Advances in Nutrition 16 (2025) 100376

American Society for Nutrition
Excellence in Nutrition Research and Practice

Advances in Nutrition
AN INTERNATIONAL REVIEW JOURNAL
journal homepage: https://advances.nutrition.org/

Review

Promotion of Healthy Aging Through the Nexus of Gut Microbiota and Dietary Phytochemicals

Laura M Beaver [1,2], Paige E Jamieson [1,2], Carmen P Wong [1,2], Mahak Hosseinikia [1,2], Jan F Stevens [1,3], Emily Ho [1,2,*]

[1] *Linus Pauling Institute, Oregon State University, Corvallis, OR, United States;* [2] *School of Nutrition and Public Health, Oregon State University, Corvallis, OR, United States;* [3] *Department of Pharmaceutical Sciences, Oregon State University, Corvallis, Oregon, United States*

A B S T R A C T

Aging is associated with the decline of tissue and cellular functions, which can promote the development of age-related diseases like cancer, cardiovascular disease, neurodegeneration, and disorders of the musculoskeletal and immune systems. Healthspan is the length of time an individual is in good health and free from chronic diseases and disabilities associated with aging. Two modifiable factors that can influence healthspan, promote healthy aging, and prevent the development of age-related diseases, are diet and microbiota in the gastrointestinal tract (gut microbiota). This review will discuss how dietary phytochemicals and gut microbiota can work in concert to promote a healthy gut and healthy aging. First, an overview is provided of how the gut microbiota influences healthy aging through its impact on gut barrier integrity, immune function, mitochondria function, and oxidative stress. Next, the mechanisms by which phytochemicals effect gut health, inflammation, and nurture a diverse and healthy microbial composition are discussed. Lastly, we discuss how the gut microbiota can directly influence health by producing bioactive metabolites from phytochemicals in food like urolithin A, equol, hesperetin, and sulforaphane. These and other phytochemical-derived microbial metabolites that may promote healthspan are discussed. Importantly, an individual's capacity to produce health-promoting microbial metabolites from cruciferous vegetables, berries, nuts, citrus, and soy products will be dependent on the specific bacteria present in the individual's gut.

Keywords: diet, dysbiosis, gut health, gut microbiome, healthspan, lifespan, microbial metabolite, phytochemicals

Statement of significance

This comprehensive and novel review highlights the critical connection between dietary phytochemicals, gut microbiota, and healthy aging. In particular, the review focuses crucial insights on how specific phytochemicals and gut microbiota interact to generate unique plant-derived microbial metabolites that have profound potential to positively influence healthspan by preventing or delaying the development of age-related diseases.

Introduction: Interconnections Between Diet, Gut Microbiota, and Aging

Aging is associated with changes in molecular, cellular, and systemic processes that leads to impaired function and progressive deterioration in health. The hallmarks of aging include deregulated nutrient sensing, chronic inflammation, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and dysbiosis. Dysbiosis is characterized by an imbalance in gut microbial composition and changes in microbial metabolite profile in the gastrointestinal (GI) tract [1]. Dysbiosis interacts closely with other hallmarks of aging and plays a significant role in age-related chronic diseases [2]. Slowing the progression of the hallmarks of aging, such as gut dysbiosis, is an important

Abbreviations: AhR, aryl hydrocarbon receptor; BBB, blood–brain barrier; GI, gastrointestinal; IKK, IκB kinase; Keap1, kelch-like ECH-associated protein 1; LCA, lithocholic acid; NF-κB, nuclear factor kappa B; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; SCFA, short-chain fatty acid; SFN, sulforaphane; UM, urolithin metabotype; Uro, urolithin.

* Corresponding author. *E-mail address:* Emily.Ho@oregonstate.edu (E. Ho).

https://doi.org/10.1016/j.advnut.2025.100376
Received 25 October 2024; Received in revised form 20 December 2024; Accepted 14 January 2025; Available online 19 January 2025

strategy to improve both lifespan and healthspan (the length of time an individual is in good health and free from chronic diseases and disabilities of aging) [3]. Healthy centenarians, individuals who successfully achieved a long healthspan, have gut microbial signatures that are more consistent with microbial signatures found in young populations that lack dysbiosis and produces health-promoting metabolites [4,5]. A person's diet is one of the most promising and practical strategies to intervene in the aging process by affecting the microbiota and the hallmarks of aging [6,7]. Consumption of a healthy diet is associated with a reduction in age-associated diseases like cancer, neurodegenerative, cardiovascular, and metabolic diseases and has been proposed to decelerate the aging process and promote healthy gut microbiota [8,9].

Reducing the intake of excess sugar and unhealthy fats, as well as providing essential nutrients and fiber are important ways that a healthy diet promotes health aging [8,10]. Healthy diets are high in plant-based foods like legumes, whole grains, nuts, fruits, vegetables, and herbs, which are a rich source of phytochemicals. Phytochemicals are defined as nonnutritive bioactive compounds produced by plants and typically give plants their color, flavor, and smell [9]. Phytochemicals can promote a long healthspan and healthy gut microbiota [8,11]. Many dietary phytochemicals, and in particularly polyphenols, can be metabolized by gut microbiota to create new bioactive microbial metabolites [12]. Importantly, both phytochemicals from the diet and their microbial metabolites can impact local tissues, making them particularly suited for improving gut health [13].

In this review, we explore the interconnection between dietary phytochemicals and gut microbiota in promoting both gut health and healthy aging and explore how microbial metabolites may prevent or delay the development of age-related diseases including cancer, neurodegeneration, cardiovascular and metabolic diseases, and disorders of the musculoskeletal and immune systems (Figure 1). The influence of gut microbiota on the development of age-related diseases, through its impact on gut barrier integrity, immune function, mitochondria function, and oxidative stress are discussed. As the GI tract is at the intersection where diet and the microbiota converge, we also discuss the mechanisms by which phytochemicals affect gut health, inflammation, gut microbiota balance, and diversities. This may be especially important in mitigating age-related chronic inflammation, which is one of the underlying mechanisms that contributes to age-related diseases. We also provide insights on the role microbial metabolites play in gut health and healthspan. Microbial metabolites can be derived from dietary sources (like phytochemicals or fiber), host metabolites, or secreted directly from bacteria. In this review, we will discuss two categories of microbial metabolites produced in the intestine that are at the nexus between gut microbiota and dietary phytochemicals. The first category can be derived from a number of sources and include short-chain fatty acids (SCFAs), secondary bile acids, and indoles produced from tryptophan. These metabolites are produced by bacteria and can be modulated indirectly by phytochemicals effects on gut microbiota balance. The second category discussed in detail are compounds produced by bacterial metabolism of phytochemicals (phytochemical-derived like urolithins) (Figure 1). Overall microbial metabolites are a significant and rapidly expanding field, which provide us with novel opportunities to identify new compounds, which may prevent or delay the development of age-related disease like heart attacks, strokes, type 2 diabetes, dementia, sarcopenia, osteoporosis, and cancers.

