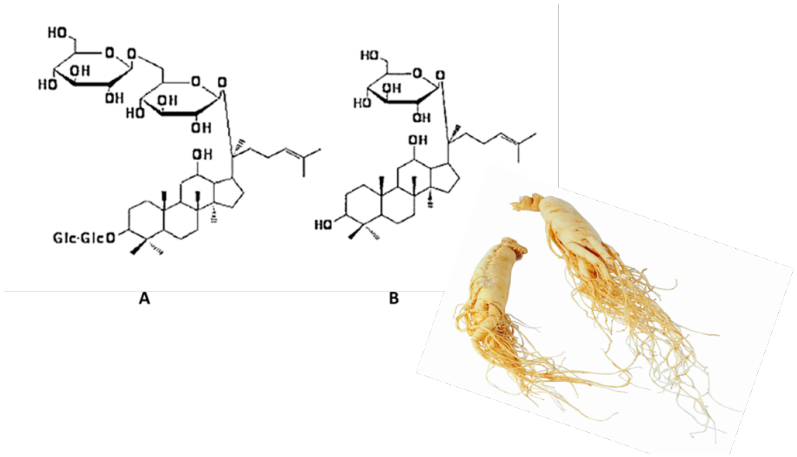

Fig. (1). The chemical structure of Rb 1 (**A**) and M1 (**B**). *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Table 1. Some of the main bio-activities attributed to *P. Ginseng*.

Biological Activities of *Panax Ginseng*				
Neuroendocrine	**Cardiovascular**	**Metabolic**	**Immune system**	**Gastrointestinal**
-Adaptogen and anti-stress activity (physical and/or psychic) -Stimulation of the HPA axis -CNS stimulation -Increased physical and mental performance -Anti-amnesic -Neuroprotective action -Aphrodisiac actions (increase of LH in males)	-Stimulation of the cardiovascular system -Antiplatelet activity	-Hypoglycemic activity -Antioxidant activity	-Immunostimulating activity and synergy with influenza vaccines	-Gastroprotective activity (gastritis and gastroduodenal ulcers) -Increased microbiotal eubiosis

conventional medical treatments but acts as an adjuvant to them [15, 16].

These activities are presumably related to the ability of ginsengs' active ingredients to induce (a) stimulation of the hypothalamus-pituitary-adrenal (HPA) axis, with increased production of glucocorticoids (b) CNS stimulation, (c) non-specific stimulation of the immune system and (d) amelioration of metabolic homeostasis [18]. Interestingly, subjects receiving ginseng extract have shown a lower incidence of flu and common cold, high antibody titers and a more efficient activity of natural killer lymphocytes. Indeed, daily administration of the extract (100 mg for 12 weeks) improved the effectiveness of the multi-purpose flu vaccine in healthy subjects, when given in the fourth week [19]. Moreover, a more efficient immune response with a reduction of acute exacerbations of chronic bronchitis has been highlighted in patients treated with antibiotics and ginseng extracts [20, 21]. A more detailed exploration of the mechanisms underlying the effects of ginseng on learning (working memory and recent memory) and memory consolidation comes from experimental studies. In the elderly rat (an experimental model of amnesia) the beneficial effects of ginseng have been ascribed to the ginsenoside Rb1, which is converted into the mono-glycoside protopanaxadiol (M1). Repeated treatment with ginseng leads M1 to increase the release of ACh from hippocampal neurons, and the subsequent increased uptake of choline (main precursor of acetylcholine) in cholinergic neurons would, in turn, stimulate the choline acetyltransferase (ChAT) activity to synthesize more ACh. The higher availability of ACh will enhance the long-term potentiation at the hippocampus level, thus reinforcing the process of long-term memory. On the same line, it has also been observed that the administration of ginsenosides increases the development and maturation of the CNS in mice, with a marked action on the neuronal synapses of the hippocampus at the CA3 area, directly involved in learning and memorization processes [22, 23]. In mouse models of

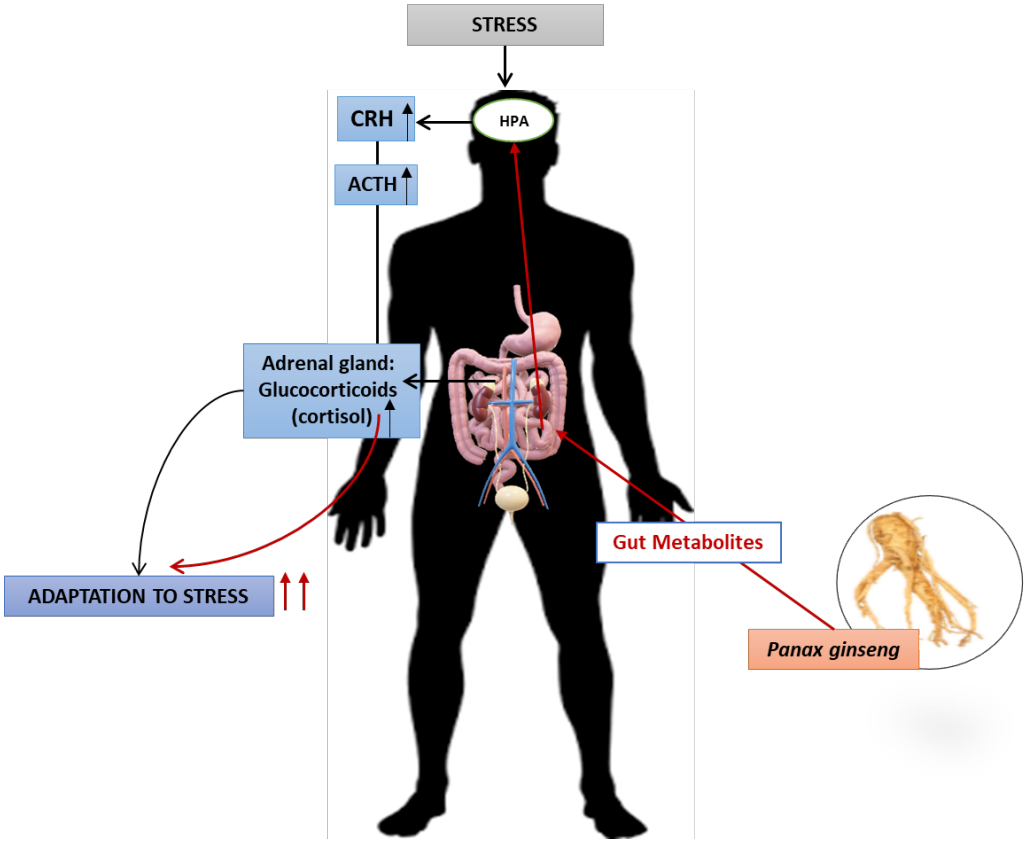

Fig. (2). The amount of active ingredients in ginseng is believed to stimulate the pituitary and adrenal endocrine system and facilitate the release of hormones, responsible for delaying the onset of fatigue. During stress conditions, increase glucose metabolism and have a reduction of inflammatory and immune responses. Glucocorticoids produced in response to stress can inhibit the arachidonic acid cascade (inhibition of phospholipase A2), prostaglandins and leukotrienes, reduce the levels of lymphocytes and macrophages, the production and action of interleukins (such as IL-1, IL-2 and other). This reduction causes a reduced capacity of the body against infections. Instead, the metabolites of ginseng through the gut microbiota further facilitate this adaptation process. (17) Credits: Original figure by I.A. Charitos. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

