EXPLORING THE SYNERGISTIC EFFECTS OF POLYPHENOLS AND GUT MICROBIOTA ON METABOLIC HEALTH

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ABSTRACT: Dietary polyphenols are secondary metabolites and are one of the most abundant natural products present in the kingdom Plantae. They have high therapeutic potential and have been employed in the treatment of many diseases such as cardiovascular, neurodegenerative, obesity, diabetes, etc. According to much research, it has been seen that high consumption of these compounds impart many benefits to human health. However, it is difficult for the human digestive tract to digest these vital compounds, and they may accumulate in the large intestine where they are combined with the gut microbiota. The gut microbiota is a collection of different kinds of microorganisms such as bacteria present in the gut system. These microorganisms help in digesting polyphenolic compounds and impart various health benefits to humans. They along with phenolic compounds showed a variety of bioactivities such as anti-inflammatory, antidiabetic, antioxidant, etc. This review presents a comprehensive study of the mechanism of gut microbiota-polyphenolic interactions and their biological effects.

Keywords: Polyphenols, gut microbiota, health benefits, bioactivity, therapeutic potential.

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INTRODUCTION

Most antioxidants in our daily lives are presumably polyphenols, defined as plants' secondary metabolites. Fruits, vegetables, cereals, green tea, coffee, and other foods are the primary dietary sources of these drugs [1] (Figure 1). They are a great research interest because of their potential health benefits, like anti-inflammatory, anti-cancer, antioxidant, and anti-microbial characteristics. Moreover, polyphenols are also attributed to the prevention of chronic diseases like diabetes, obesity, and cardiovascular, and neurological disorders [2–5]. An adult's daily consumption of dietary polyphenols can reach up to 1 gram, which is approximately ten times more than their intake of vitamin C and even 100 times more than their intake of carotenoids and vitamin E [6]. New studies suggest that consuming polyphenols may improve human health through many mechanisms, which could make them peculiar therapeutic targets for numerous illnesses [7-10].

According to reports, the small intestine does not absorb the majority of the consumed dietary polyphenol, but the gut bacteria may collect and comprehensively metabolize the unabsorbed portions in the large intestine [11]. The gut microbiota, mainly made up of bacteria, viruses, fungi, protozoa, and archaea, is a rich and ample microbial community that lives in the human intestine, an intricate system [12]. The gut microbiota significantly influences the host's physiology. It is commonly known that the gut microbiota and the host have a close, symbiotic interaction. This link is intricate and multifaceted, influencing the gut-lung, gut-skin, gut-brain, gut-muscle, and gut-adipose tissue axis, among other things (13-16). Because of the increasing evidence linking the gut microbiota's composition and activity to a range of health and disease states, the scientific community is increasingly focusing on the microbiota as a critical determinant of health and homeostasis [17]. The host's defense against infections is greatly aided by the gut microbiota's interactions with the immune system. A few examples of these mechanisms are the synthesis, absorption, and metabolism of a variety of nutrients; changes to the bioavailability of various dietary molecules, such as vitamins and specific organic compounds like polyphenols; and host defense against pathogens through competitive exclusion and modulation

of immune cell activity, thus actively participating in the immune system's functioning [18, 19].

As a result, gut bacteria are essential for the biotransformation and structure conversion of the original polyphenolic into easily absorbed, low-molecular-weight metabolites that support host health. However, not much is now understood about the potential relationship between gut microorganisms, host health, and dietary polyphenols. Through associations between gut microbial composition and health status, studies done within the last ten years have demonstrated the significant impact of gut microbiota on human health [20]. Examining the relationships between these entities is essential because of the gut microbiota's crucial involvement in food metabolism and absorption as well as the possibility that consuming polyphenols may vary the gut microbiome. Clarifying the processes behind the health advantages of polyphenols and suggesting new therapeutic uses involve an understanding of these interactions [21].