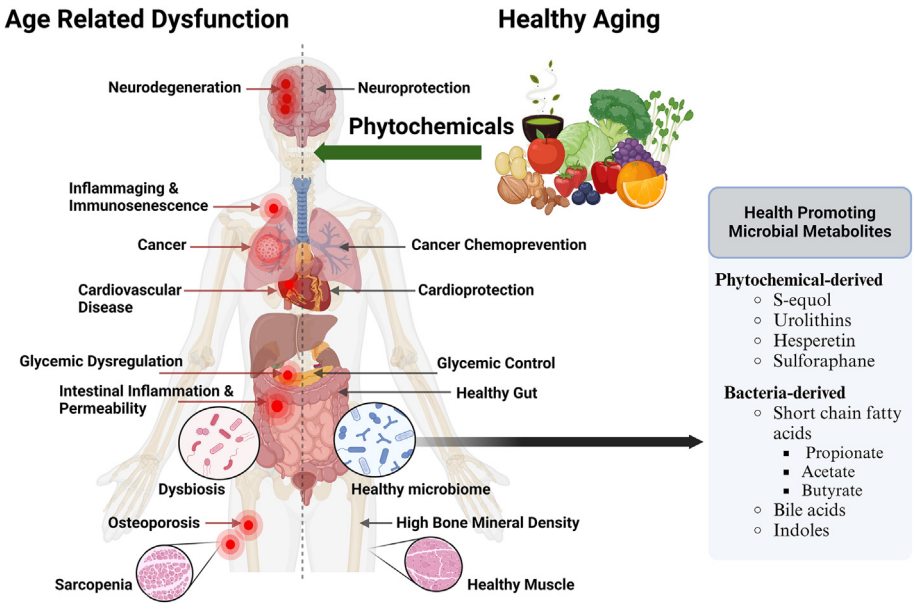

FIGURE 1. Aging is typically associated with cellular and tissue level dysfunction that adversely affects healthspan and lifespan and promotes the development of cancer, osteoporosis, sarcopenia, neurodegeneration, and cardiovascular and metabolic diseases. Consuming foods or supplements with phytochemicals can promote a healthy gastrointestinal tract, which in turn can promote healthy aging. Additionally some bacteria in the gut can produce metabolites that act locally (e.g. improve intestinal barrier function) or are absorbed and act in distant tissues (e.g. brain and muscle) to improve healthspan. Created in BioRender. BioRender.com/a48l667.

Gut Microbiota and Aging

The role of the gut microbiota in health and aging

The human microbiome plays a significant role in aging and health and encompasses a diverse community of microorganisms composed primarily of bacteria but also includes viruses, fungi, and archaea. The gut microbiota serve many important functions to the host, including maintaining intestinal barrier function, protection against exogenous pathogens, and nutrient and drug metabolism (e.g. folate, riboflavin, and vitamin B-12 production) [2]. Beyond the GI tract, microbial metabolites that enter systemic circulation can act as signaling molecules that mediate host-microbiota communications and exert influence and modulate host immune, metabolic, and neurologic function in distant organs. Various interrelated factors influence the composition and function of the gut microbiota, including host genetics, age, diet, medication, health status, as well as physical activity and social/living environment [2]. Age-related dysbiosis is associated with alterations in the composition, diversity, and function of the microbiota. In general, there is reduced microbial diversity, a decrease in dominant commensal taxa and a replacement of other commensals with pathobionts with aging [14]. Although diversity and uniqueness of the gut microbiota are linked to aging, they alone cannot define healthy compared with unhealthy aging [15]. Instead, considering the proportions and relative abundance of health-associated and disease-associated microbial taxa detected in an aging microbiome serve as more accurate predictors of health status [15]. The causal relationship among dysbiosis, aging, and health is difficult to untangle in human studies. Direct evidence connecting dysbiosis with health outcomes were primarily demonstrated using fecal microbiota transplant in animal models, which showed the microbiota plays a causal role in aging, inflammatory disease, cardiometabolic disease, cancer, and neurodegeneration [2,16]. In these studies, disease conditions can be transferred from the host to the recipient solely via replacement of the recipient microbiota. Conversely, fecal transplants from healthy donors can ameliorate disease conditions in the recipients. The functional consequence of dysbiosis include increased intestinal permeability and altered microbial metabolite profiles (loss of beneficial metabolites and the gain of harmful metabolites) that impact both local and systemic inflammation status, host metabolism, and disease risk [2,16]. At the same time, other hallmarks of aging including immune aging, cellular senescence, and mitochondrial dysfunction also have reciprocal relationship with dysbiosis that collectively amplify the intestinal inflammatory response as well as systemic chronic inflammation that contributes to neuroinflammation and age-related diseases (Figure 2). Although bacteria are the most studied members of the gut microbiome and is the focus of this review, there is emerging evidence highlighting the importance of viruses (gut virome) and fungus (gut mycobiome) in maintaining a balanced bacteria community, and play a role in health and longevity [17,18].