cerebral ischemia-reperfusion (I/R) injury, ginsenosides counteract the ischemic damage induced by excitatory intracellular accumulation of some amino acids and reduce the extent and severity of cerebral hypoxia [23, 24]. On the same line, ginsenosides have been observed to ameliorate the cardiac ischemic damage induced by ligation of the coronary arteries in animal models of myocardial I/R [25]. An in vitro study on murine cardiomyocytes exposed to hypoxia-reoxygenation (H/R) induced damage suggests that pretreatment with ginsenoid RK3 prevents injury and apoptosis via AKT/Nrf-2/HO-1 and MAPK pathways [26]. Additional cardio-protective and neuro-protective activities of ginsenosides have been ascribed to their antioxidant potential, related to the increased synthesis and release of nitric oxide (NO) in the vascular endothelium of specific districts [27]. Stimulated release of NO is involved in the mechanism by which ginsenoside Rb1 facilitates the secretion of luteotropic hormone (LH), with resulting ex novo synthesis of androgens (testosterone) by Leydig cells (LH/CG receptors) [28]. In erectile dysfunction, the reported ginsenoside-mediated effect might depend on the direct and indirect stimulation of NO release, responsible for vasodilation and relaxation of the corpora cavernosa [29]. Ginsenoside Rb1 possesses a dose-dependent hypoglycemic action lasting approximately 4 hours and not reduced by repeated administrations. It has been noted that, compared to baseline conditions, Rb1 increases glucose consumption by 24 ± 5% in adipocytes, and favors glucose uptake in peripheral tissues, albeit with effects lower than those elicited by insulin [30, 31]. To a lesser extent, ginsenosides Rb2, Rc, Rf, Rg1, Rg2 and Re display similar activities. Clinical studies have highlighted the hypoglycemic potential of ginseng in humans, both in healthy subjects and in patients suffering from type 2 diabetes mellitus [32, 33], observing a decrease in plasma glucose and glycosylated hemoglobin A1c (HbA1c) levels in diabetic patients treated with ginseng with respect to controls (placebo). Among potential mechanisms of action, an increased expression of the glucose transporters (GLUT2 in the liver, and peripheral transporters GLUT1 and GLUT4) has been proposed [31-33]. The presence of active components interacting with several biological pathways and cell activities suggests that, despite interesting and protective beneficial effects, ginseng administration should require some precaution: indeed, if taken inappropriately and together with a high amount of stimulating substances (such as caffeine), the excessive stimulation of the nervous system may occur, and promote side effects such as insomnia, irritability, hives, headache, diarrhea, and even cardiac arrhythmias [34] Gin-

Table 2. The dosages by the formulations with which ginseng is present on the market.

Recommended adult oral dose			
Decoction	**Dust**	**Dry extract**	**Tincture**
0.5-2 g of finely chopped ginseng root per day, boiled with water and then left to infuse for 5-10 minutes. The decoction thus prepared must be consumed once a day, in the morning, for 4 weeks	1 g of ginseng root powder per day.	1 tablet of dry extract per day, preferably in the morning. Taking ginseng after mid-afternoon could cause difficulty falling asleep	30-50 drops of ginseng mother tincture, diluted in water, 1-2 times a day

seng is a plant whose root is used in phytotherapy; roots that are at least 5-7 years old are preferred since they have a better relationship between the pharmacologically active substances (ginsenosides, between Rg1 and Rb1). Generally, the recommended dosage of ginseng for adults is 200-400 mg per day. The average daily dosage of ginseng corresponds to a dose of approximately 20-25 mg/day of ginsenosides (Table **2**) [35, 36].

The side effects appear especially when is administered in doses higher than recommended. The most frequent side effects are headache, sleep disturbances and gastrointestinal disorders. Excessive use of *P. ginseng* has been associated with heart palpitations, vomiting, nausea, and headache (ginseng abuse syndrome) (Fig. **3**).

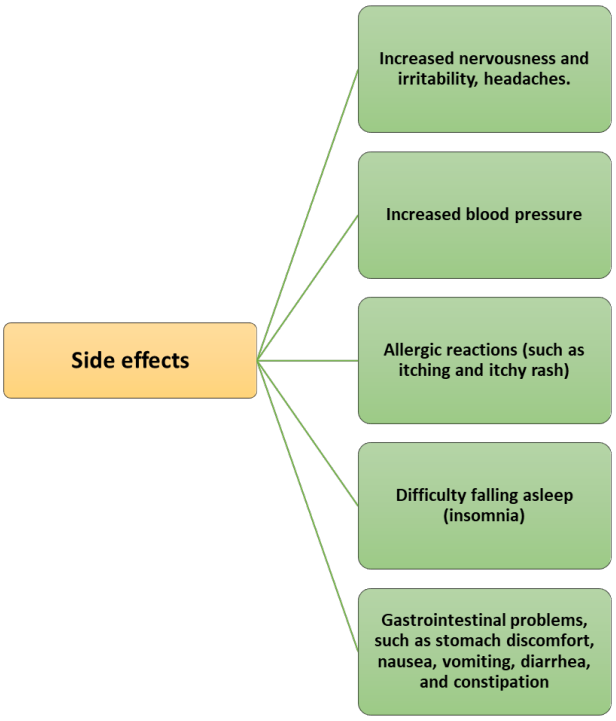

Fig. (3). As a rule, ginseng appears to be free of unwanted effects (side effects) at prescribed doses. Some side effects have been described following the intake of very high doses of ginseng and/or for a prolonged period. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

The risk of side effects is greater with preparations that contain, in addition to ginseng, other phytotherapeutic remedies. There are possibilities of interaction with other drugs, foods (such as the natural xantine actine gradients into coffee, tea, chocolate, etc.), and supplements that have stimulating effects and with those that have effects on reducing blood sugar levels (hypoglycemics) [35, 36].

Its interaction with antidepressant drugs as well as with anticoagulant drugs is possible, but not clearly demonstrated (Fig. **3**). Ginseng is contraindicated in cases of hypersensitivity, in patients with previous estrogen-dependent breast or endometrial cancer, since it could enhance the proliferation of tumor cells, during pregnancy and during breastfeeding (safety and tolerability in women pregnant or breastfeeding has not been established; furthermore, the estrogenic activity attributed to the drug does not recommend its possible use during breastfeeding) [37]. Ginseng can interact with cytochromes P450 through its constituents and metabolites that are formed in the intestine. Furthermore, the effects observed between ginseng and cytochrome enzymes gave different results depending on the type of analysis: in vitro, *in vivo*, and clinical reaserch. Naturally occurring ginsenosides have shown weak or no inhibition of the cytochrome enzymes CYP3A4, 2D6, 2C9, 2A6 or 1A2. The intestinal metabolites of ginseng were found to inhibit cytochrome-dependent metabolism. Compound K, protopanaxadiol (PPD) and protopanaxtriol (PPT) showed weak inhibitory activity on CYP2C9; PPD and PPT have also shown strong inhibitory activity on CYP3A4 [38] (Tables **3** and **4**).

2. THE HUMAN INTESTINAL MICROBIOTA

2.1. The Microbial Communities

The human intestinal microbiota, consisting of bacteria, viruses, protozoa and ~~archa~~ *archaeobacteria*), is the wide community of microorganisms located in the various cavities of the human gastrointestinal tract [48]. These microbes form a complex and interconnected micro-ecosystem including trillions of microorganisms belonging to about 500 different genera. By interacting with each other and with the host human immune system, these germs contribute importantly to the body's homeostasis (Table **4**).

