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Review article

Bioactive Phytochemical Compounds between Gut Microbiota, Cancer and Physiological Dysfunction

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Abstract

Gut microbiota mainly dominated by bacteria attribute to the divisions *Bacteroidetes* and *Firmicutes*, plays an important role in host physiology and influences several relevant functions. Bacteria diversity in gut microbiota driven by dietary factors and influences metabolic and immune functions of the host's physiology. Imbalance in the gut microbiota, named dysbiosis, can lead to the development of various diseases, such as cancer and even psychological dysfunction. Therefore, Gut microbiota is an appropriate target for nutritional interventions to improve health. These facts motivate us to highlight on the influence of phytochemicals on gut microbiota and look for an alternative treatment of inflammatory diseases by using nutritional supplements. Among dietaries phytochemicals elements we found several chemical compounds such as polyphenols and their derivatives, carotenoids, and thiosulfates. Polyphenols as the largest group can gather four main groups: flavonoids, phenolic acids, stilbenoids, and lignans. These compounds, which constitute a natural reservoir, have proved their efficiency as antioxidant and anti-inflammatory molecules. From this point, we may classify these compounds as an alternative molecule to treat or prevent the development of cancer or even psychological dysfunction.

Keywords: Gut microbiota; dietaries phytochemicals; polyphenols; cancer; psychological dysfunction.

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INTRODUCTION

Human body host an important microbial diversity, over than 10^{14} bacterial cells and 10^{24} viruses in and on our body. The major part of this microbial diversity identified in the intestinal tract. Microbiota related to all microbial organisms that live in and on the human body, which is general named "microbiome". This microbial community is characterised by an important diversity of microorganisms such as bacteria, eukaryotes, viruses and even microorganisms from archaeon taxa. We may highlight that even this high diversity in host, but bacterial microflora identified in given body area are more similar than those described in different body. In comparison, oral bacterial flora between individuals resembled than those on the skin and mouth of an individual. In addition, with each body area there is also an important inter individual diversity **(1).**

The gut microbiota dominated by bacteria affiliated to the divisions *Bacteroidetes* and *Firmicutes* **(2).** The gut microbiota can be distinguee into one of three enterotypes based on the dominant genera (*Bacteroides, Prevotella,* or *Ruminococcus*). We may characterized these cluster as a ratio of the dominance of *Bacteroides* and *Prevotella*, with the *Ruminococcus* enterotype affiliated with the *Bacteroides* group. The gut microbiota diversity mainly affected by diet. **(3.4).** Nutrition involves in the gut microbiota shaping, thus influencing on host's health status. Numerous components of food influent on gut microbiota diversity. Thus, the consumption of protein extracts of whey and pea increase gut commensal bacteria including Bifidobacterium and Lactobacillus. While, whey decrease *Bacteriodes fragilis* and *Clostridium perfringes* charge **(5).** Diets containing high saturated fat elements increase the *Faecalibacterium prausnitzii* load **(6).**

Gut microbiota involved in modulation of host immune system. Indeed, influencing on the integrity and function of biological barriers. *Bifidobacteria* as commensal gut microbiota have an important impact on homeostatic functions including immunologic, humoral and metabolic. Involvement of Mucosal-Associated Invariant T (MAIT) cells with *Bifidobacterium* could have a preventive or curative effect on colorectal cancer patient **(7).** However, the gut microbiota can affect central nervous cells **(8).** In addition, the gut microbiota interacts with the immune system, involving in the maturation of immune cells and the normal development of immune functions **(9).** However, gut bacteria microflora has a significant role in metabolic, gastrointestinal, immune diseases and cancer development **(1).** Mycosporin-like amino acids low weight molecule with prebiotic effects and ability to modulate host immunity. They can regulate the proliferation and differentiation of epithelial cells, macrophages and lymphocytes involved in inflammatory response. Using *Bifidobacterium animalis subspecies lactis* engineered to produce mycosporin-like amino acids may provide a positive effect on colorectal cancer **(10).**