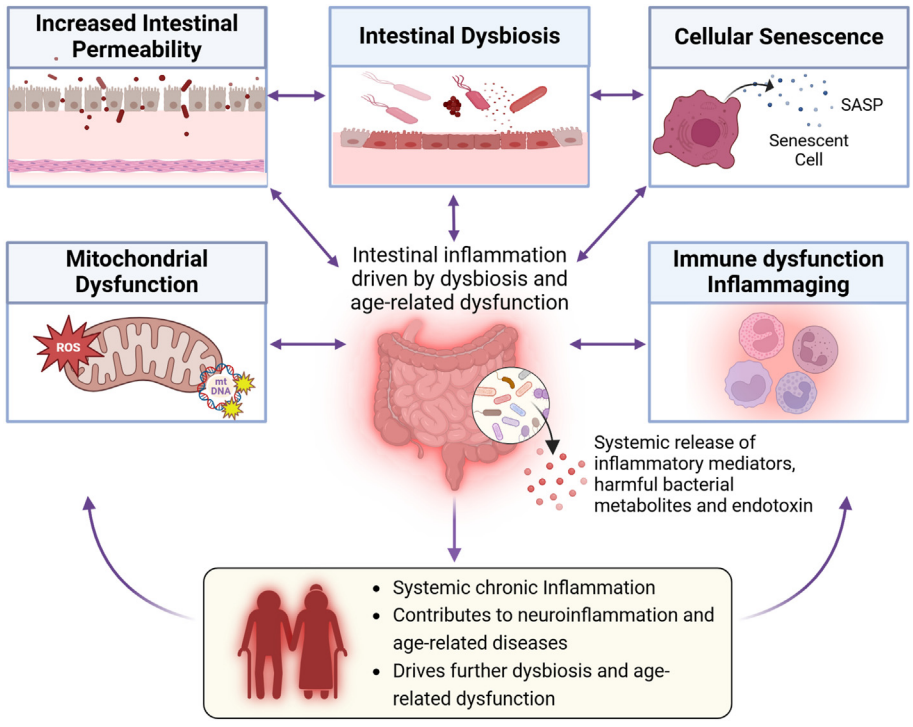

FIGURE 2. The interplay between age-related dysbiosis, intestinal permeability, and other hallmarks of aging that results in local and systemic inflammation. Dysbiosis contributes to increased intestinal permeability, altered microbial metabolite production, and release of microbial products and endotoxin into circulation that contributes to systemic inflammation. At the same time, mitochondrial dysfunction, cellular senescence, and inflammaging trigger local inflammatory response that further drives dysbiosis. Systemic chronic inflammation in turn further amplifies dysbiosis and age-related dysfunction that contributes to neuroinflammation and age-related diseases. Created in BioRender. BioRender.com/y74r211. mtDNA, mitochondrial DNA; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype.

Interplay among dysbiosis, aging, and inflammation

In the gut, the intestinal mucosal barrier acts as a semi-permeable barrier that allows the selective absorption of nutrients and water and protects against pathogens and harmful substances from the external environment [19]. Under healthy conditions, the microbiota protects the mucosal barrier directly by regulating the production and secretion of mucin to maintain the mucus layer, modulating tight junction protein expression, and through the production of microbial metabolites that have downstream targets to maintain gut health (see Key Mechanistic Targets of Dietary Phytochemicals in the Gut section for details) [20]. Changes in microbiota composition can alter the penetrability of the mucus layer and intestinal barrier integrity, resulting in increased intestinal permeability [21]. Aging is associated with gradual deterioration of the intestinal barrier function, where age-related dysbiosis and increased intestinal permeability can lead to local mucosal inflammation and the release of bacterial endotoxin into circulation, which triggers systemic inflammation [22]. Various hallmarks of aging are closely associated with dysbiosis that collectively lead to local and systemic inflammation (Figure 2). Aging of the immune system, in particular inflammaging (age-related chronic inflammation) is associated with increased morbidity and mortality in the elderly and is a risk factor for developing age-related diseases including neurodegenerative diseases and autoimmune diseases [23]. Cellular senescence is a major determinant of inflammaging [24]. Senescent cells of both immune and nonimmune origin acquire an inflammatory senescence-associated secretory phenotype that secretes a host of proinflammatory and immune-modulatory factors that results in systemic inflammation and tissue damage, including senescence-associated secretory phenotype–driven inflammation that increases intestinal permeability and drives dysbiosis [25]. The gut microbiota in turn plays an important role in modulating various aspects of host immunity, including inflammation [23] and is associated with the development of immune disorders where dysregulated inflammatory response plays a role in disease pathogenesis, including multiple sclerosis, rheumatoid arthritis, and type 1 diabetes [26].

Another hallmark of aging is mitochondrial dysfunction, where a progressive decline in mitochondrial function with age is implicated in numerous age-related diseases including neurodegenerative and cardiovascular disorders, diabetes, obesity, and cancer [27]. Mitochondrial dysfunction is attributed to the accumulation of mitochondrial DNA mutations, increased reactive oxygen species (ROS) production, and mitochondrial oxidative stress [28]. In the gut, mitochondrial dysfunction results in intestinal epithelium inflammation and oxygenation, which results in alteration to the microbial composition and the induction and amplification of senescence-induced inflammation [29]. At the same time, the gut microbiota influences mitochondrial function and metabolism in intestinal cells, mediated through bacterial metabolites including SCFAs and secondary bile acids [30]. Decreased SCFA production (e.g. butyrate) due to dysbiosis can lead to altered mitochondrial metabolism and increase oxygenation in the gut and encourage expansion of pathogenic bacteria [31]. Dysbiosis associated with inflammatory bowel disease and colorectal cancer involves both alterations in microbial composition (e.g. depletion of butyrate producers) and microbial metabolites (bile acids and B vitamins) and contributes to mitochondrial dysfunction and disease pathogenesis [32].

Gut microbiota have also been shown to play an important role in the communications between the GI tract and the central nervous system, termed the gut–brain axis, which is also important for healthy aging. Microbiota have been demonstrated to affect memory, cognitive behavior, microglia maturation, and blood–brain barrier (BBB) integrity [33,34]. Alterations in microbial metabolites can influence the gut–brain axis by modulating BBB permeability, neuroinflammation, and oxidative stress in the central nervous system [34]. Age-related chronic inflammation, which is promoted by dysbiosis, extends to neuroinflammation in the central nervous system, and chronic unresolved neuroinflammation can lead to neurodegeneration and promote the development of age-related disease [35]. Dysbiosis is associated with neurodegenerative diseases including Alzheimer disease, Parkinson disease, dementia, moderate cognitive impairment, and amyotrophic lateral sclerosis [36].