Table 3. Some of the bacterial phyla with indicative bacteria at genus levels compose the adult human intestinal microbiota.

Bacterial phyla					
Pseudomonadota	***Bacillota***	***Actinomycetota***	***Fusobacteria***	***Bacteriodetes***	***Verrucomicrobia***
Genus					
Brucella *Neisseria* *Richetiza* *Bordettella* *Coxiella* *Legionella* *Pseudomonas* *Vibrio* *Aeromonas* *Enterobacter* *Escherichia* *Salmonella* *Aggregatibacter* *Haemophilus* *Pasteurella* *Campylobacter*	*Clostridium* *Lachnospira* *Faecalibacterium* *Ruminococcus* *Stafilococcus* *Bacillus* *Lactobacillus* *Pediococcus* *Enterococcus* *Streptococcus* *Lactococcus*	*Mycobacterium* *Microbacterium* *Bifidobacteriaceae*	*Fusobacterium* *Steptobacillus*	*Bacteroides* *Porphyromonas* *Prevotella* *Flavobacterium*	*Verrucomicrobium*

Table 4. Some interactions with other compounds and drugs [39-47].

Alcohol	Antiplatelet agents:	Warfarin	Insulin and oral hypoglycaemics	Chemotherapeutics	Antioestrogens	Lamotrigine	Phenelzine	Midazolam	Caffeine	Gingko biloba
In vivo studies, it appears that ginseng increases alcohol release by stimulating the activity of alcohol dehydrogenase and aldehyde dehydrogenase, the two enzymes involved in alcohol metabolism	Can induce a reduction in platelet aggregation. Furthermore clinical studies the results have been conflicting)	Reduce the anticoagulant action of warfarin in healthy volunteers	Probably have a modest hypoglycemic effect. Increase in insulin sensitivity index at fasting and oral glucose load test (33% increase)	Interactions have occurred between ginseng and campothecin, cyclophosphamide, taxanes, Vinca alkaloids, epipodophyllotoxin and EGFR-TK inhibitors	Stimulate estrogenic and progesterone receptors, and the proliferation of breast cancer cells	Has been reported he suffered symptoms such as headache, abnormal urine colour, myalgia, emesis	Has been associated with the onset of mania	Lead to 34% reduction in plasma levels of midazolam	Lead to hypertension	Can lead to an improvement in cognitive functions in the elderly

The intestinal microbiota has been entrusted with important functions including, among others, the synthesis of vitamins, the catabolism of biomolecules, the metabolism of bile salts and the regulation of inflammatory reactions [49, 50]. The microbiota differs between individuals and varies with the age of the same person, therefore creating a unique microbial profile for everyone (that can be considered as a "fingerprint") [50]. Owing to the progress in genomics and bioinformatics research, intestinal microbiota can now be studied individually, providing useful information for characterizing and improving the health of patients with gastrointestinal and other diseases. Current studies show that changes in the microbiota equilibrium (dysbiosis) are directly related to pathological conditions such as inflammatory bowel diseases, eating disorders, and allergies, up till the development of some forms of bowel cancer. Therefore, data obtained from studies on the gut microbiota via the microbiome may provide significant information in the fields of research and therapy [49, 50]. During the early stages of development, the intestinal microbiota plays a fundamental role in the evolution and functioning of the human immune system given its influence on both innate and acquired immunity. First, by colonizing the intestinal mucosa, the gut microbiota creates a protective biochemical barrier. Importantly, the gut-associated lymphoid tissue (~~GULT~~), whose function is promoted by the intestinal microbiota through antigenic stimuli, influences the humoral cellular and immunity (antibody-mediated immunity, about 80% of B lymphocytes and 60% of T lymphocytes are detected in the intestinal tract) [50-53]. Indeed, by focusing on mechanisms explaining how our immune system evolves to allow the symbiosis with microorganisms of the human microbiota while maintaining the abil-

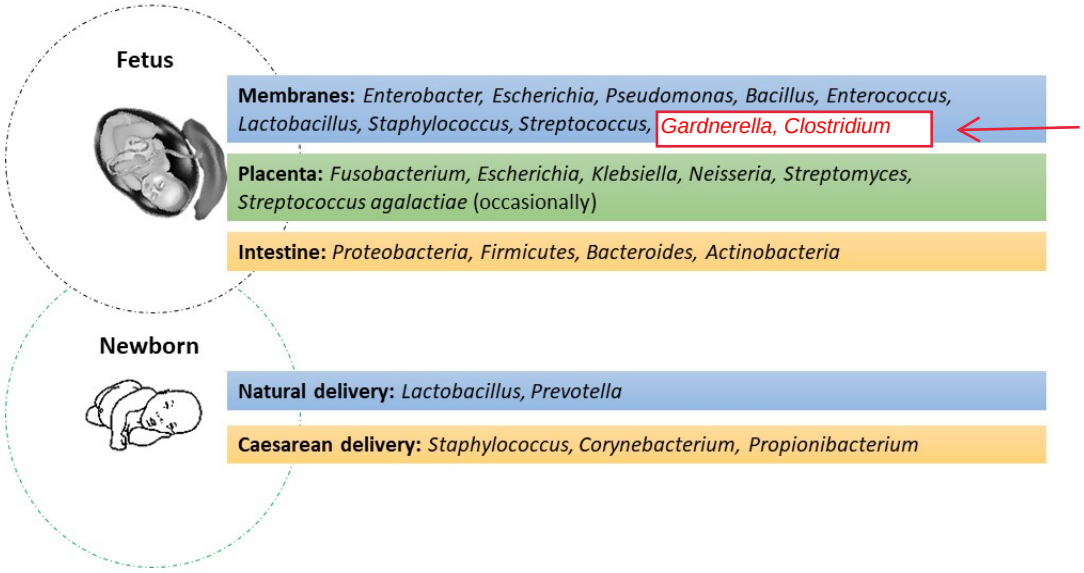

Fig. (4). The main phyla present during fetal life and according to the delivery mode. Credits: Original figure by I.A. Charitos. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

ity to address exogenous pathogenic microorganisms [33] research may provide a clear knowledge of the crosstalk between the intestinal microbiota and the immune system. This may lead to important information for the successful treatment of both gastrointestinal tract and, immune system diseases [50, 53].

2.2. Modifications of the Intestinal Microbial Composition from Infancy to Elderly

The intestinal microbiota should be considered an independent "organ" that actively participates in bio-humoral pathways of human physiology by storing, converting, and recycling large amounts of energy. According to the numerical predominance of the genus of microbes, the gut microbiota of each person can be categorized into one of three basic enterotypes: *Bacteroides* (enterotype 1), *Prevotella* (enterotype 2) and *Ruminococcus* (enterotype 3). The prevalence of these genera is largely determined by nutritional and environmental factors, and while microbial populations can change throughout a person's life, bacterial strains and population ratios are relatively constant [54-56]. From this point of view, the composition of the gut microbiota is not only relatively stable but also characteristic of everyone. However, as mentioned above, the intestinal microbiota of each person changes significantly throughout their entire life. Recent studies highlight how, in addition to the delivery modality, bacteria present in the amniotic fluid, placenta, and umbilical cord, may affect the fetal intestinal microbiota even during pregnancy (Fig. **4**) [50, 57, 58]. Thus, maternal stress or antibiotic intake can influence the development of fetal intestinal microbiota.