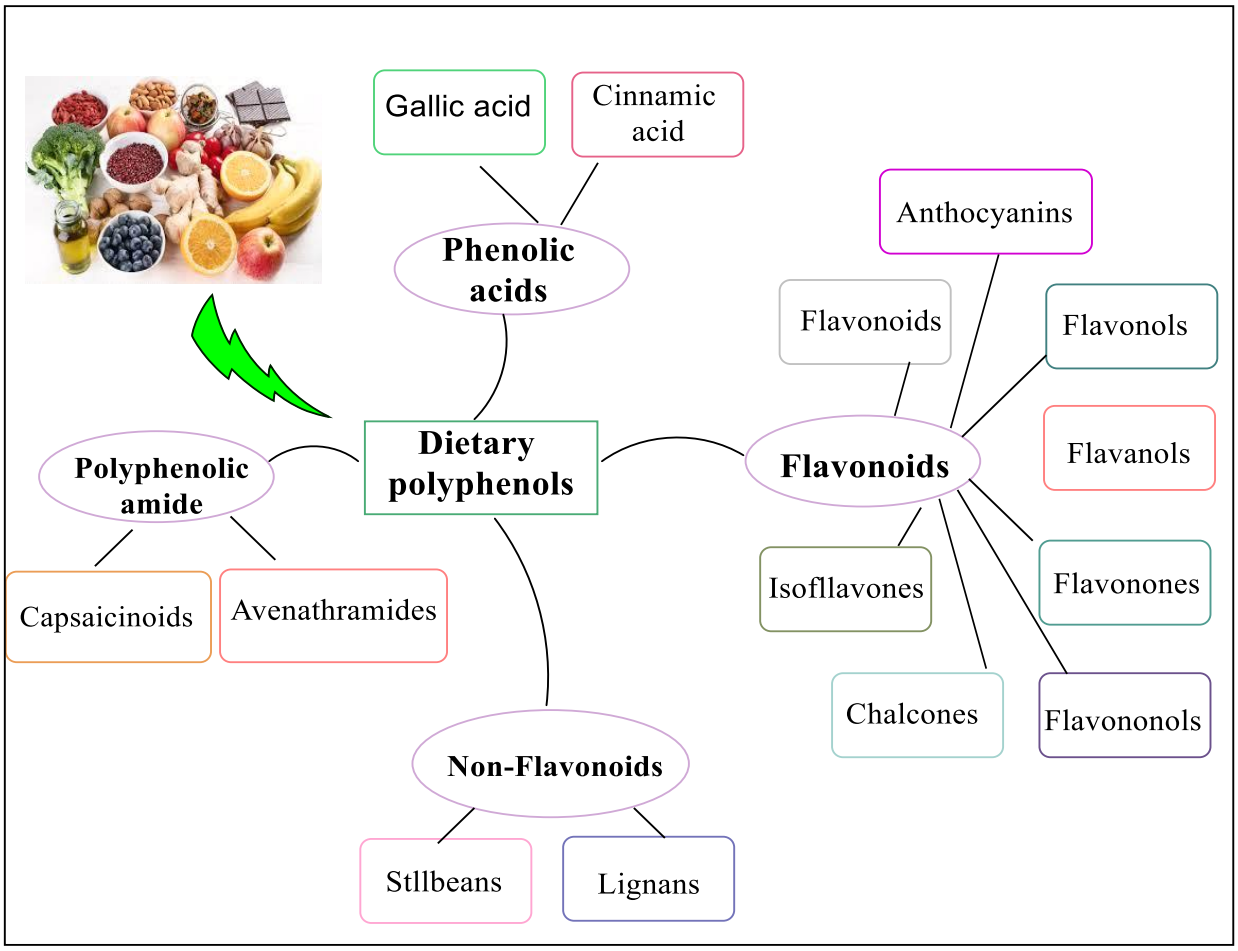

Fig. 1. Dietary Polyphenols and their types

Polyphenols, Gut Microbiota and Health

Dietary Polyphenols and Their Sources: One of the most prevalent and plentiful naturally occurring compounds found in plants is dietary polyphenols. Currently, dietary polyphenols are categorized into four groups on the basis of their structure: polyphenolic amide, flavonoids (the largest subclass of polyphenols), phenolic acids, and other non-flavonoids (Figure 1). Phenolic acids are further classified n two classes based upon their C1–C6 and C3–C6 backbones: benzoic acid (1) and cinnamic acid (2) derivatives [22]. Chalcones (3), flavonoids (4), flavanones (5), isoflavones (6), flavanonols (7), flavonols (8), and many more are examples of flavonoids [23]. N-containing functional substituents are found in polyphenolic amides capsaicinoids (9) and avenanthramides (10) are two examples. The two main non-flavonoids are stilbenes (12) and lignans (13). Other non-flavonoid polyphenols that are thought to be significant for human health include curcumin, ellagic acid and its derivatives, resveratrol, and others, such as phenolic acids, flavonoids, and phenolic amides. They are divided into phenolic monomers and polymerised polyphenols because of the varying amounts of phenolic hydroxyl

groups in their chemical structures. Both flavonoids and non-flavonoids are phenolic monomers. Two benzene rings are joined through a linear three-carbon chain in the former, involving a common carbon skeleton of diphenyl propane, whereas the vinyl group connects the two benzene rings in the latter [24]. Monomers called tannins polymerise oligomers or polymers to form polymeric polyphenols. Fruits, vegetables, honey, beans, coffee, cereals, tea, and red wine are the primary sources of dietary polyphenols, but polyphenols are also found in many other foods in nature. The phenolic acids that are most commonly found in food are specifically ferulic acid and caffeic acid. Ferulic acid is mostly found in rice bran, wheat bran, and other cereals, whereas caffeine is found in large quantities in vegetables, fruits, and coffee. Onions are a common source of quercetin, the most prevalent flavonoid. Catechins (11), also known as flavanols or flavan-3-ols, are found in large quantities in lotus root, chocolate, and red wine. The leguminous family of plants contains the majority of isoflavones. Plants mostly include glycosidic forms of anthocyanidins, which are often referred to as anthocyanins [25] (Figure 2).