In summary, age-related dysbiosis is intimately related to other hallmarks of aging. Increased intestinal permeability and cellular senescence leads to local mucosal inflammation and the release of bacterial endotoxins into the circulation, which triggers systemic inflammation including neuroinflammation. Chronic inflammation and mitochondrial dysfunction can drive further alterations in the microbiota, exacerbate gut permeability, and further amplify the inflammatory response. The importance of microbiota in multiple facets of health, and its involvement in the development and progression of age-related diseases, is unequivocal. Strategies to reset and restore the balance of a healthy microbiota, with the aim of improving gut health, will have great impacts toward promoting healthy aging, and thus, there is great interest in using diet and phytochemicals to promote a healthy microbiota in aging individuals.

Key Mechanistic Targets of Dietary Phytochemicals in the Gut

There are >100,000 known phytochemicals including but not limited to polyphenols, carotenoids, isothiocyanates, alkaloids, phytosterols, and saponins [37,38]. When consumed as part of a diet, phytochemicals have various degrees of bioavailability, which depends on their size, lipophilicity, chemical stability and reactivity, how they are complexed in the matrix of food, and to what extent they are metabolized by gut microbiota. Many phytochemicals, particularly polyphenols, are poorly absorbed; however, this characteristic allows the phytochemicals to reach the large intestine, where they interact with gut microbiota and can be metabolized to create new bioactive microbial metabolites [37,39].

Phytochemical effects on inflammation for gut health

There is a dynamic interplay between the local mucosal immune system and gut microbiota, which balances inhibition of pathogens, promotion of commensal microbes, and prevention of overall bacterial overgrowth [1]. Chronic, unresolved inflammatory processes in the gut can lead to aging-associated dysregulated functions both locally and systemically [19]. Phytochemicals from food and dietary supplements can play an

important role in modulating inflammatory processes as many have well-established anti-inflammatory, antioxidant, and immune-modulatory effects (Figure 3). Many phytochemicals, particularly polyphenols, are colloquially referred to as antioxidants due to their physiochemical properties. Although some phytochemicals have free radical–scavenging capabilities in vitro, it is unlikely that intracellular levels, which rarely reach micromolar concentrations, would be able to compete with the two foremost small-molecule antioxidants, ascorbic acid and glutathione, which are both present in cells at low millimolar concentrations. Instead, the consensus regarding the mechanisms of action for many phytochemicals' antioxidant and anti-inflammatory effects in vivo stem from induction of endogenous immune modulatory and antioxidant defense systems, as well as indirect effects on gut microbiota composition. In this section, we discuss the effects of phytochemicals on transcription signaling pathways involved in inflammatory response and the role of phytochemicals in modulating the structure and function of the gut microbiota.

Effects of phytochemicals on nuclear factor κB

In a healthy gut, the mucosal immune system balances proinflammatory and anti-inflammatory responses, which allows for defense against pathogens, while preventing an overwhelming response to harmless food antigens and commensal microbes. Central to these processes is the transcription factor, nuclear factor kappa B (NF-κB). NF-κB activation leads to induction of a number of proinflammatory genes and results in expression of proinflammatory cytokines, including the common biomarkers of inflammation, tumor necrosis factor alpha (TNF-α) and IL-6. There is convincing evidence that many age-related changes to the gut microbiota are initiated by these inflammatory signaling molecules. For example, old TNF knockout mice do not display the same degree of gut dysbiosis as observed in old wild-type mice [40]. A variety of stimuli can activate NF-κB (e.g. inflammatory cytokines, bacterial endotoxins, and ROS), which involves the enzyme IκB kinase (IKK) phosphorylating the inhibitory subunit, IκB. This leads to degradation of IκB and translocation of NF-κB to the nucleus. A chemically diverse range of phytochemicals are reported to inhibit NF-κB and subsequent expression of inflammatory genes. Polyphenols broadly exhibit NF-κB inhibition. A comparison of 36 different polyphenols found that daidzein, genistein, isorhamnetin, kaempferol, quercetin, naringenin, and pelargonidin reduced nitric oxide production, a downstream marker of NF-κB activity at micromolar concentrations in macrophages exposed to an inflammatory stimulus [41]. This established a mechanism explaining why these flavonoid compounds are anti-inflammatory. Similarly, several phytochemicals are reported to inhibit NF-κB upstream through inhibition of IKK-α or the IKK-γ subunits, preventing nuclear translocation of the NF-κB active subunit. Numerous phytochemicals inhibit NF-κB activation by affecting the abundance or phosphorylation of IκB. For example, capsaicin, a pungent component of hot chili pepper, was shown when applied in a topical cream to inhibit IκB-α degradation in female mice, explaining a mechanism by which it achieves its anti-inflammatory properties and suggesting that capsaicin could possibly be used for chemoprevention of skin cancer. Gingerol, one of the primary phytochemicals from ginger root, was also shown in mice skin cells to phosphorylate the IκBα and p65 subunits, thereby inhibiting NF-κB signaling [42,43].

Toll-like receptors are cell membrane receptors that mediate the recognition of pathogen-associated molecular patterns. Activation of toll-like receptors leads to inflammatory cytokine expression through signaling pathways that ultimately converge on NF-κB. Several phytochemicals, including epigallocatechin-3-