At birth, the newborn is exposed to the environment and the germ colonization begins. It has been observed that newborns with natural delivery (exposed to maternal germs) develop a different microbiota than those born by caesarean mode [50, 59]. From the initial child's microbiota development to a relatively stable microbial composition four subsequent phases can be recognized. In the first phase, during and immediately after birth, the main species are represented by *Enterobacteriaceae*, *Enterococci* and aerobic bacteria such as *Clostridia* (derived from the mother), whereas *Lactobacillaceae* family is still undetected [50, 60]. The second phase corresponds to the length of milk feeding: now aerobic species decrease, and anaerobic bacteria increase, with levels of *Enterococci* and *Enterobacteria* still elevated. In the third phase, when the child begins weaning with the addition of solid foods to milk, the colonization by *Enterococci* increases and the amount of *Enterobacteria* remains stable, while *Lactobacillaceae* family starts to increase. The fourth phase covers the age after weaning, when the child's intestinal microbiota starts to resemble that of the young adult reaching its full and relatively stable composition at approximately two and a half years [60]. Thus, during the first year, the newly formed child microbiota begins its interaction with the developing immune system, and the intake of breast milk plays a decisive role in this process. During adulthood, around 35%-50% of colon microorganisms consist of bacteria and archaea [50]. Most bacteria are anaerobic, and the main genera belong to *Bacteroides*, *Bifidobacterium*, *Eubacterium*, *Propionibacterium*, *Clostridium* while the aerobic ones belong mainly to *Enterobacteria* such as *Escherichia coli*. The composition of the adult intestinal microbiota can be influenced by a variety of exogenous factors such as dietary habits, alcohol consumption, hygiene conditions, or medications. In the elderly (from the age of 65 or 67 onwards 80+), the intestinal microbiota composition may change significantly, because of aging (for example, reduced number of teeth and digestion issues) or because of pathological conditions that negatively affect the gastrointestinal function [50, 59]. These changes may decrease the intestinal amylolytic capacity and increase the proteolytic activities and help to explain why proper nutrition is considered a particularly important factor for the maintenance of microbiota's eubiosis in adulthood and old age [59, 60].

2.3. Changes in Microbiota's Composition and Function Under Diseases

Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal tract with pain, diarrhea, and weight loss as the main symptoms. In the acute phase, several complications may require hospitalization and even surgery. The most common conditions include ulcerative colitis and Crohn's disease, whose incidence in the Western world has been constantly increasing in recent decades [61]. Ulcerative colitis is characterized by inflammation of the lining of the lower gastrointestinal tract (colon, caecum, rectum, sigma and anus) that extends systematically and perimetrically around its original focus and can lead to perforating ulcers. Crohn's disease is characterized by multiple foci of inflammation in different parts of the gastrointestinal tract that can lead to several longitudinal ulcers but with as less frequency of perforation. Although the causative agents have not been identified, factors such as immune overstimulation, heredity, diet, stress conditions and several bacterial pathogens appear to be involved in the onset and progression of these diseases [62, 63]. Thus, the characteristics of intestinal microbiota have been evaluated to detect potential factors that may play a decisive role in the disease's development. Among microorganisms apparently associated with the etiology of intestinal inflammation, none has been fully identified. However, both Crohn's disease and ulcerative colitis display characteristic changes in the intestinal microbiota composition. In patients with idiopathic IBD, strains such as *Lactobacillaceae* family and *Bifidobacteria* spp are reduced while the number of microbes in the intestinal mucus increases [50, 63], In irritable bowel syndrome (IBS), a chronic functional gastrointestinal disorder characterized by abdominal pain, discomfort, and abnormal bowel motility without any underlying pathological cause identified, the worsening of symptoms is directly related to psychological factors such as stress. IBS is therefore considered a ~~disorder of the intestinal~~, and an imbalance in gut bacterial communities, or "dysbiosis", maybe a contributor to the pathophysiology of IBD [61]. In recent years, targeted research studies have investigated the mechanisms through which the intestinal microbiota is involved in the occurrence of obesity and other metabolic diseases [64, 65]. The composition and function of the intestinal microbiota appear to differ in obese versus non-obese individuals, with consequences on food catabolism, intestinal permeability, mucosal inflammation, and immune functions [64, 66]. The question of whether specific genes from the intestinal microbiota have a causative role in obesity may open the road to new therapeutic approaches. A key observation is that overweight subjects have lower bacterial diversity than normal-weight individuals and that in obese subjects the communities' populations of the genus *Bacillota* are increased compared to *Bacteroidia* [50, 66]. Conditions that impair the function of the intestinal barrier allow the passage of bacterial lipopolysaccharides (LPSs), characteristic endotoxins of the outer membrane of Gram-negative, that may promote chronic intestinal inflammation, often associated with obesity [67-69]. Another observed change involves the reduction of angiopoietin-like protein 4 (ANGPTL4), which modulates triacylglycerol homeostasis, and has been observed under intestinal dysbiosis. Since this protein inhibits lipolysis, its reduced activity may contribute to increased fat deposition [70]. In the association between the deregulated activity of intestinal bacteria and obesity, another factor might be the impaired catabolism of fibers into short-chain fatty acids (SCFAs). SCFAs, such as butyric acid, are used for energy production, maintenance of a healthy intestinal barrier, and for physiological production of neurotransmitters (such as serotonin). The correct fiber catabolism may protect against obesity by contributing to the production of adipokines and appetite-regulating hormones that increase the feeling of satiety and help reduce fat deposition [50, 71]. On the same line, the myristoleic acid (acid 9-tetradecenoic acid), an omega-5 unsaturated Long Chain Fatty Acid (LCFA) produced by *Enterococci*, has been shown to counteract obesity through the activation of brown adipose tissue (BAT), thus suggesting the existence of an intestinal microbiota/LCFA/BAT axis [70].

Type 2 Diabetes Mellitus (T2DM) is a metabolic disorder with high morbidity and mortality characterized by high levels of blood glucose, reduced insulin secretion by pancreatic β-cells, and peripheral insulin resistance. A common feature of T2DM and obesity is the chronic low-grade inflammation (metaflammation) that occurs in metabolic tissues such as muscles and liver [71-73]. T2DM is thought to depend on a combination of hereditary and environmental factors such as stress conditions, diet, and infections. Intestinal dysbiosis may contribute to the onset and progression of T2DM by mechanisms like those described for obesity, involving changes in the catabolic activity of intestinal bacteria, and increased intestinal permeability. In this condition, the dysfunctional gut microbiota may increase the intestinal absorption of monosaccharides as well as the levels of triglycerides in the liver, directly related to insulin resistance [74, 75]. As for obesity, the increased absorption of bacterial endotoxins due to abnormal intestinal barrier under dysbiosis may contribute to insulin resistance in T2DM [71-73]. Similarly, decreased levels of SCFAs may concur with the development of T2DM. The ability to modify the release of incretins is another hypothesis proposed to interpret the role of the intestinal microbiota in the development of T2DM. Incretin peptides are metabolic hormones produced by the intestinal mucosa to favor the secretion of insulin. Recent studies have observed that improving the balance of the microbial communities of the gut microbiota may contribute to increased incretin secretion, and therefore ameliorate insulin resistance [76, 77]. This reinforces the concept that the onset and progression of T2DM are related to the overall imbalance of the intestinal microbiome rather than the reduction or increase of individual microorganisms [30, 77, 78]. The colon/rectal cancer (CRC) is common worldwide [50, 79]. The switch of an intestinal dysplastic adenoma to adenocarcinoma is associated with the presence of specific mutations in defined oncogenes/tumor suppressor genes. However, environmental factors, diet, and certain extra-digestive diseases seem to play an important role in the development of CRC, while intestinal inflammations (such as ulcerative colitis) seem related to the occurrence of intestinal adenocarcinomas. The proposed role of intestinal microbiota in carcinogenesis lies in the anti-inflammatory abilities of the eubiotic microbiota, whereas intestinal dysbiosis due to poor eating habits or other causes may contribute to reducing the defensive mechanisms [80]. In patients with CRC, previous and more recent