Understanding the function and stability of gut bacteria microflora in human body, may lead to an important step in prediction of any physiological dysfunction, thus construct a therapies strategies to

correct dysbiosis. It is evident that diet, disease, and environment are constant; gut microflora are stable within healthy adult individuals over time **(11, 12, 13, 1).** Unless, dietary influence on microbiota, human physiology cannot be affected. Turnbaugh and co-workers show in mice that ever changing to a high fat, high-sugar ‘‘Western’’ diet from a low fat, plant polysaccharide-rich diet can modify the microbiota within 24 hours **(2).** The same result observed within humans, changing from a high-fat/low-fibre diet to a low-fat/high-fibre diet induced important changes in the gut bacterial microflora within a day **(4).** In this review, we highlight on bacterial diversity in human gut and theirs relation between microbiota dysbiosis and human diseases. Then we focused on the biotransformation of phytochemical compounds by gut microbiota and his relation in preventing or treating diseases.

Gut microbiote diversity and human diseases

At the first years of life, bacterial and virus diversity in gut is very low. However, years by years the microbial diversity change and new species introduced. As the gut initially contain oxygen molecules, the first bacterial colonisers are aerobic. However, by the time those bacteria changed to the anaerobic bacteria **(14).** Sequencing analysis show that bacteria prevalence changed through the time, those present at abundance at the earlier age are below the actual detection threshold. It is evident that phylogenetic diversity increases gradually during the time. These modifications are associated with life events, the use of antibiotic and the introduction of solid foods **(15).**

Human intestinal tract is an environment rich in nutriment provided by human diet. This environment harbour up 100 trillion microbes. Our colon has the highest bacterial density (10^{11}-10^{12} cells/ml) **(16).** When we born, bacterial communities are originate from vaginal or Caesarean section delivery. New born gut microbiome mainly contains *Bifidobacterium* species first week, after that *Lactobacillus* genus mainly keep dominant species, born method is important about new born gut flora but only this reason doesn’t provide mainly new born gut dominant. New-borns delivered by Caesarean section have microbiota dominant in skin flora such as *Staphylococcus* species. From this step, the diet liquid or solid changes the new born gut microbiota diversity. Ingestion of solid food is involved within an increase in gut *Bacteroidetes*. Bacterial microflora diversity in children gut approximates the bacterial diversity seen in adults by the age of three years **(17).**

From human intestinal sample, the 16S rRNA sequences affiliated to seven divisions of Bacteria including *Firmicutes, Bacteroidetes, Actinobacteria, Fusobacterium, Proteobacteria, Verrucomicrobia* and *Cyanobacteria* **(16).** Healthy adults gut microbiota is mainly composed of *Bacteroides, Firmicutes* and *Actinobacteria*. Whereas, *Proteobacteria, Verrucomicrobacteria* and other bacterial species account for a minor quantity. Gut microbiota diversity and distribution are mostly influenced by individuals age, health status, diet and living environment **(18**). The antibiotic use may induce the charge arise of *Clostridium difficile* colitis in human gut **(17).**

The gut bacterial microflora have an significant role in different physiological functions in host body, such as degradation of fibrous foods, energy supply and harvest, lipid storage and metabolism, synthesis of vitamins, reducing of pathogenic bacteria load and maintain of intestinal barrier integrity **(19).** Moreover, gut microbiota are also involved in the development and expansion of gut mucosal and systemic immune system **(20).**

With deep focus on human gut microbiota, it become more evident to report that gut microbiota has tiny link with health and human diseases **(16)**. Investigation on gut microbiota bacterial diversity and immune response performed on germ free animals models reveal that the number of immune cells decreased and several local and systemic lymphoid structures decreased. While, once this germ free animal treated with specific bacterial cells or his compounds immune cells are restored **(21).** Bacterial species belonging to *Bacteriodes* and *Lactobacillus* are involved in the regulation of Th17 cells and dendritic cells **(22).** Investigations done by Johansson and Kelsall reveal that gut mucosa associated immune cells are different from systemic immune cells. This related to physiological mechanism who may give more tolerance to gut environment **(23).** Toll like receptors (TLRs), pattern recognition receptors that function as sensors of microbial products like LPS, launch the inflammatory response. The TLRs have an important role to prevent any gut dysbiosis, it detect commensal bacteria and protect against gut injury and maintaining homeostasis**. (17)**