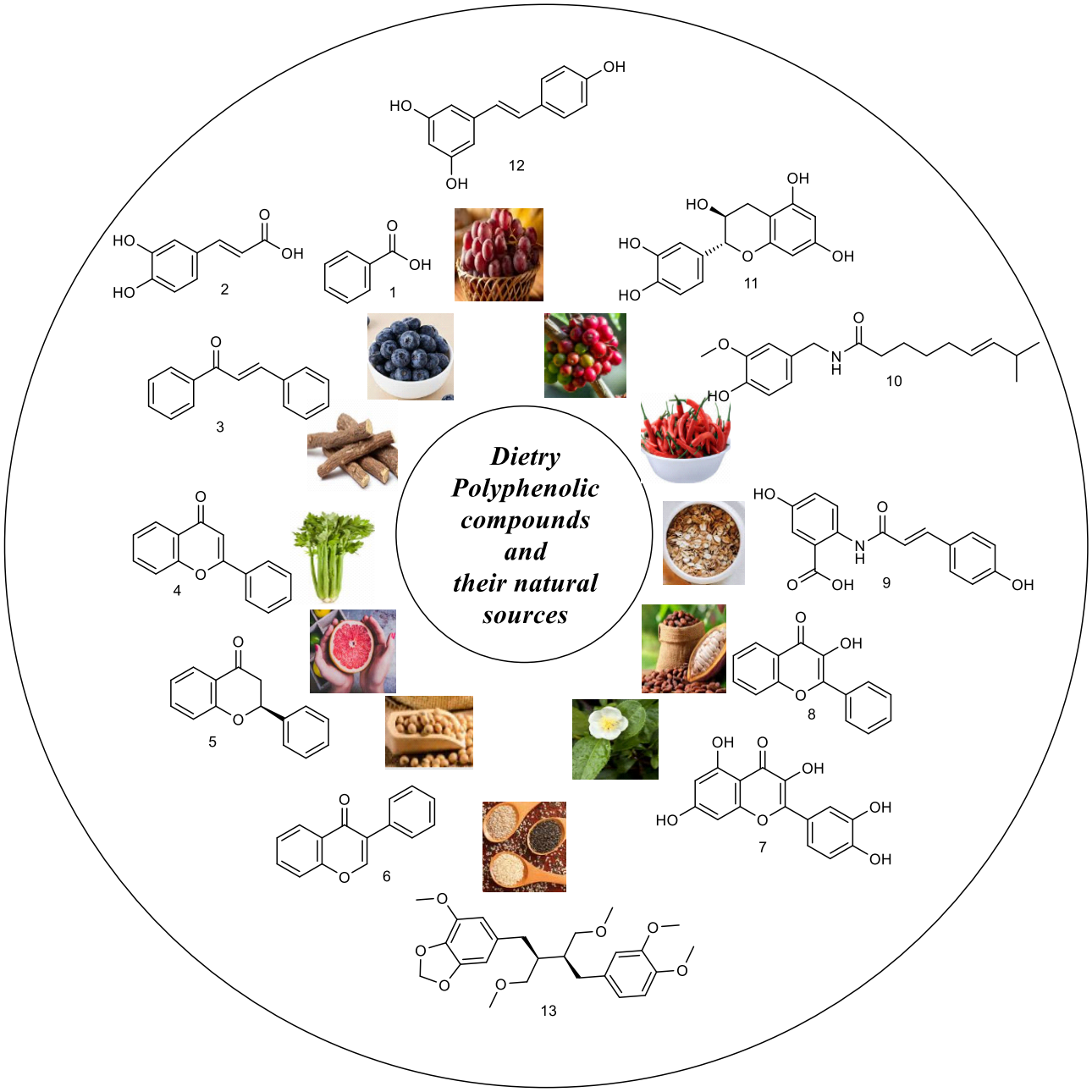

Fig. 2. Dietary phytochemicals and their sources

The Gut Microbiota and its Involvement in Host Health: Approximately 1014 metabolically active bacteria live in the human gastrointestinal (GI) tract [26]. A few numbers of bacterial phyla, including Firmicutes, Bacteroidota [27], which make up approximately 90% of the GI microbiota, Verrucomicrobia, Proteobacteria, and, Actinobacteria are the primary representatives of the gut microbiota [28]. With over 250 species, Firmicutes is the biggest phylum in humans and animals, despite significant inter-individual variability [29]. Additionally, there are about 20 genera in the phylum Bacteroidota, with the most common being the genus Bacteroides [29]. Several probiotics have been found from the phylum Actinobacteria, which includes the species Bifidobacterium, is less frequently found to be dominant and makes up only 5% of all bacteria [30]. Lastly, the genus Akkermansia spp., which is found in small amounts (3–5%) and is currently regarded as a next-generation probiotic, is a member of the phylum Verrucomicrobia [31]. The gut microbiota typically encodes 40 times as many genes as its human host [32], giving it a greater metabolic capability that is primarily focused on the breakdown of intricate substances obtained by nutrition.

The gut microbiota, the "second largest gene pool" in the body, is made up of the symbiotic and pathogenic bacteria that reside in our digestive tracts [33]. Along with the main representative groups, Bacteroidetes, Actinobacteria, Myxococcus, Proteobacteria, and Firmicutes, the gut microbiome contains more than 1,200 different species of bacteria [34]. The activities of the metabolites of the gut microbiota can prevent and control most illnesses. Intestinal microbes are essential for preserving the balance of bone health because they affect host metabolism, immune response, hormone release, and the gut-brain axis [25, 26]. These combinations may result in osteoporosis.

The Effects of Dietary Polyphenols and Gut Bacteria on Host Health: Through a mutually beneficial connection of the gut microbiota with the host preserve the intestine's normal physiological function and morphology. The gut microbiota produces short-chain fatty acids and other metabolites that control host health in addition to acting as a link between the host and the diet in the digestion of dietary food complexes. Due to the presence of thousands of genes used for the digestion of complex carbohydrates, the gut microbiota is particularly used to break down the plant components [35] (figure 3).