studies on microbiota have reported the increased presence of specific genera, such as *Clostridium* spp, *Bifidobacterium* spp and *Fusobacterium* spp (such as *F. nucleatum*), whose augment in the intestinal lumen might support carcinogenesis. Accordingly, patients at lower risk for carcinogenesis have been observed to carry abundant lactic acid-producing bacteria such as *Lactobacillaceae* family [80-83]. Although differences in the gut microbiota composition of patients with CRC or polyposis (which may promote carcinogenesis) have been extensively studied, whether dysbiosis is a cause of carcinogenesis or, instead, alteration of the mucosa may help the development of certain onco-pathogenic bacteria remains to be clarified. In any case, intestinal inflammation - either the cause or result of intestinal dysbiosis - is likely to represent a carcinogenesis-permissive environment [57, 80]. The inflammatory environment affects the permeability of the intestine and promotes the growth of bacteria-producing toxins that in turn may damage the epithelial cells of the intestinal mucosa, and impair the metabolic activity of the intestinal microbiota with their catabolic products. Thus, inflammation and intestinal dysbiosis may reciprocally influence and exacerbate each other [40]. Collectively, research on genetic and metabolic dynamics of the intestinal microbiota may help to clarify to which extent eating habits, nutritional supplements (including probiotics and/or prebiotics), and other environmental factors may influence the microbiota-associated ability to contain or encourage carcinogenesis [84-86]. This last concept deserves further attention since the existence of cross-talking axes between intestine/lung, intestine/brain, intestine/skin, intestine/liver, and bladder/intestine underlines the potential modulatory role of microbiota on the physiology of multiple organs and the systemic immune function. The above-mentioned list of coordinated activities justifies the definition of microbiota as a host's "local microbial-brain organ", able to act on distant systems. This relationship occurs through the immune system (which stimulates the migration of cells from the intestinal tract to peripheral tissues), through the systemic diffusion of coexisting microbial products and metabolites, through the translocation of certain bacteria following the breakdown of the barrier integrity, or, as for the intestinal/brain axis, via an effect on afferent sensory nerves [40, 87, 88]. For example, *Lactobacillaceae* family produces gas transmitters such as nitric acid (HNO3), and hydrogen sulfide (H2S), and may modify ion homeostasis by triggering nerve signals that control bowel motility and regulate pain sensation. In addition, the enteric nervous system is a major receiver of bacterial metabolism products [88, 89], and bacteria-produced SCFAs can stimulate the parasympathetic nervous system and modulate serotonin secretion, thereby influencing memory and other higher cognitive functions [89]. This is a major paradigm to comprehend why eating habits or medications that affect the composition and metabolic function of intestinal bacteria may significantly influence both the perception and behavior of the host. In turn, the brain regulates, independently and in parallel with the enteric nervous system, the motility of the gastrointestinal tract, the secretion of gastric fluid and mucus, and the local immune responses. Because of this two-way interaction in the intestinal/brain axis, stressful conditions may affect the composition and balance of the intestinal microbiota as well. Even short-term stressful stimuli, acting on the afferent branches of the autonomic nervous system (ANS), have the potential to affect the proportions of different microorganism populations: these effects depend on the secretion of signaling molecules by CNS neurons and the activation of immune cells [40]. The influence of CNS signals on the intestinal microbiota is largely based on the presence of neuroregulatory receptors on the surface of intestinal bacteria [89]. Interestingly, different stressful stimuli have dissimilar effects on the intestinal mucosa. Thus, the instantaneous stress after an intense acoustic stimulus generates an effect different from the generalized and long-term stress of everyday life, with this last able to induce drastic changes in the balance of the intestinal microbiota that may significantly disturb the quality of gastrointestinal function (Fig. **5**) [40].

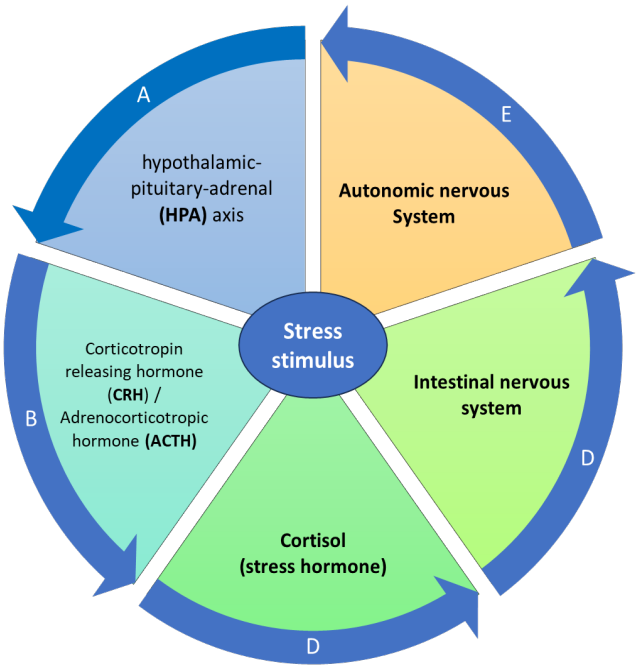

Fig. (5). Intestinal/brain axis: the neural control of the gastrointestinal tract depends on the autonomic nervous system (ANS, sympathetic and parasympathetic), and on the networks of the enteric nervous system (ENS) which works autonomously (assisting the motor and secretory activities of the gastrointestinal tract). This two-way interaction helps to explain how the afferent pathway and any stimuli (such as biogenic ones) may cooperate to promote various functional gastrointestinal disorders, such as irritable bowel syndrome and certain eating disorders (follow the letters in the arrows that indicate the process). Credits: Original figure by I.A. Charitos. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

3. THE BIO-INTERACTIONS BETWEEN INTESTINAL MICROBIOTA AND GINSENG ACTIVE COMPONENTS

In the last few years, an increasing number of research studies have actively investigated the medicinal benefits and safety concerns of the active ingredients of *P. ginseng*, administered as an extract or in combination with probiotics (Table **4**).

The metabolites of ginsenosides generated by the gastrointestinal microbiota play a decisive role in the organism. Differences in lifestyle, diet, alcohol assumption, and drug

Table 5. The table summarizes some of the experimental and observational studies of the last 4 years regarding the use of *P. ginseng* in various pathological conditions and the potential mechanisms involved.