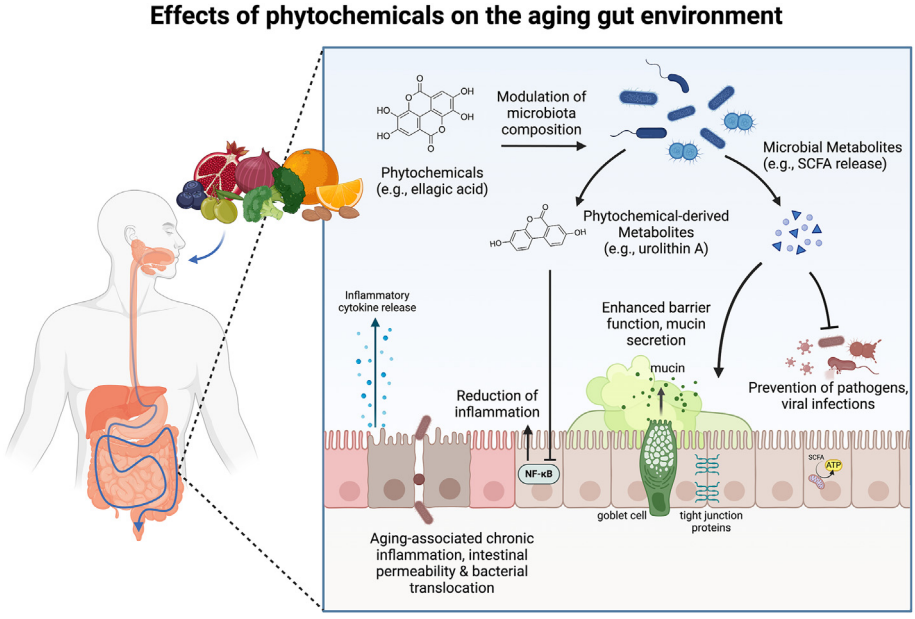

FIGURE 3. Phytochemicals' multifaceted effects on an aging gut environment with intestinal permeability and chronic inflammation. Many phytochemicals have direct anti-inflammatory effects by targeting cellular signaling pathways. Phytochemicals can also promote intestinal homeostasis by modulating microbial composition, improving function of the gut microbiota by producing microbial metabolites, like SCFAs. Phytochemicals can also be metabolized by gut microbiota into more potent compounds, which act directly on the intestinal mucosa and in some cases are absorbed and enter circulation. Created in BioRender. https://BioRender.com/j57f597. SCFA, short-chain fatty acids.

gallate [44], luteolin [45], and resveratrol [46], inhibit these pathways, at 0-50 μM concentrations in cultured macrophages, representing a parallel route to NF-κB inhibition. Taken together, NF-κB plays an important role in gut health, and because NF-κB is a key mediator of inflammatory processes, phytochemical inhibition of NF-κB can protect against chronic inflammation.

Effects of phytochemicals on nuclear factor erythroid 2-related factor 2

Chronic mucosal inflammation results in elevated infiltration of macrophages, which produce ROS as signaling molecules that activate NF-κB. With prolonged activation, ROS can cause extensive oxidative stress and damage to local tissues, contributing to a weakening gut barrier with age. An endogenous mechanism to reduce oxidative stress involves a transcription factor called nuclear factor erythroid 2-related factor 2 (Nrf2), which regulates detoxification and antioxidant defense systems through transcription of phase II detoxifying and antioxidant genes. Nrf2 has pleiotropic roles in controlling inflammation, metabolism, autophagy, and mitochondrial activity [47]. Under homeostatic conditions, Nrf2 is bound to the repressor protein called Kelch-like ECH-associated protein 1 (Keap1), and degraded by the proteasome, leaving low amounts of Keap1-Nrf2 in the cytosol. During periods of oxidative or electrophilic stress, Keap1 repression of Nrf2 is diminished, allowing Nrf2 to accumulate, translocate to the nucleus, and bind to antioxidant response elements in DNA, promoting transcription of a wide variety of genes. Numerous phytochemicals regulate the Nrf2 signaling pathway, some at considerably low concentrations. Xanthohumol, a chalcone derived from the hop plant, induces quinone reductase, an enzyme regulated by Nrf2 in Hepa1c1c7 hepatoma cells at 1–2 μM concentrations [48]. Xanthohumol modifies cysteine residues of Keap1, preventing Nrf2 ubiquitination [49]. Sulforaphane, an isothiocyanate from cruciferous vegetables such as broccoli, has been shown *in vitro*, in animal models, and in clinical trials (using broccoli sprouts) to induce phase II detoxification enzymes through activation of the Nrf2 pathway [50]. Evidence suggests that Nrf2 and NF-κB pathways bidirectionally interfere with one another at the transcriptional level [51]. Thus, phytochemical-driven inhibition of NF-κB likely adds to increase Nrf2 induction [51]. Collectively, phytochemical induction of Nrf2 protects the gut barrier and works in sync with NF-κB inhibition to promote gut health.

Phytochemicals as prebiotics and modulators of gut microbial communities

More recently, the focus of phytochemical research turned to interaction with the gut microbiota as a mechanistic target for their bioactivity. Previously, the primary mechanisms of action were focused on cellular receptors involved in antioxidant and inflammatory pathways alone. It was the observation that many orally administered phytochemicals appear in circulation at pharmacologically low concentrations, as glucuronide conjugates, or are poorly correlated to changes in relevant biological end points [52]. With increasing awareness toward the relationship between the gut microbiota and health, many researchers shifted the focus of phytochemical research toward metabolism of phytochemicals, interactions with the gut microbiota, and bioactivity of metabolites. Furthermore, many phytochemicals interact with gut microbiota bidirectionally, whereby they not only are metabolized by microbes but also modulate microbial composition. These observations have raised the question as to whether the primary mechanism for many phytochemicals' health-promoting effects is through enhancing abundance of beneficial taxa and inhibiting potentially pathogenic taxa.

Prebiotics were narrowly defined as nondigestible carbohydrates. However, the definition has been expanded to include noncarbohydrate substances, such as certain phytochemicals, utilized by microorganisms, which confer a health benefit [53]. Polyphenols have garnered much attention for their dynamic influence on microbes, promoting beneficial taxa and inhibiting pathogenic ones, which has been shown to correlate with healthy aging [15]. In models of intestinal inflammation, one of the most consistent reports is that polyphenols increase alpha-diversity, which is commonly lost with aging [16]. For example, tangeretin, a polyphenol extracted from citrus peel, supplemented in the diet increased alpha diversity measures in mice with chemically induced intestinal inflammation [54]. In this model, tangeretin treatment reduced the severity of colitis, increased colon length, attenuated colon tissue damage, improved intestinal barrier function, and decreased the expression of colonic inflammatory cytokines. Microbial taxa that are overwhelmingly seen as beneficial, such as SCFA-producing clades like lactobacilli and bifidobacteria, seem to benefit from phytochemical supplementation as well. In the same study, tangeretin increased Lachnospiraceae, which produce SCFAs through the fermentation of soluble dietary fiber. SCFAs increased significantly in the treated group as well, likely contributing to its protective effect. Another example of how phytochemicals effect the gut microbiota was found in a study using a colorectal cancer mouse model that showed anthocyanins from black raspberry rescued inflammatory-driven changes to the gut microbiota, increasing *Eubacterium rectale*, *Faecalibacterium prausnitzii*, and *Lactobacillus* sp., and caused changes in gene expression consistent with colon cancer chemoprevention [55]. The changes in gut microbiota observed are functionally important because *F prausnitzi* produce the important SCFA, butyrate, which inhibits intestinal inflammation through the NF-κB cellular signaling pathway [55].