According to studies, the majority of polyphenols (90–95% of the total intake) are transferred to the human large intestine, whereas the small intestine absorbs a small percentage (5–10%) of polyphenols [36]. Dietary polyphenols have the ability to change the makeup of gut microbes, and the gut microbiota can also increase the bioavailability of polyphenols by converting them into bioavailable metabolites. In addition to glycans, the gut microbiota converts xenobiotics, ferments and synthesize proteins and host's bile acids, to provide the body vital vitamins [37, 38]. Short-chain fatty acids (SCFA, mostly acetate, propionate, and butyrate), indoles, neurotransmitters, and gasotransmitters (ex. H2S, NO) are among the advantageous bacterial metabolites that are formed as a result of this high activity [39]. As discussed earlier, the SCFA are closely related to immunological signalling, fat storage, insulin response, and energy balance [40, 41]. Among the SCFA, butyrate stimulates dendritic cell development, inhibits proinflammatory effectors in macrophages, and strengthens the intestinal mucosal barrier [42, 43]. Furthermore, detrimental metabolites such pcresol, p-tyramine, trimethylamine-N-oxide, and several secondary bile acids can also be produced by gut microbial activity [44, 45].

Furthermore, polyphenols encourage the formation of good bacteria in the stomach by acting as a "prebiotic." Although the effects of different plant polyphenols on the gut microbiota can differ, most of them generally increase the growth of good bacteria [46, 47]. It should be noted that the majority of plant polyphenols have health benefits that come from a "two-way interaction" with intestinal microbes.

The ability of some bacterial phylotypes to trigger advantageous immune responses and reduce the severity of inflammatory disorders has been demonstrated in numerous research. In the cases of obesity and ulcerative colitis [48-51]. Intestinal inflammation and metabolic abnormalities are reduced by *Lactobacilli* and *Bifidobacteria* species. The intestinal inflammation is reduced by reducing the levels of plasma proinflammatory cytokines, for example, some probiotic strains, like L. plantarum WCFS [49]. A. muciniphila, B. thetaiotaomicron, and F. prausnitzii are among the other pertinent microorganisms that are thought to be next-generation probiotics. They are closely interacting with the host's immune system and show positive effects on the host [52-54].

Inflammatory bowel disease IBD: IBD is a collection of recurring and long-term inflammatory diseases of the colon and intestines. These diseases need to have their symptoms managed for the rest of one's life because there is no known treatment. Numerous factors, such as surroundings, genetic predisposition, intestinal dysbiosis, and immunological dysregulation, contribute to the etiology of IBD. Urban living, tonsillectomy, smoking, appendectomy, antibiotic use, vitamin D deficiency, oral contraceptive use, poor diets, and enterohepatic Helicobacter species that are not Helicobacter pylori-like are environmental variables linked to an increased risk of IBD [55, 56].