Furthermore, short-chain fatty acids products of bacterial fermentation by commensals have anti-inflammatory properties in multiple immune cell types. Some *Clostridium* strains in the gut show anti-inflammatory properties, by induction of the anti-inflammatory cytokine IL-10 and CD4+ regulatory T cells **(17).** Moreover, commensal microbes can promote inflammatory T helper responses (Th1 and Th17), in order to ensure the protection of human body from any potential pathogenic attack. Bozkurt and Kara reported that *Bifidobacterium animalis subsp. lactis BB-12* could decrease the charge of $CD14^{+}HLA\text{-}DR^{+}$cells that expressed TLR-2 in peripheral blood and oral administration of *Bifidobacterium animalis subsp. lactis BB-12* increase dextran sodium sulfate (DSS)-induced colitis, thus contribute in the suppressing tumor necrosis factor (TNF)-α-mediated gut epithelial cell apoptosis. Moreover, co-culture of *Bifidobacterium animalis subsp. lactis BB-12* with intestinal dendritic cells reduces pro-inflammatory cytokine IL-10 levels **(24).** Thus, with the reduction or complete absence of the gut bacterial microflora, pro-inflammatory responses reduced. The measurement of cytokines interferon IFNδ and interleukin (IL-17) can confirm that. On another hand, the rate of CD4+, CD25, FoxP3, regulatory T (Treg) cells enhanced in the periphery **(8).**

Our body record a stability of microbiome, suggesting a presence of beneficial exchange between microbiota and human host. Thus, any disturbance in the microbiota allow predicting the disease **(25).** Dysbiosis in gut bacterial microbiota and microbial metabolites related with irregularity of gut barrier integrity and enhanced pro-inflammatory cytokines. With the old persons, these entire elements are

responsible of various metabolic diseases including l adiposity, insulin resistance, fatty liver and hepatic steatosis atherosclerosis, cardiovascular diseases and diminishing motor activities **(26).** Moreover, alterations in gut microbiome can also have an impact on gut brain axis. Thereby, affecting neuronal, endocrine, nutrient and immunological signals between gut and brain through enteric nervous system (ENS). Moreover, it could also be involved in diseases of central nervous system (CNS) including multiple sclerosis, autism, depression and anxiety **(27).** As previously highlighted; *Bifidobaterium* play an important role on host immunology and Bifidobacterium engineered to produce Mycosporin-like Amino Acids (MAAs) could modulate host immunity. Recently Bozkurt and Kara reported that MAAs could modulate NF-KB and tryptophan metabolism, thus inducing a beneficial effect on central nervous cascade **(28).** On another hand, Gut microbiota and lung microbiota developed at the same time after birth and it clear that there is gut lung axis dialog **(38).** Patients with respiratory infections generally have gut dysfunctions complications, which related to more server occurs in gut microbiote, indicating gut-lungs crosstalk **(12)** In ARDS, the lung microbiota shows an important diversity in gut bacteria such as *Bacteroides* and *Enterbacteriaceae*. From this situation, mucosal gut increases his permeability so that, bacteria can translocate through the colon wall to reach the lung and trigger the inflammation. Indeed, specific gut microbiota is involved in immunological phenotypes or cytokines responses, which may influence disease pathogenesis or pathology **(13).**

On another hand, intestinal microbiota involved in the development of colon cancer. Sequencing analysis on microbiota of colon carcinomas and adenomas and non-cancerous tissue samples reveal important load of *Fusobacterium* species within cancerous tissue compared to non-cancerous tissue samples. Stool samples from patients suffering with colorectal cancer, and colon adenomas reveal an important charge of *Fusobacterium* species, increase of opportunistic pathogens and decrease of butyrate producing bacteria. These variations may influence on the inflammatory environment, promoting tumorigenesis **(17).** Furthermore, gut metabolite including trimethylamine-N-oxide (TMAO) defined as a pro-atherosclerotic metabolite of phosphatidylcholine in the intestine, is involved in cardiovascular disease. Tag and his co-authors, reported an important baseline plasma levels of TMAO with aging patient. Thus, related with the increase of cardiovascular events after adjustment of standard risk factors. This finding reveals a presence of association between the metabolite produced by gut microbiota and cardiovascular disease **(29).** However, Bozkurt and Kara reported that administration of *Bifidobacterium animalis subsp. lactis* and xyloglucan combination mediate a positive effect in the mucosal healing and resolution of colonic symptoms in unresponsive ulcerative colitis patients **(24).**