Authors/Year	Type of Research	Summary of Findings
Young Kyun Kim et al, 2022 [90]	Human	Red ginseng increases gut microbiome richness (increasing the number of some strains) reducing harm to the gut microbiome,
Liang W et al, 2021 [91]	Animal model	Ginsenosides are involved in modulating the gut microbiota, a potential agent for the prevention of Nonalcoholic fatty liver disease through the integration of prebiotic, anti-inflammatory
Jeon H et al, 2021 [92]	Animal model	Korean Red ginseng prevents MPTP-induced dopaminergic neuronal death, activation of microglia and astrocytes, and accumulation of α-synuclein in the SN, and the regulation of inflammation-related factors in the colon
Xu Y et al, 2021 [93]	Animal model	*Panax notoginseng* saponins exerted hepatoprotection against Nonalcoholic fatty liver disease, ameliorated hepatic steatosis and fibrosis
Chen H et al, 2021 [94]	Animal model	Ginsenoside Rk3 reduce chronic obesity-induced colitis.
Yang Y et al, 2021 [95]	Animal model	In dextran sulfate sodium-induced colitis one-week ginseng treatment enhanced colonic accumulation while not altering the systemic exposure of cyclosporine A after a single oral dosing, indicating pharmacokinetic compatibility between the two medications.
Qu Q et al, 2020 [96]	Animal model	Fermented *Panax ginseng* Meyer, (0.5 g/kg/d) relieved some of the symptoms of antibiotic-associated diarrhea, reduced the expression of the immune factors TLR4 and NF-κB and inflammation in the colon
Xu Y et al, 2020 [97]	Animal model	*Panax notoginseng* saponins murine in the gut microbiome increasing the abundance of Akkermansia muciniphila and Parabacteroides distasonis and can be used as an intervention in the treatment of obesity.
Zhu JH et al, 2021 [98]	Animal model	Ginseng metabolism in immunosuppressed rats was significantly different from that in normal ones, which might be partly attributed to the changes in the intensity of specific gut bacteria.
Xu J et al, 2020 [99]	Animal model	25-hydroxyl-protopanaxatriol (T19) can regulate glucose and lipid metabolism
Xie Y et al, 2020 [100]	Animal model	Fermented feeds with ginseng polysaccharides may be used as effective alternatives to antibiotics for improving intestinal morphology and microbial composition
Luo Z et al, 2020 [101]	Review	Ginseng saponins and their secondary metabolites have a preventive effect on metabolic syndrome and the effective targets are distributed in the intestine and other organs in the human body
Wang JL et al, 2020 [102]	Animal model	The extracts of Ginseng Radix et Rhizoma, Notoginseng Radix et Rhizoma and Chuanxiong Rhizoma could improve the intestinal flora structure and create a good intestinal environment by increasing the B/F ratio, which provides a new possible pathway for lowering blood glucose and blood lipids and delaying vascular aging
Kim JK et al, 2020 [103]	Human	The gut microbiota may play an important role in the bioavailability of the nonpolar RG ginsenosides by affecting the biotransformation of the ginsenosides
Chen L et al, 2020 [104]	Animal model	Played an important role in the prevention of the progression of colorectal cancer, due to their regulation of the microbiome balance and microbial bio-converted product with anti-colorectal activity.
Guo YP et al, 2020 [105]	Animal model	Gut microbiota played a profound role in the biotransformation of *Panax notoginseng* saponins in vivo.
Yang L et al, 2020 [106]	Review	Gastrointestinal microbiota plays a decisive role in bioactivities of ginsenosides.
Chen H et al, 2020 [68]	Animal model	Rb1 exerts neuroprotective effects.
Han SK et al, 2020 [107]	Animal model	Ferment Red Ginseng mitigated anxiety/depression and colitis by regulating NF-κB-mediated BDNF expression and gut dysbiosis.
Quan LH et al, 2020 [108]	Animal model	The gut microbiota-LCFA-BAT axis plays an important role in host metabolism, which may provide a strategic advantage for the next generation of anti-obesity drug development
Zhang J et al, 2020 [109]	Animal model	In the biotransformation of *Panax notoginseng* saponins gut microbiota play an important role in vivo.

(Table 5) Contd…

Authors/Year	Type of Research	Summary of Findings
Fan J et al, 2019 [110]	Animal model	Fermented ginseng could alleviate the alcoholic liver injury and disorder of the intestine by adjusting the intestinal flora.
Zhou SS et al, 2020 [111]	Animal model	Stronger anti-obesity effect with white ginseng. The carbohydrates and ginsenosides present more structural and compositional specificity to the obesity-associated gut bacteria, allowing more beneficial effects of white ginseng on the gut microbiota dysbiosis.
Zhang T, 2020 [112]	Animal model	Treatment with Icariin and *Panax notoginseng Saponins* ameliorated memory impairment in an Alzheimer's Disease mouse model.
Qi YL et al, 2019 [113]	Animal model	Water-soluble ginseng neutral polysaccharide could improve the gut microecology by recovering the ileum structure and improving the diversity and composition of the gut microbiota in antibiotic-associated diarrhea mice.
Guo YP et al, 2019 [114]	Animal model	Gut microbiota plays an important role in biotransformation of *P. notoginseng* saponins into metabolites in vivo
Kim JC et al, 2019 [115]	Animal model	Korean Red Ginseng and probiotics administration ameliorated Nonalcoholic fatty liver disease symptoms in a mouse model of dyslipidemia by reducing weight gain and liver inflammation.
Zhou P et al, 2019 [116]	Review	Ginsenoside Rb1 may be developed as a potential anti-obesity, anti-hyperglycemic, and anti-diabetic agent with multi-target effects.

abuse (methamphetamines and other) reflected in the composition and biological activities of the intestinal microbiota, which in turn may modify the metabolic transformation of ginsenosides producing different therapeutic effects in response to equal doses of active ingredients from the ginseng root [80, 96, 100, 114]. Interestingly, *P. notoginseng* saponins administered in pseudo-germ-free rat plasma could not be effectively bio-transformed into metabolites in vivo when the gut microbiota was disrupted [114]. A study on 34 healthy Korean volunteers receiving Korean red ginseng or fermented ginseng observed that the intestinal microbiota is involved in the biotransformation of ginsenosides, by converting polar ginsenosides into non-polar bioactive ginsenosides [103]. In another study evaluating the in vivo metabolic profiles of *P. notoginseng* saponins in animal models, it has been reported that the gut microbiota plays a fundamental role in the biotransformation of *P. notoginseng* [105].

4. INFECTIONS

The importance of probiotics (such as fermented milk), prebiotics and symbiotics to restore intestinal eubiosis under several diseases and infections (such as the new pandemic from the SARS-CoV-2 [117] is well established. In Sprague-Dawley rats treated with antibiotics and fermented glycosides of ginseng (G1 to G5), the amelioration of symptoms of colonic inflammation and diarrhea was associated with the decreased expression of immune factors TLR4 and NF-κB in the colon [96]. Similarly, administration of the neutral polysaccharide ginseng was able to increase the Lactobacillus population and significantly decrease the relative abundance of *Bacteroides, Streptococcus, Ochrobactrum* and *Pseudomonas* at the genus level in intestinal microbiota in mice, concomitantly reducing symptoms of antibiotic-induced diarrhea, inflammation, and edema of the ileum, and increasing intestinal villous length [116]. In other experimental models, fermented feeds with ginseng polysaccharides have been proposed as effective alternatives to antibiotics for improving intestinal morphology and microbial composition. For example, in Xuefeng black-bone chickens fed a basal diet fermented by *Bacillus subtilis, Saccharomyces cerevisiae, Lactobacillus plantarum,* and *Enterococcus faecium*, ginseng polysaccharides significantly increased villus height and villus height to crypt depth ratio and decreased crypt depth in the jejunum. These changes were correlated with a specific microbiota profile, with *Sutterella* abundance positively correlated to villus height and villus height to crypt depth ratio, and negatively correlated to crypt depth, and *Asteroleplasma* abundance positively correlated to crypt depth and negatively correlated to villus height to crypt depth ratio. At the species level, the group treated with ginseng polysaccharides showed significantly increased *Bacteroides vulgatus* and *Eubacterium tortuosum* and decreased *Mycoplasma gallinarum* and *Asteroleplasma anaerobium* abundance [100].