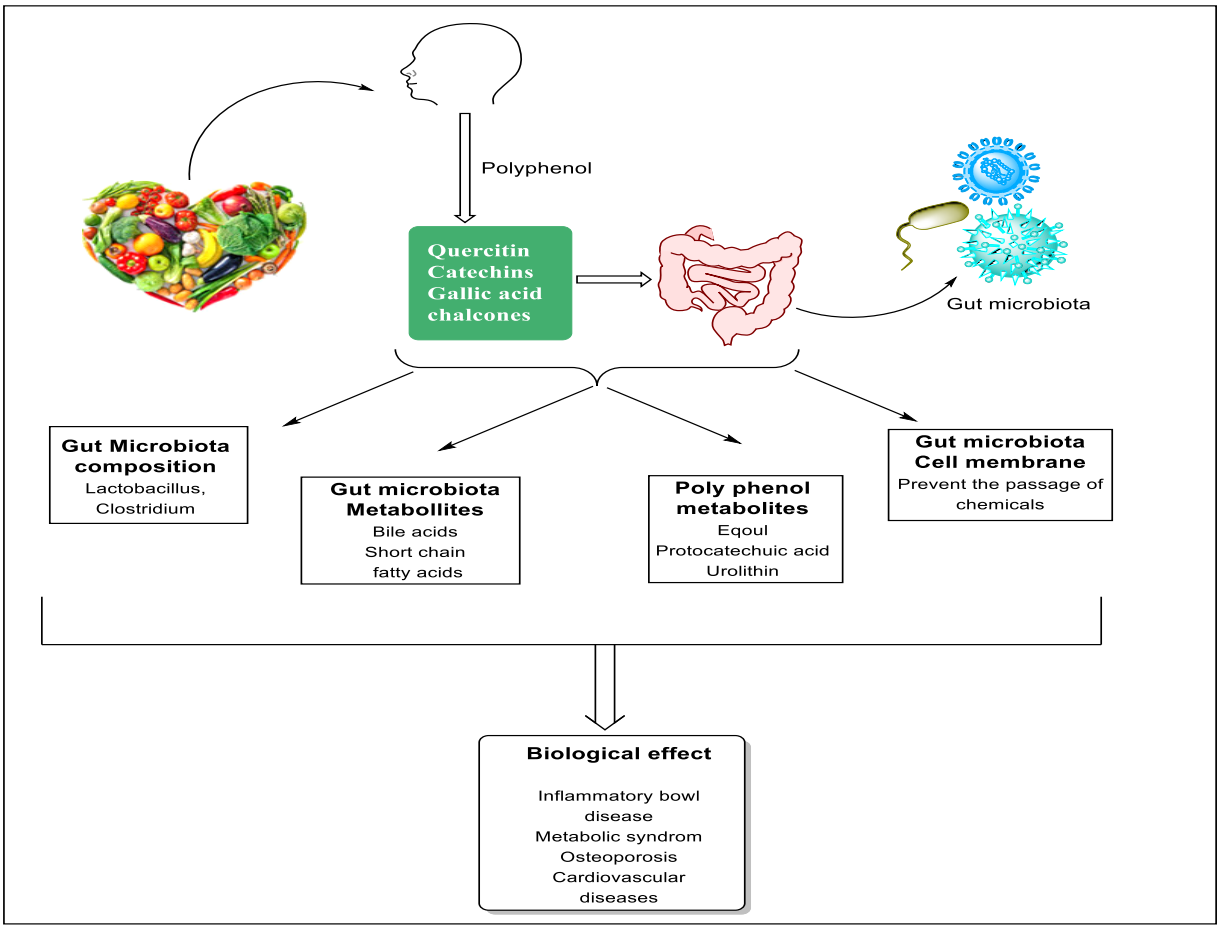

Fig. 3. Polyphenolic compounds-Gut microbiota interactions

Gut dysbiosis, which encompasses any alteration in the microbial composition or bowel eubiosis, is one of the variables that contribute to the development of IBD. The microbiota in unhealthy individuals maintains gut homeostasis by digesting indigestible polysaccharides, producing SCFA, synthesizing certain vitamins, providing energy, protecting the intestinal mucosa, and suppressing pathogenic microorganisms. Firmicutes, Actinobacteria, Bacteroidetes, and Proteobacteria comprise around 90% of the significant human gut bacteria [57]. A reduction in variety, an increase in pathogens, and a loss of good bacteria are the three forms of gut dysbiosis. These three forms of dysbiosis typically coexist [58]. Type-2 diabetes, obesity [59] atherosclerosis [60], and dysbiosis of the gut have all been linked to the development of these conditions [61] Patients with IBD typically have a less diverse gut microbiome [62]. The two factors that are constantly observed in gut dysbiosis in IBD patients are the increase in Proteobacteria and a decrease in Bacteroidetes and Firmicutes [63,64].

In patients with IBD, polyphenols improved the diversity of gut microbiota [65], boosted beneficial bacteria, decreased dangerous bacteria, and reduced pro-inflammatory cytokine levels [66]. Polyphenols have been shown to preserve the intestinal barrier, inhibit the production and release of inflammatory cytokines, and stop colon shortening [67]. The most often used in vitro models for IBD research were Caco-2, HT-29, and CCD18-Co cells generated from human colons [68–70]. In vitro studies showed that polyphenols reduced the expression of cytokines while enriching tight junction proteins in intestinal epithelial cells or monolayers [71]. Anaerobic fermentation tests showed that the gut microbiota breaks down polyphenols and that polyphenols promote good bacteria and inhibit bad bacteria [72].

Certain microbial metabolites of polyphenols have been demonstrated to be helpful in the management of IBD. Following four days of treatment with 4% DSS water to induce colitis, male Fischer 344 rats were fed a supplemented diet of hydrocaffeic acid for eighteen days at a rate of 50 mg/kg/day. Hydrocaffeic acid is one of the primary metabolites of caffeic acid and chlorogenic acid in the colon that are created by gut microorganisms. The results demonstrated that hydrocaffeic acid reduced colitis by reducing the production of inflammatory cytokines such as TNF-α and IL-8.90. In another research, urolithin A, a product of ellagic acid produced

by gut microbes, enhanced tight junction proteins in HT-29 cells [73]. Three 4-dihydroxyphenylpropionic acid (14) and three-dihydroxyphenylacetic acid (15) are microbial metabolites of several polyphenols. These metabolites significantly decreased the production of pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 at a concentration of 1 μM in LPS-stimulated peripheral blood mononuclear cells isolated from healthy persons, indicating their potential to treat IBD [74]. These studies provided valuable insights into the bioactivities of polyphenol microbial metabolites for the treatment of IBD. Eubacterium and Clostridium are the two main genera in the phylum Firmicutes that have the ability to catabolize flavonols, flavanones, and flavan-3-ols. Numerous species, such as Enterococcus, Lactobacillus, and Bacteroide, are involved in the metabolism of isoflavone [75].

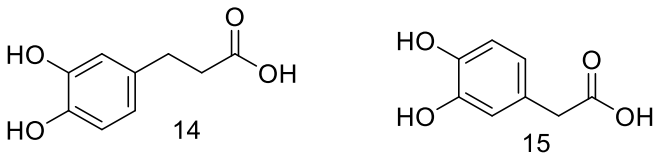

Fig. 4. Polyphenol metabolites

Metabolic syndrome: Metabolic syndrome (MetS) is the term used to describe the co-occurrence of multiplex and linked risk factors for type 2 diabetes and atherosclerotic cardiovascular disease (ASCVD) [76]. Insulin resistance, poor glucose tolerance, hyperinsulinism, obesity, prothrombosis, hypertension, and atherogenic dyslipidemia are additional co-occurring conditions associated with MetS [77]. Pro-inflammatory states, polycystic ovarian syndrome, oxidative stress, hepatosteatosis and non-alcoholic fatty liver disease, hyperandrogenism, vascular dementia, and Alzheimer's disease are among the many clinical diseases that have been linked to MetS in recent studies [78, 79]. Different metabolic syndrome components have been linked to an elevated risk of cardiac mortality [80]. MetS and its constituents are connected to both mortality and the development of cancer, including pancreatic and colon-rectal cancer [81].