Biotransformation of phytochemical compounds by gut microbiota

Herbal medicines defined by their origin; active compounds obtained from roots, steam, leaves or fruit of plant. With the technology advancement, the use of herbal medicines is more widespread in the treatment of chronic and degenerative diseases including cancer. Herbal medicines can administered

in several ways such as orally and externally. The oral administration is the most commune. Once herbal medicines enter the body through oesophagus arrived to the gut and actives compounds mainly polyphenols interact with gut microbiota in the intestine. The polyphenol compounds can exert their biological effects after gut microbiota chemical modifications **(30).** Investigating on the interaction between the gut microbiota and herbal medicines reveal the involvement of two possible pathways. The first one is that herbals medicines digested by the gut microbiota and transformed into active small molecules able to be absorbed by intestinal cells and induce physiological changes. The second pathways is that herbal medicines change the gut microbiota and its secretion, inducing physiological changes in human body **(18).**

Herbal medicines have an important proportion of polysaccharides, which cannot digested by the gut digestion enzymes. For that, human organism cannot use them. However, with the intervention of gut microbiota elements, -*Bifidobacterium* and *Bacteriodes*- complexes molecules proteins and carbohydrates from herbal medicines converted to smaller molecules ready to be absorbed by human organism. This bioconversion mediated by hydrolases and reductases (α and β-glucosidases and β-glucuronidase) secreted by gut microbiota. β-glucosidase known as significantly cleaving the glycosidic bonds of flavonoids to release aglycones **(16).** Glycosides converted into secondary glycosides or smaller aglycones with lower polarity and stronger lipophilicity. Thus, absorbed into blood to improve disease fighting **(31).** Deglycosylation one of the most common reaction in the metabolism of herbal medicines mediated by gut microbiota **(32).** During this metabolism, deglycosylation accompanied by oxidation and reduction **(33**). Ginseng, rod of *Panax ginseng*, have ginsenosides as major constituents, known for numerous biological activities including anti-inflammatory and anti-tumour effects. After orally taken, ginseng saponin is metabolised by human gut microbiota by one of these bacterial strains, *Bifidobacterium* specially *B .longum H-1* **(33, 34).** According to Akao and his collaborators, ginsenoides Rb1, Rb2 and Rc are transformed to 20-O-β-D- glucopyranosyl-20 (S)- protopanaxadiol (Compound K) by human intestinal bacteria and entering the blood stream **(35).** The compound K express potent anti-tumour, anti-inflammatory and anti-allergic mediators **(32).**

One of the most dominant compound in Fructus Corni (*Cornus officinalis Sieb.*) traditional Chinese medicine are iridous glycosides. Laganin and marroniside are the two main bioactive constituents who have an important role in the treatment of chronic nephropathy. Tao and his collaborators, reveal that these compounds are metabolised by intestinal bacteria from normal rat and rat with chronic nephropathy. Loganin and marroniside flow metabolic routes including deglucosylation, demethylation and hydroxylation **(32).**

Naringin, natural flavanone (2.3 dihydroflavonoid) extract from medicinal plant (Citrus plant). Naringin express large pharmaceutical bioactivities especially against oxidative stress, inflammation and pulmonary diseases. Orally taken, naringin metabolised by liver (cytochrome P450) and gut

microbes. Human intestinal microbe are involved in biotransformation processes of naringin and yield with 3-(4'-hydroxyphenyl)-propanoic acid (HPPA), one of naringin metabolite who could effectively supress influenza infection **(36).**

The rhizome of *Zingiber officinale Roscoe (Zingiberaceae*) widely used as a common condiment for a variety of foods and beverages. Ginger plant known for therapeutic effect, it used for his stomachic, carminative, stimulant, diuretic, bechic, and antiemetic properties (6). Gingerol is the principal actives compound of ginger (6). Gingerol express numerous pharmacological effects including analgesic, antipyretic, cardiotonic effects and inhibition of spontaneous motor activities and prostaglandin biosynthesis.