Phytochemicals in concert with probiotics may provide added benefit as a synbiotic. A synbiotic refers to a combination of probiotics and prebiotics, which are designed to work synergistically to promote health. In some cases, the probiotics may even use the prebiotics, enhancing their survival and activity in the gut. There is burgeoning evidence that synbiotics improve several age-related health conditions. For example, elderly patients receiving a synbiotic for two months experienced statistically significant improvements in waist circumference, fasting plasma insulin, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, high-sensitivity C-reactive protein, and TNF-α levels, both compared with baseline and the control group [56].

Phytochemicals may exert antibacterial, antifungal, and antiviral properties through interacting with microbial proteins, disrupting DNA synthesis and replication, interfering with bacterial cell walls, disrupting biofilms or quorum sensing, and inhibiting energy metabolism. Importantly, multiple lines of evidence suggest that phytochemicals exert antimicrobial activity selectively, inhibiting pathogenic microbes or behaviors to a

greater extent than the commensal majority [57]. Some mechanisms of phytochemical inhibition of bacteria specifically target gram-negative bacteria by binding lipopolysaccharide (LPS, endotoxin) in their cell walls. LPS triggers immune responses, particularly when cells are lysed. Age-associated changes to the gut microbiota have shown increases in gram-negative bacteria and LPS secretion [58]. Highly polymerized proanthocyanidins bind LPS in the outer membrane of gram-negative bacteria and prevent interactions with mammalian TLR4, inhibiting proinflammatory pathways through NF-κB [59]. Many phytochemicals inhibit microbial growth by chelating and depriving microbes of essential micronutrients, such as iron and zinc, which can disproportionately inhibit potentially pathogenic bacteria. For example, *Escherichia coli* is inhibited in vitro in the presence of tannic acid, but its growth is restored by the addition of iron [60]. Beneficial bacteria, such as bifidobacteria and lactobacilli do not require iron for growth, contributing to resistance against the antimicrobial actions of these phytochemicals. Antivirulence activity of phytochemicals disrupts pathogenic behavior of microbes, thereby reducing damage to the host and impairing the ability of the organism to initiate disease processes. For example, several terpenoids, such as thymol from thyme (*Thymus vulgaris)*, carvacrol from oregano (*Origanum vulgare*), and hinokitol from cypress (Cupressaceae), are found to strongly inhibit resistant strains of *Candida albicans* by disrupting biofilm formation.

Influence of phytochemicals on microbiota composition that effects the generation of SCFAs, secondary bile acids, and indoles

In addition to host metabolism and immune processes, the gut microbial community carry out a variety of metabolic activities that influence the local intestinal tissues, as well as distal organs through the production of metabolites that are absorbed and distributed through circulation (Figure 3). Microbial metabolites have far-reaching consequences on health and healthspan. In this section, we discuss SCFAs, secondary bile acids, and tryptophan metabolites, all impacting mechanisms that promote healthspan. The generation of these microbial metabolites can be modulated by phytochemicals effect on gut microbiota composition.

Short-chain fatty acids

SCFAs are a common example of bacterial metabolites, originating from indigestible dietary fiber, which play a central role to the host physiology. Enterocytes use SCFAs as energy substrates, particularly in the colon, and transport excess SCFAs into circulation where they are used by other tissues. As previously mentioned, SCFAs have been shown to be beneficial to intestinal homeostasis, metabolism, and brain function [61]. They are also known to bolster immune response and host defense against pathogens. Butyrate, a SCFA produced by the fewest number of bacteria within the phyla Firmicutes, differentiates macrophages that displays enhance antimicrobial activity and antimicrobial peptide production without increasing an inflammatory cytokine response [62]. Amounts of microbial SCFA production decreases with age [63], and the proportions of butyrate-producing Firmicutes are reported to be significantly lower in older individuals than those in young adults [64]. Furthermore, SCFAs, specifically propionate and butyrate, affect epigenetic hallmarks of aging through inhibition of histone deacetylases [65]. Gut microbial dysbiosis and decreased production of SCFAs are associated with the pathogenesis of GI diseases, including inflammatory bowel disease and colorectal cancer [32].

Phytochemicals likely contribute directly and indirectly to SCFA production. Many phytochemicals occur as glycosides in nature, bound to one or more sugar moieties. Bacteria can hydrolyze the glycone and further metabolize it into SCFAs. However, the contribution of phytochemicals directly to SCFA production is likely insignificant compared to the millimolar concentrations produced in the proximal colon from dietary soluble fiber [66]. Rather, phytochemicals may elicit a greater response in SCFA production by encouraging SCFA-producing microbes, such as lactobacilli and bifidobacteria, increasing the capacity of the gut microbiota to generate SCFAs from dietary sources. Phytochemicals are frequently reported to help rescue the loss in SCFA production that results from chemically induced colitis in animal models. Rats given a polyphenol-rich beverage derived from mango for 3 wk had greater butyric and valeric acid concentrations after a dextran sodium sulfate (DSS) challenge compared with control, showing that concentrations of polyphenols achievable in diet can affect SCFA production in this model [67]. Further analysis revealed the beverage was rich in monogalloyl glucoside, gallic acid, *p*-hydroxybenzoic acid glycoside, coumaric acid glycoside, and dihydrophaseic acid glucoside. The increase was concomitant with increases in SCFA-producing lactobacilli, as well as butyrate-producing *Clostridium butyricum*. In a similar study, tangeretin helped mice recover from chemically induced colitis, which corresponded to greater acetic, butyric, and valeric acid production as compared to controls [54]. The gut microbiome of the tangeretin group had increased Lachnospiraceae and Lactobacillaceae abundance, as well as improved tight junction protein expression and reduced inflammatory cytokines. Galangin is a natural flavonoid found in honey and, when administered to mice before DSS-induced colitis, alleviated the pathologic changes to the colon, as well as SCFA amounts, including acetic, propionic, and butyric acid. Similarly, *Lactobacillus* and *Butyricimonas* species abundances were rescued, thought to be linked to galangin's protective effect [68].