Hyperglycemia, hypertension, dyslipidemia, and insulin resistance are some of the etiologies of metabolic syndrome, which increase the risk of various diseases such as diabetes, obesity, and cardiovascular events [76-78]. Research demonstrates that intricate relationships between nutrition and genetic modification are a real contributing factor to the development of persistent low-grade inflammation. Oxidative stress and this kind of inflammation are important components of the underlying MetS linked to chronic illnesses. The positive impact of polyphenols on the management of metabolic diseases is an important topic that draws the attention of researchers. Modifying the microbiota is one of the mechanisms by which the polyphenols show anti-obesity and antidiabetic effects [82].

Studies have shown that diets high in polyphenols encourage rats' gastrointestinal Bacteroidetes species to become more prevalent [83], which is linked to an enhanced ability to break down glycans. Additionally, cranberry extract rich in polyphenols has been utilized to stop rats from developing obesity and belly fat due to a high-fructose, high-sucrose diet. Additionally, cranberry extract therapy reduces the production of triglycerides, inhibits hepatic inflammation, and so improves insulin sensitivity. Grape polyphenol treatment has been shown to significantly alter the makeup of the gut microbial community in rats on a high-fat diet, including reducing the ratio of Firmicutes to Bacteroidetes [84]. Additionally, it has been demonstrated that giving mice grape polyphenols stimulates the growth of Akkermansia muciniphila, and these modifications have been found to shield mice against the harmful effects of a high-fat diet [85]. Moreover, procyanidin (16) administration has been shown to protect against obesity and related health risks. Administration of this chemical decreased obesity gain, improved dyslipidemia, and boosted energy expenditure. Procyanidin-treated mice lost 7% of their body weight after 12 weeks [86]. Procyanidin's anti-obesity effect is linked to intestinal microbiome modulation, which increases β-diversity and Bacteroidetes abundance while decreasing Firmicutes to Bacteroidetes ratio [86].

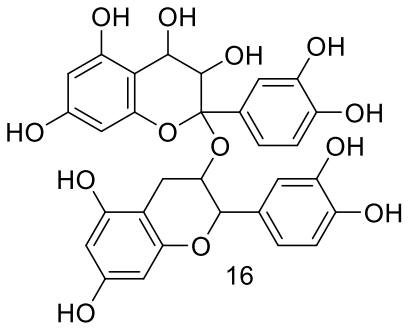

Fig. 5. Structural representation of Procyanidin

One of the main indicators of dysbiosis linked to obesity is an increase in the Firmicutes/Bacteroidetes ratio. Higher Lachnospiraceae species were linked to the development of type 2 diabetes and weight increase in mice, according to another study [87]. The amount of Lachnospiraceae also decreased when procyanidin was supplemented, indicating that procyanidin's anti-obesity effect was accomplished by changing the gut microbiota Lachnospiraceae [87]. By regulating several important genes associated with hepatic cholesterol homeostasis, including increasing the mRNA expression of the farnesoid X receptor and the small heterodimer partner,

decreasing the mRNA levels of 3-hydroxy-3-Methylglutaryl-CoA reductase, and enhancing the mRNA expressions of ATP-binding cassette transporter-1, procyanidins derived from the litchi pericarp reduced elevated cholesterol levels in rats [88].

Osteoporosis: Osteoporosis has emerged among one of the top levels of many chronic disorders, as the population aging continues. Osteoclast upregulation is the main cause of osteoporosis and is characterized by deterioration of bone tissue microstructure and ultimately bone mass loss which is a chronic condition [89]. Osteoblasts are the bone tissue-producing cells that are required for skeletal growth and maintenance [90]. Many in vivo studies have suggested that local oxidative inflammation and hormonal imbalance can affect the equilibrium between osteoclasts and osteogenesis leading to destruction of bone microstructure and reduction in bone strength [91, 92]. The decreased level of osteogenic proliferation and marrow-based mesenchymal stem cells intraosseous angioplasty occurs simultaneously increasing bone fragility and fracture susceptibility [93, 94].

The gut microbiota has the ability to convert apigenin, a flavonoid found in fruits and vegetables, into p-coumaric acid (17). P-coumaric acid possesses a number of anti-inflammatory and antioxidant qualities that can improve human health in general [95]. In a cell line investigation, it has been demonstrated that 4-hydroxycinnamic acid which is also a flavonoid metabolite showed significant anti-inflammatory properties in LPS-stimulated macrophage cells. It has been seen that nitric oxide synthase can be inhibited by 4-hydrocinnamic acid which ultimately lowers the synthesis of nitric oxide (NO). Nitric oxide plays a significant role in producing inflammation. The compound inhibits the enzyme by altering the iNOS pathway in immune cells. In vitro, investigations on rats' femoral tissues have suggested that this compound can affect bone metabolism and increase calcium contents. These findings suggest that the compound has beneficial effects on the treatment of osteoporosis and bone health [96].