Once oral administration of (6)gingerol, two reaction involved including conjugation, and w-1 oxidation and β-oxidation of a phenolic side chain in rat intestinal mucosa, then in the liver and other tissues **(37).**

Another alimentary complement add in our meal is curcuma. Curcumin one of the principal compound of curcuma. This polyphenol molecule have a positive effect on neurodegenerative and neurological diseases. The poor aqueous solubility, bioavailability, and pharmacokinetic profiles may reduce the therapeutic effect of curcumin. Therefore, oral administration of curcumin could express regulation effects in the gastrointestinal tract and act secondarily on the central nervous system by influencing the "microbiota – gut-brain axis" **(38).** Once consumed, phenolic compounds of curcumin continue their simple transit to the large intestine without any biotransformation. Arrived to the intestine, curcumin modified following phase I enzymes (Cytochrome P450) where catalyses a substrate hydroxylation. From phase I host organism obtain three metabolites, such as tetrahydrocurcumin (M1), hexahydrocurcumin (M2), and octahydrocurcumin (M3). Then, corresponding glucuronide and sulfate O-conjugated metabolites yielded from curcumin and the phase I metabolites conjugation via phase II metabolism **(39).**

From newborn to elderly person, gut microbial diversity and the commensal bacterial carriage including *Bacteriodes, Bifidobacteria* and *Lactobacillus* reduced, while the levels of opportunists such as *Entrobacteria, Clostridium perfringens* and *C .difficile* increased. Moreover, reduction microbiota related metabolic capacity in old age might be associated aging relation maladies including arthritis, sarcopenia, diabetes, etc. **(22).** From this point, gut commensal bacteria have an important impact on host nutrition and metabolism, in fact on microbiota-derived metabolites.

Enzymes produced by the gut microbiota mediate biotransformation of active compound from herbal medicines. *Escherichia coli* enteric bacteria able to biotransform curcumin. Curcumin id first converted by the enzyme NADPH-dependent curcumin/dihydrocurcumin reductase (CurA) converts into the intermediate, dihhydrocurcumin to obtain at the end tetrahydrocurcumin **(40)**. *Blautia s*p. is

involved in biotransformation of the curcumin molecule. From curcumin derivatives, demethylcurcumin and bisdemethylcurcumin obtained by demethylation reaction **(41).** *Escherichia fergusonii* (ATCC 35469) and two *Escherichia coli* strains (ATCC 8739 and DH10B) are able to modify curcumin and produce dihydrocurcumin, tetrahydrocurcumin, and ferulic acid **(42).**

Other gut microbiote bacteria contribute in the biotransformation of curcumin including *Bifidobacteria longum BB536, Bifidobacteria pseudocatenulatum G4, Escherichia coli K-12, Enterococcus faecalis JCM 5803, Lactobacillus acidophilus,* and *Lactobacillus casei* **(43).**

Moreover, bacteria from colon may conjugate glucuronide and sulfate O-conjugated inactive metabolites produced by phase II enzymes and reconvert them to the corresponding phase I active metabolites **(44).**