5. BOWEL DISEASES

The effects of ginseng, alone or in combination with probiotic strains (such as *the Lactobacillus fermentum*), have been investigated for improvement of the intestinal microbiota and correlated relief from ulcerative colitis symptoms [117]. Red ginseng promotes the growth of beneficial probiotic bacteria in vitro and relieves the symptoms of ulcerative colitis in vivo in rats. Indeed, the orally administered vinaginsenoside R2 and majonoside R2 isolated from *P. vietnamensis* can reduce the binding of LPS to TLR4 on macrophages and may contribute to explain, at least in part, the decreased inflammatory process [114, 117]. Interestingly, in experimental ulcerative colitis induced by dextran sulfate sodium (DSS), the administration of ginseng extract improved the immunological safety of cyclosporine (CsA)-mediated immunosuppression. DSS-induced colitis significantly altered oral CsA disposition by dysregulation of intestinal and hepatic P-gp and CYP3A. One-week treatment with oral ginseng mitigated DSS colitis-induced down-regulation of CYP3A and P-gp expression, therefore facilitating intermediate HO-CsA production, biliary excretion, and colonic sequestration, without interfering with CsA oral systemic exposure (91). A potential protection of *P. notoginseng* saponins on the progression of CRC associated with colitis has

been studied in mouse models of azoxymethane/DSS-colitis. *P. notoginseng* administration increased the abundance of *Akkermansia* spp., whose decreased presence in the animal model has been correlated positively with CRC progression [104].

6. METABOLIC DISEASES

As mentioned, previously, pathogen metabolites of a dysfunctional gut microbiota may contribute to promoting and enhancing biomolecular mechanisms involved in the metabolic syndrome (MetS), a condition characterized by insulin resistance, obesity, dyslipidemia, elevated fasting blood glucose, and fatty liver disease. Ginseng's saponins and their secondary metabolites have been proposed to have a protective role in MetS via multiple effects on specific targets in the intestine and other organs [99]. Ginsenoside Rk3 (Rk3), already known for some protective effects in obesity-induced T2DM, acts as a natural anti-inflammatory agent to reduce chronic obesity-induced colitis. In high-fat diet-induced obesity mice, Rk3 facilitates the expression of tight junction proteins (zonula occludens-1, claudin and occludin), thereby decreasing levels of inflammatory cytokines, free radicals, and macrophages infiltration helping to restore the intestinal barrier function. This effect appears to involve a significant reduction of *Bacillota* and the inhibition of the TLR4/NF-κB signaling pathway [107] In the same animal model, treatment with *P. notoginseng* saponins increases the abundance of *Akkermansia muciniphila* and *Parabacteroides distasonis* and promotes the brown adipose tissue thermogenesis and beige adipocyte reconstruction by activating the leptin-AMPK /STAT3 signaling pathway, with subsequent promotion of energy expenditure [97]. According to some comparative studies, the chemical profile of white ginseng components seems to account for the most effective anti-obesity protection [109]. The intestinal/liver axis is involved in the development of non-alcoholic fatty liver disease (NAFLD), an obesity-related comorbidity. In high-fat diet and obesity-prone leptin-deficient (Lepob/ob) mice, *P. notoginseng* saponins demonstrate potent anti-lipogenesis and anti-fibrotic effects involving TLR4 inhibition, claudin-1 and ZO-1 protein restoration, and reduced translocation of SCFAs from the gut microbiota to the liver [93]. The supplementation with glycogenoside extract for 12 weeks significantly alleviated the symptoms of high-fat diet-induced NAFLD in a dose-dependent manner [91], modulated intestinal microbiota dysbiosis and reduced metabolic endotoxemia. On a molecular level, glycogenoside extract was able to contain the activation of NF-kB/IIB signaling and reduce the mRNA levels of proinflammatory factors (TNF-α, IL-1β and IL-6), concomitantly promoting hepatic lipolytic genes (CPT-1a), and inhibiting lipogenic genes (SREBP-1c, FAS, ACC-1), which improved leptin resistance [71]. Recently, the 25-hydroxyl-protopanaxatriol (T19), a new ginsenoside from ginseng, has been shown to possess an important inhibitory effect on α-glucosidase and protein tyrosine phosphatase 1B in vitro. In vivo, T19 demonstrated the ability to reduce blood glucose and lipid levels, insulin resistance, and to improve histological abnormalities of liver and pancreas in high-fat diet/STZ-induced mice; these effects were ascribed to the potential regulation of AMP-activated protein kinase and phosphoinositide-3-kinase signaling pathways [99]. Interestingly, T19 administration was associated with a remarkable amelioration of intestinal microbiota, with a decrease in the *Bacillota/Bacteroidota* ratio, and a noticeable increase in the relative abundance of *Lachnospiraceae*, whose beneficial effects can contribute to regulating glucose and lipid metabolism [99]. The positive influences of fermented ginseng on the microbiota intestinal/liver axis have been observed also in experimental models of alcoholic liver damage. In C57BL/6N mice exposed to alcoholic damage, increased ALT, AST, TNF-α, and IL-6 levels with degeneration of liver cells and hepatic steatosis, are commonly associated with intestinal dysbiosis. Treatment with *Limosilactobacillus fermentum* and KP-3-fermented ginseng reduced the amounts of *Verrucomicrobia* phylum and restored the population of *Lactobacilli*, *Bifidobacteria, Akkermansia, Allobaculum, Ruminococcus* and *Adlercreutzia* genera, therefore leading to eubiosis changes on mice gut microbiota and concomitantly resulting in amelioration of alcohol liver injury [110].