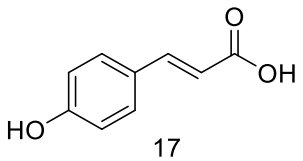

Fig. 6. Apigenin metabolite

According to research, certain gut microbes can convert significant flavonoid daidzein, obtained from soy, to equol (18). This transformation has been associated with improved therapeutic outcomes in those using soy in their diet. For females with osteopenia, ingesting red clover extract (RCE) and probiotics two times per day for a year has been shown to significantly prevent the progression of bone mineral loss due to estrogen shortage.

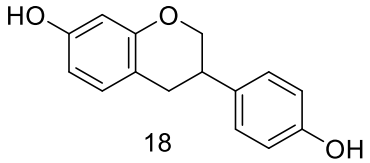

Fig. 7. Structural representation of equol

Phlorizin, a naturally occurring chemical present in numerous fruit trees, is also an ingredient in food [97]. Its constituents are phloretin (19) and phloroglucinol (20). The compound phloretin and its glycosyl derivatives are naturally produced dihydrochalcones present in a variety of plants, vegetables, and fruits such as apples, kumquats, pears, and strawberries [98]. Apple tree leaves were investigated for their osteoprotective potential in female mice with ovariectomized (OVX) C57BL/6 to study its potential against bone loss prevention [99].

The investigators found that the compound altered the ASK-1-MAPK regulatory pathway, leading to the apoptotic gene's transcription. This approach substantially inhibits the absorption of osteoclast caused by estrogen deprivation, indicating phloretin's potential to reduce bone loss [100]. Finally, phloridzin metabolites regulate bone dynamics while strengthening the number of bone minerals and composition.

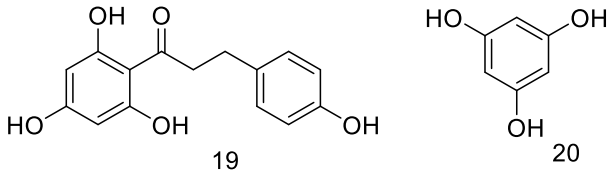

Fig. 8. Chemical constituents of Phlorizin

Another secondary metabolite, "Genistein" (21) present in seeds, legumes, vegetables, and fruits. It refers to the isoflavone family of phytochemicals and has phytoestrogenic properties. Genistein, a plant estrogen, can replicate the chemical structure and activity of 17b-estradiol, an estrogen found in animals. Many investigations have found that genistein taking in higher amounts can lead to an increased bone mineral density (BMD) in females in the postmenopausal phase. The specific methods by which genistein affects the condition of bones are still being investigated. Genistein is thought to affect the estrogen receptor pathway and exhibit estrogenic actions on bone tissue, perhaps improving bone density. Indeed, more study, including future research and medical investigation, is required to acquire a more complete knowledge about the relationship between genistein use and its detrimental osteoprotective impact in various age populations [101]. In tests on

ovariectomized mice, an oral dose of 10 mg/kg for 12 weeks for genistein was demonstrated to increase the formation of bone while inhibiting bone resorption [102].

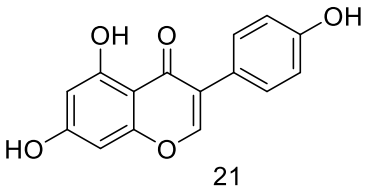

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Fig. 9. Phytoestrogen genistein

Diabetes Mellitus: Numerous animal and human studies have demonstrated that phytochemicals such as resveratrol, quercetin epicatechin, and chlorogenic acid (CGA) present a variety of health benefits to diabetes mellitus (DM) patients [103]. Phenolic chemicals can control high blood sugar levels and insulin resistance. Furthermore, these phytochemicals are proven to exhibit systemic anti-inflammatory and antioxidant activities, as well as enhance microbiota health in the gut, which may be advantageous for the prevention and management of diabetes and its related illnesses [104].

Diabetes-associated complications such as diabetic nephropathy (DN) can be cured by the action of gut microbiota and phytochemicals. Many clinical and preclinical investigations have suggested that gut microbiota and its action on secondary metabolites have been linked to the treatment of DN development [105].

Short-chain fatty acids (SCFAs), generated by gut bacteria, have been shown to slow the course of diabetes problems [106]. It was demonstrated in investigations that mice were given a diet containing or excluding resveratrol (0.4%) for 84 days. This phenolic compound administration was found to ease DN progression and reduce tubulointerstitial fibrosis. Other preclinical research might show that resveratrol can change microbiota dysbiosis, defined by the proliferation of SCFA-producing bacteria such as Faecalibaculum and Lactobacillus, resulting in elevated amounts of SCFA (especially acetic acid in human waste [107, 108]. These data have shown that resveratrol-stimulated alteration in the gut microbiota has a significant character in its mechanism of action in DN supporting the gut-kidney axis.

Chlorogenic acid (22) can decrease the synthesis of triglyceride (TG) and the transport of fatty acid has been linked to improved glycemic tolerance, possibly by stimulating hepatic lipolysis and gluconeogenesis [105]. Yang et al. [106] investigated the efficiency of CGA's protective mechanism against hyperglycemia by systemically delivering CGA or metformin to diabetic mice. By upregulating the expression of CPT1a (carnitine palmitoyltransferase), ACOX1 (acyl-CoA oxidase), ATGL (adipose triglyceride lipase), and HSL (hormone-sensitive lipase), exogenous CGA administration was observed to decrease hepatic lipid content. However, the antilipidemic advantages seem advantageous.