Bile acids

Bile acids are endogenous metabolites derived from cholesterol generated in the liver, which facilitate the digestion of lipids. A small proportion of bile acids escape absorption and reach the large intestine where they are modified by microbiota, producing secondary bile acids. The role of bile acids in aging physiology was first observed in a mouse model where increased bile acid concentrations upregulated xenobiotic detoxification genes through farnesoid-X receptor (Fxr), increased resistance to a number of xenobiotics, and increased lifespan by 20% [69]. The capability of the gut microbiota to produce certain secondary bile acids may contribute to the longevity in humans since the gut microbiota of centenarians are enriched in microorganism capable of generating unique isoforms of the secondary bile acid, lithocholic acid (LCA) [4].

Phytochemicals can modulate the bile acid pool, through remodeling of the gut microbiota, exemplified in animal models of intestinal inflammation. Dihydromyricetin, a flavonoid from the fruit of the Japanese raisin tree (*Hovenia dulcis*), restored LCA and chenodeoxycholic acid concentrations in mice, which were

significantly reduced in chemical-induced colitis [70]. LCA and chenodeoxycholic acid are agonists from the bile acid receptors, Takeda G protein-coupled receptor 5 (Tgr5) and Fxr, respectively, which both play a role in mediating intestinal inflammation [71–73]. In a similar experiment in rats, dihydromyricetin significantly upregulated Tgr5 and Fxr expression. However, antibiotic treatment disrupted the induction of these receptors, demonstrating that the effect on the gut microbiota was critical to dihydromyricetin's effect on receptor expression. A similar study demonstrated that phloretin, a polyphenol found in apples, normalized total bile acids and secondary bile acids, LCA and deoxycholic acid, in chemically induced colitis in mice [74]. Along with amelioration of intestinal inflammation, phloretin increased mRNA expression of intestinal Tgr5, likely through secondary bile acid signaling. Berberine, an alkaloid found in many plants in the species *Berberis*, protected chemically induced dysbiosis to gut microbiota in mice. These changes resulted in normalization of the bile acid pool composition, including increases in secondary bile acids similar to controls [75]. Berberine promoted expression of Tgr5 and Fxr in the colon. Conversely, berberine failed to induce expression of Tgr5 and Fxr in the colon tissue of gut microbiota-depleted mice, again, suggesting modulation of the gut microbiota are necessary in mediating its effects.

Tryptophan-derived and dietary indoles

Tryptophan is an essential amino acid and a biosynthetic precursor to a large number of microbial and host metabolites. Tryptophan biotransformation follows three primary pathways in the GI tract, one of which is carried out by gut microbiota to produce indole and indole derivatives [76]. Tryptophan metabolism by gut microbiota play a key role in maintaining intestinal homeostasis and preventing inflammaging. For example, indole-3-carbinol suppresses proinflammatory cytokines and increased anti-inflammatory IL-10 levels from dendritic cells after LPS activation [76]. Indoleacetic acid and indole-3-propionic acid are known to affect intestinal permeability and host immunity [77]. The fecal metabolome is reportedly enriched in microbial tryptophan metabolites in centenarians compared to younger individuals [14]. At the same time, fecal indole metabolites are reported to be dramatically reduced with age [78]. Animal models suggest phytochemicals can be used to improve the tryptophan metabolism pathways of gut microbiota. A polyphenol-rich extract from turmeric recovered inflammatory markers in mice after a DSS challenge [79]. The recovery coincided with significant reduction in tryptophan and elevated tryptophan metabolites, indole-3-acetic acid and indole-3-propionic acid, which correlated with increased *Lactobacilli* sp. abundances, a known tryptophan-metabolizing taxon. Consistently, the turmeric extract treatment restored the aryl hydrocarbon receptor (AhR) and IL-22 concentrations in colon tissue, as well as tight junction proteins (occludin, ZO-1, and claudin-1). The AhR plays a central role in immune homeostasis, epithelial barrier integrity, and xenobiotic metabolism. Indol-3-carbinol, a metabolite of glucobrassicin in cruciferous vegetables, significantly reduced intestinal inflammation and the loss of tight junction proteins in DSS-challenged mice. Moreover, T_H17 cells reduced significantly, although Treg cells increased significantly compared with DSS-only treatment. These improvement in immune system regulation and barrier function were not observed in $Ahr^{-/-}$ mice, suggesting Ahr is critical to indol-3-carbinol improving the colitis phenotype [80]. Indoles can be directly obtained in the diet by consuming brassica vegetables, such as broccoli, cabbage, and cauliflower. Thus, these dietary phytochemicals may contribute directly to some of the cellular mechanisms listed previously, such as AhR agonism, as well as through modulation of gut microbiota. Indoles from diet have also been shown to promote healthy aging by inhibiting the progression of tumor growth and metastasis [81].

Collectively, phytochemicals—abundant in dietary fruits, vegetables, whole grains, spices, and certain drinks—play a pivotal role in fostering gut health, promoting healthy aging, and enhancing healthspan. These bioactive compounds exhibit multifaceted effects, notably reducing inflammation and oxidative stress through direct cellular signaling pathways. This may be especially important in mitigating inflammaging, as well as age-related diseases. Moreover, phytochemicals act as modulators of gut microbiota, promoting the growth of beneficial bacteria although suppressing harmful ones, thus maintaining a balance crucial for GI health. Phytochemicals also in turn influence the metabolic milieu produced by these bacteria, which serve as signaling molecules for a resilient gut environment, namely through enhancing barrier function, regulating immune function, and further modulating microbial composition. These characteristics, which may be afforded through a phytochemical-rich, healthy diet, ultimately provide resilience against environment and lifestyle factors that contribute to age-related diseases.