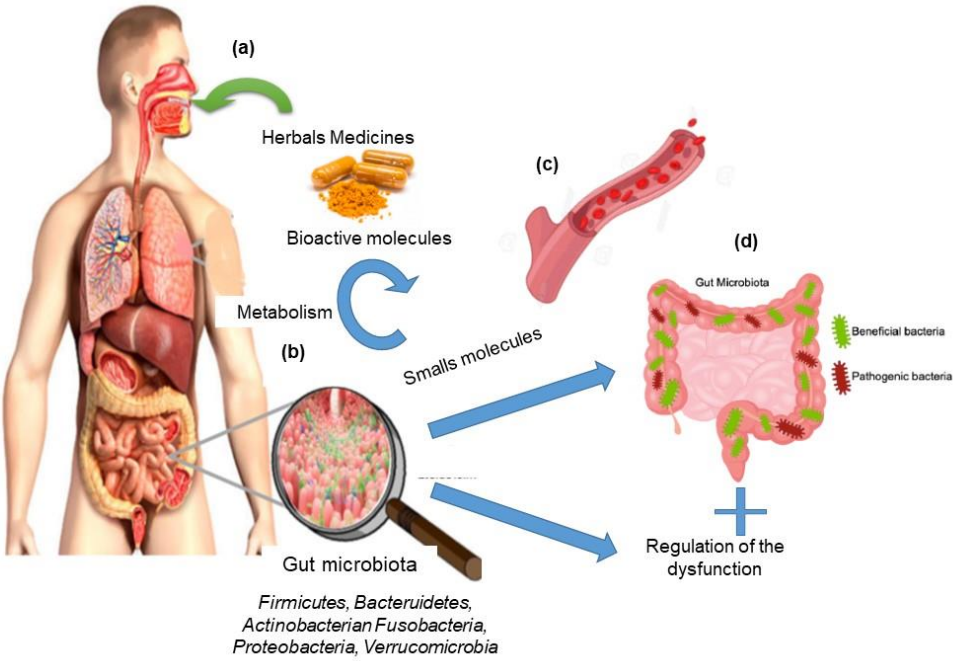

Figure 1. Gut microbiota and bioactive molecules. **(a)** After oral administration the bioactive molecules, **(b)** biotransformed to small molecules, **(c)** entering to bloodstream, **(d)** Arrived to the intestine they could modify the microbial diversity and charge, or /and regulate the physiological dysfunction.

Curcumin and its metabolites are involved in restoring dysbiosis of gut microbiome. Therefore, gut microbiota have an important role in the action of bioactive molecules from herbal medicines. All this finding highlight on therapeutic effects of tetrahydrocurcumin and curcumin metabolite in neurodegenerative diseases. They contribute in the inhibition of prominent cytokines' release, such as interleukin-6 (IL-6) and tumor necrosis factor α (TNFα), or by inhibition of NF-$_{\kappa}$B activation. More than, curcumin increases the activity of one important antioxidant enzymes including superoxide dismutase (SOD). This enzyme is able to dismutate superoxide into hydrogen peroxide and oxygen **(38).**

Panax notoginseng Chinese herbal medicine used in preventing and treat cardio-cerebrovascular ischemic diseases. *Panax notoginseng* identified for his active compoundsincluding saponins, polysaccharides and flavonoids. Among saponins, ginsenoside Re could be metabolised to Rg1 and secondary ginsenosides 20 (5)-Rg2 by *Bacteroides spp.* and *lactobacillus spp.* could transform ginsenoside Rc into ginsenosides 20(5)-Rg3 and Rd **(45).**

On another hand, once active compound arrived to intestine such as curcumin, it mediate a regulation effect on the gut microbiota community affecting microbial richness, diversity and composition. After oral or intraperitoneal administration of curcumin intestinal bacterial community changer considerably. It induce the reduction of microbial charge up 15% and diversity in mice gut and reduce the abundance of some microbiota gut communities including *Prevotellaceae, Bacteroidaceae,* and *Rikenellaceae*. Those species are associated with systemic diseases **(38).** Thus, herbal medicines can change the composition of the microbiota, regulating not only the bacterial populations of the gut, but also the ability of intestinal bacterial strains to produce more active compounds from herbal medicines itself.

Conclusion

Bioactive molecules extracted from herbal medicines express an important role to human health. To enumerate its pharmacological and therapeutic advantages, it is important to consider bioactive molecules interplay with gut microbiota and the link between gut and brain or gut and immune system. In fact, gut microbiota have an important impact on bioactive molecule metabolism, providing active metabolites. On other hand, bioactive molecule can influence on gut microbiota composition allowing the growth of strains needed to maintain correct host physiology function. Analysis of gut microbiota changes in health and diseases in the presence of bioactive molecule will allow identifying bacterial strains in bioactive compound conversion.

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