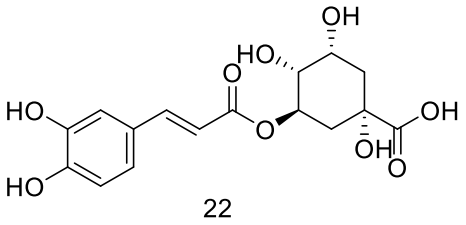

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Fig. 10. Structure of Chlorogenic acid

Preclinical investigations have found that phytochemicals like CGA can restore the expression of antioxidant enzymes like SOD1, SOD2, and GPX1 and inflammatory genes like TNF-α, IL-1β, IL-6, and IL-10, in diabetic mice [106]. Similarly, these examinations indicate that quercetin may protect rats from peripheral diabetic neuropathy [108] by enhancing microbiota health and lowering oxidative stress.

When rats with Streptozotocin-induced peripheral diabetic neuropathy are given quercetin, their levels of reactive oxygen species and dangerous microorganisms like Clostridium perfringens and E. coli may decrease. Additionally, it could raise the levels of good bacteria like Bifidobacterium and Lactobacillus [109]. Other preclinical and clinical studies have indicated that phytochemicals like CGA can increase the number of Lactobacillus, which can increase the production of GLP-1 (glucagon-like peptide-1) and insulinotropic polypeptides. This could result in increased muscle absorption of glucose and increased hepatic uptake of glucose from the bloodstream. Fort diabetic individuals experienced an improvement in their glycemic response, decreased fetuin-A levels, and higher SIRT1 expression after eight weeks of *Lactobacillus casei* treatment as compared to the placebo group. Furthermore, anthropometric characteristics, blood levels of insulin, and the HOMA-IR index were enhanced [110]. In addition, the healthy food intervention group had a considerably greater serum antioxidant activity than the individuals with no such food intakes. Thus, it is proposed that phytochemicals may help diabetes by supplementing diets with such kinds of dietary food [111]. Other clinical investigations looked into the benefits of a dietary intake that included nutritional food high in polyphenols, digestible fiber, high-quality vegetable protein, and low in glucose. The nutritional food included in the dietary portfolio may include, chia seeds, inulin, pear, soy, omega-3 3-fatty acids, dehydrated cactus, and soy proteins. In patients with type 2 diabetes, all of these substances have been studied for their potential to improve gut microbiota, reduce biochemical

abnormalities, and prevent metabolic endotoxemia brought on by microbiota dysbiosis [111].

Cardiovascular Disease: In contrast, several phenolic substances, including flavanols and resveratrol have been investigated for potential positive anti-inflammatory and cardiovascular properties in clinical and preclinical investigations [112, 113]. Initial findings suggest that phenolic molecules can decrease oxidative stress and inflammation, limiting plaque development in arteries and lowering the chance of heart disease. On the contrary, the digestive system has been identified as a target tissue for HFD-induced systemic inflammation, resulting in higher intestinal permeability and inflammation [114-116]. In preclinical studies, resveratrol (RSV) supplementation has been shown to limit the absorption of FITC-dextran and decrease blood levels of TNF-1α, IL-6, IL-2, and LPS.

In addition, resveratrol intake may reduce MCP-1 expression in white adipose tissue and jejunum of HFD mice. These findings indicate the high level of intestinal barrier that leads to inflammation [117]. Moreover, the favorable impact of RSV on inflammation of the gastrointestinal tract and intestinal barrier integrity can be stimulated by a healthier gut microbiota concentration. Particularly, resveratrol has been shown in preclinical studies to improve gut bacteria composition by regulating the abundance of the Allobaculum, Bacteroides, and Blautia genera. All of these produce short-chain fatty acids and have a deteriorated relationship with inflammation, obesity, insulin resistance, and other metabolic illnesses. Desulfovibrio, which frequently rises following a diet with high fat concentration, can be lowered with a diet containing a high amount of probiotics[118].

Another group of Parabacteroides which act as commensals prove to be incredibly effective in the gastrointestinal tract. Quercetin, a naturally occurring flavonoid, also protects against heart disease. This has been proven by clinical and preclinical tests to cause vasodilation in solitary rat arteries. Quercetin was found to lower high systolic pressure in laboratory tests utilizing hypertensive rat models. The rats were fed with a high-sucrose diet as well as a salt-sensitive angiotensin-induced diet. The same kind of results were reported in a clinical trial that showed that supplemental intake with epigallocatechin-3-gallate and resveratrol (EGCG+RES) for 12 weeks might influence the composition of intestinal microbiota in men but not in women. Also, the fundamental microorganism's composition estimated increased fat burning after EGCG+RES supplementation. The research suggests that RSV and RSV-induced gut microbiota modification have the potential to be innovative therapeutic options for managing inflammation and obesity. There are clinical findings that phytochemicals help prevent and treat cardiometabolic illness. However, further preclinical and clinical investigations are needed to show that polyphenol intake modulates the gut microbiota as an intervention or preventive tool for cardiometabolic diseases [119].

Conclusion: Research suggests that dietary polyphenols may improve gut health by interacting with the bacteria. Numerous studies, both in vitro and in vivo, suggested a link between supplementary phenolic compounds and gut microbiota. The mode of action may involve altering gut microbiota composition, producing gut microbiota metabolites, modulating intestinal barrier function, and biotransformation of dietary phytochemicals. Understanding the interactions across polyphenols and gut microbiota, including metabolic pathways, is crucial for developing potential targets for human health in the future.

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