7. BRAIN DISORDERS

The presence of a gut/brain axis underlines the potential consequences that microbiota dysbiosis -subsequent to intestinal inflammatory conditions- may have on certain psychiatric disorders, concomitantly helping to explain beneficial effects obtained with ginseng administration. For example, treatment with red ginseng either alone or fermented with *Bifidobacteria* (fRG) has been shown to mitigate the stress-induced anxiety/depression-like behaviors in mice exposed to specific stress tests. Interestingly, treated mice display a reduction of circulating corticosterone levels, with concomitant suppression of the stress-induced NF-κB activation and NF-κB+/Iba1+ cell population in the hippocampus, and a general increase in the brain-derived neurotrophic factor (BDNF) expression and BDNF+/NeuN+ cell population. At the intestinal level, treatment with red ginseng or fRG alleviates gut dysbiosis, with a significant increase in *Bacteroidota* and a decrease in the *Pseudomonadota* population [107]. Most recently, by exploring mechanisms underlying the neuroprotective action of ginsenoside Rb1, it has been observed that microbiota plays a key role in neuroprotection of Rb1. Rb1 administration can upregulate the expression of GABA-A (α2, β2, and γ2) and GABA-B (1b and 2) receptor subunits in the rat hippocampus and striatum, and this effect seems secondary to the increased abundance of *Lactobacillus helveticus*. Thus, rather than through direct distribution to the target sites, Rb1 seems to exert neuroprotective effects by regulating the composition of intestinal microbiota [105]. Similarly, in a mouse model of Alzheimer's disease, combined treatment of *P. notoginseng* saponins with plant-derived icariin improved, memory impairment, with mechanisms involving the modulation of the intestinal microbiota and the expression of three proteins related to AD: MIPT3, involved in the transport and assembly of synthesized ciliary proteins in the cytoplasm; Oasl1, a member of the 2′-5′oligoadenylate synthetase family, and TCHP, a tumor suppressor that may have pro-apoptotic activities during cell stress [112]. Interactions between the gut and the brain play an important role in the pathogenesis of Parkinson's neurodegeneration. In an experimental model of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkin-

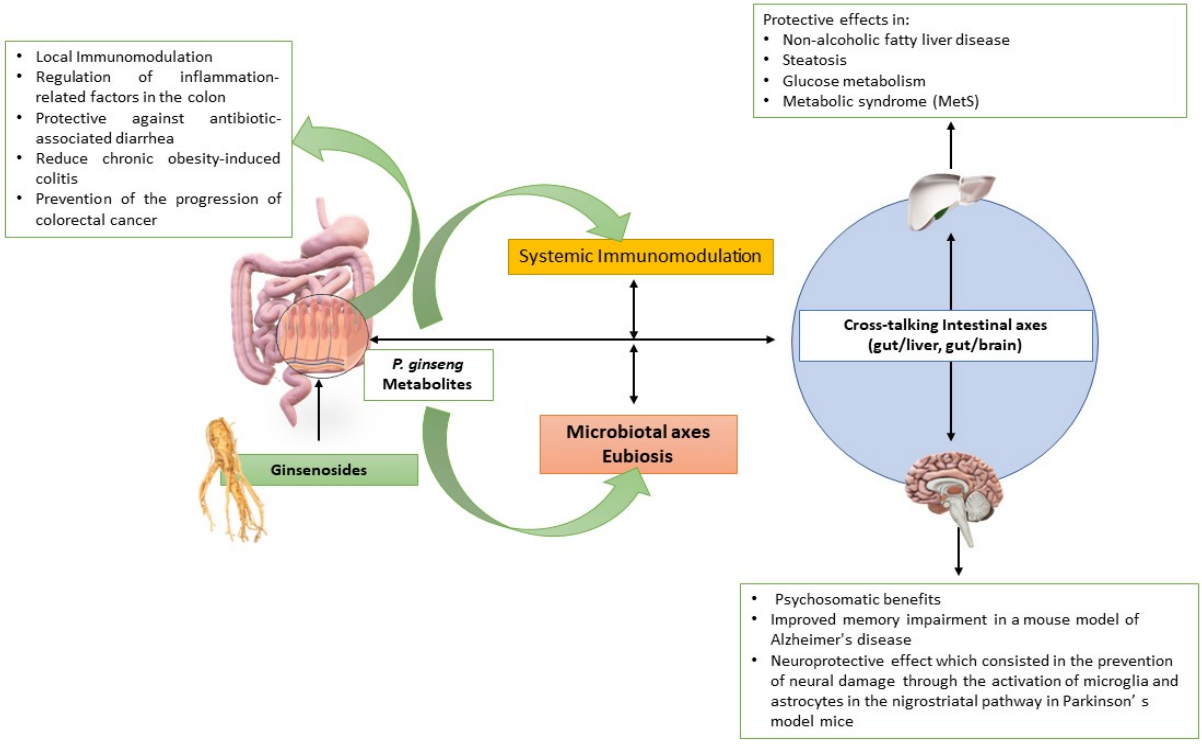

Fig. (6). An overview of the biological effects of ginseng metabolites on human organs and human microbiota. Credits: Original figure by I.A. Charitos. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

son's disease, the oral administration of Korean red ginseng (100 mg/kg, for a total of 12 consecutive days) had a preventative effect on neural damage after activation of microglia and astrocytes in the nigrostriatal pathway. KRG treatment prevented MPTP-induced behavioral impairment, dopaminergic neuronal death, and activation of microglia and astrocytes in the nigrostriatal pathway, with concomitant protective effects against disruption of tight junction and the increase in α-synuclein, IL-1β and TNF-α expression in the colon. The MPTP-dependent alteration in the number of bacterial species and their relative abundances was also partially counteracted by Korean red ginseng treatment, whose effect reduced the inflammation-related phylum *Verrucomicrobia* and genera *Ruminococcus* and *Akkermansia* and increased the abundance of *Eubacterium*, which produces the anti-inflammatory substances [92]. These observations further support the idea that the regulation of inflammation-related factors in the colon is deeply involved in the overall systemic and neural protective effects of ginseng active components (Fig. **6**).

CONCLUSION

The ginseng has been shown that prevent and ameliorate a variety of health conditions. Thus, have beneficial effects in animal models of anxiety, depression, Alzheimer's disease, and Parkinson's disease, including anxiety, physical and mental performance, and immune system defenses. The beneficial effects of ginseng may be due to its ability to modulate the gut microbiota but more research is needed to confirm the efficacy and safety of ginseng for the treatment of a variety of health conditions in humans and more research is needed to confirm the efficacy and safety of ginseng for the treatment of brain disorders in humans.

Currently, the effectiveness of ginseng in the prevention and amelioration of several distinct pathological conditions is documented by an increasing number of scientific studies in vitro and in vivo, on experimental animal and human models. Several of these scientific contributions underline the fundamental role of the intestinal microbiota in the biotransformation of ginseng in active glycosidic metabolites which, in turn, participate in intestinal eubiosis, immunoregulation, and local gut metabolism. In addition, by virtue of the intestinal/liver axis and intestinal/brain axis, biological effects of ginseng ingredients may contribute to physiological activities in distant tissues (Fig. **6**).

Overall, ginseng properties have been related to decreased anxiety, improved physical and mental performance, reinforced immune system defenses, and better protection against some specific conditions. Current knowledge therefore reinforces the proposed use of ginseng as an adaptogen drug which may function as a real adjuvant, especially for treatment and prevention of bowel diseases, cardiodysmetabolic disorders as well as for neuroprotection and memory enhancement.

AUTHORS' CONTRIBUTIONS

L.S. and M.A.P. performed the conceptualization, methodology was adopted by G.B., M.M. and E.J. were involved in the validation, I.A.C. performed the formal analysis, investigation was done by L.S. and M.C. (Colella), resources were contributed by M.C. (Corsalini) and I.A.C., data curation was performed by G.B. and I.A.C., writing-original draft preparation was done by I.A.C. and M.C. (Colella), M.C. (Corsalini) and G.B were involved in the writing-review and

editing, visualization was performed by M.C. and A.D.G., L.S. supervised the study and L.S. was involved in the project administration. All authors have read and agreed to the published version of the manuscript.

LIST OF ABBREVIATIONS

ChAT = Choline Acetyltransferase

HPA = Hypothalamus-Pituitary-Adrenal

I/R = Ischemia-Reperfusion

LH = Luteotropic Hormone

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

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