Microbial Metabolites Produced From Dietary Phytochemicals and Their Health Benefits

In this section, we discuss microbial metabolites produced from bacterial metabolism of dietary phytochemicals and focus on how they can promote gut health and healthy aging. Microorganisms in the gut collectively house a large and flexible metabolism, capable of enzymatic conversion of numerous phytochemicals. Thus, the composition of the gut microbiota impacts the metabolism and pharmacokinetics of dietary phytochemicals. Some phytochemical-derived microbial metabolites that are of particular interest in the field of aging include urolithins, equol, hesperetin, and SFN although other microbial metabolites of interest are also explored (Table 1) [82–123]. We summarize the food sources, parent phytochemicals, and bacteria that are known to make these metabolites. Importantly, an individual's capacity to produce these microbial metabolites after consuming foods (like strawberries, walnuts, citrus fruits, cruciferous vegetables, and soy products) will be dependent on the specific bacteria present in the individual's gut microbiota. More specifically, the presence of a specific metabolic pathway among the microbiota that make up the microbiome, will determine whether the health-promoting microbial metabolite is made [124]. An individual's microbiota could be a significant driver of interindividual variation in bioactive metabolite generation and response to foods and their phytochemicals. This variation in metabolite production is described in the literature as people having different metabotypes, or as responder and nonresponders populations [125]. The production of microbial metabolites is also interconnected to factors affecting gut health, like intestinal permeability and aging (described in Introduction: Interconnections Between Diet, Gut Microbiota, and Aging and Gut Microbiota and Aging sections).

TABLE 1
Microbial metabolites with health-promoting properties.

Microbial metabolite	Phytochemical	Plant source	Method[1]	Health effect, dose[2]
Baicalein	Baicalin	*Scutellaria baicalensis* Georgi[3]	I, A	Colorectal cancer chemoprevention, 0–40 μM [82]
			A	Protects from neuroinflammation, 100 mg/kg [83]
		Scutellaria lateriflora	A	Decrease risk of sarcopenia, 1–10 mg/kg [84]
			I	Promotes dental health, 200 μM [85]
			I, A	Neuroprotective, 3.5 μM [86]
			H	Clinical trials primarily establishing safety and pharmacokinetics, 100–800 mg [87]
Capsiate	Capsaicin	Peppers	I	Anti-inflammatory, 0.01 g/100 g diet [88]
			I, A, H	Improved glucose regulation, 100 μM [89]
			I, A, H	Reduced joint degeneration and osteoarthritis, 10 mg/kg [90]
			H	Improved bone mineral density, 9 mg/d [91]
			H	Variable effects on strength and fat storage, 12 mg [92]
			H	Decrease risk of sarcopenia, FFQ [93]
Tetra-hydrocurcumin	Curcumin	Turmeric	A	Protection against diabetes, 100–200 mg/kg [94]
			A	Colon cancer chemoprevention, 8–162 mg/kg [95]
			A	Antioxidative and anti-inflammatory, 40 mg/kg [96]
			A	Neuroprotective, 60–80 mg/kg [97]
			I, A	Cardioprotective, 50 mg/kg [98]
			H	Clinical trial on skin repigmentation, topical cream [99]
Protocatechuic acid	Anthocyanin	Fruits (blackberries)	A	Protects the liver, 0.025% or 0.1% [100]
		Vegetables (red cabbage)	A	Protects against ulcerative colitis, 5–20 mg/kg [101]
		Legume (black beans)	I, A	Cardioprotective, 250 mg/kg [102]
		Drinks (wine)	A	Cancer chemoprevention, 500 ppm [103]
			I, H	Protects skin from aging, lotion with 0.02% [104]
Enterodiol and enterolactone	Lignans (e.g. matairesinol, secoisolariciresinol, and glycosides)	Flaxseed	I	Cancer chemoprevention, 1–5 μM [105]
		Nuts	I	Immune modulatory, 0–1000 μM [106]
		Legumes	H	Decreased cognition, FFQ [107]
		Whole-grain products	H	Improved glycemic control, 360 mg [108]
			H	Safety and pharmacokinetics, 25–172 mg [109]
Hydroxytyrosol	Oleuropein	Olive skin, flesh, seed and leaves	H	Cardioprotective, 2.5 mg [110]
			A	Neuroprotective, 50 mg/kg [111]
			I	Cancer chemoprevention, 0–200 μM [112]
			I, A	May decrease inflammaging, 0–80 μM [113]
			H	Decreased pain associated with joint damage, 22% [114]
Naringenin	Naringin	Citrus fruits	I	Cancer chemoprevention, 500 nmol/mL [115]
		Rosemary	A	Protects against osteoporosis, 100 mg/kg [116]
		Oregano	H	Cardioprotection, 200 mg [117]
			A	Protective inflammatory bowel disease, 25 mg/kg [118]
			A	Renal protective effects, 50–100 mg/kg [119]
			H	Protects against hepatic steatosis, 200 mg [120]
			H	Being tested for effect cognitive decline, 3 mg [121]
Prenylnaringenin	Xanthohumol	Hops	I	Estrogenic activity, 4 nM [122]
Dihydroxanthohumol	Xanthohumol	Hops	A	Antihyperglycemic activity, 0–60 mg/kg [123]

[1] Letters indicate the methodologies that were used in conducting research: A, animal model; I, in vitro; H, humans.
[2] Dose is a dose used in the cited reference as an example of work done in this area, milligrams per kilogram doses given daily or before injury, FFQ indicates the data were collected from a cross-sectional study of dietary intake.
[3] Plant used in traditional Chinese medicine.

Other factors that can influence the production of microbial metabolites include the presence of a disease, use of drugs (like antibiotics), genetics, and environmental factors.

Urolithins from ellagitannins and ellagic acid

Urolithins are compounds produced when the human gut microbiota metabolizes ellagitannins and ellagic acid, present in foods like pomegranates, strawberries, and walnuts [126]. The microbial metabolites of ellagic acid, urolithins, are thought to drive its health-promoting effects. Urolithins are known for their antioxidant and anti-inflammatory properties and are produced via a series of biochemical reactions. Ellagitannins undergo hydrolysis in the stomach and intestines to form ellagic acid, which is further metabolized in the colon by specific bacteria into bioavailable urolithins. Bacteria that can produce urolithins include *Gordonibacter urolithinfaciens*, *Gordonibacter pamelaeae*, *Bifidobacterium pseudocatenulatum* INIA P815, *Lactococcus garvieae* FUA009, *Enterococcus faecium*, and *Streptococcus thermophilus* FUA329 [127–129]. Three different urolithin metabotypes (UM) have been identified according to their ability to generate urolithins, UM-A, UM-B and UM-0. Individuals in the UM-0 category do not produce urolithins, highlighting the crucial role of gut microbiota composition in processing ellagitannins and generating compounds that may offer health benefits [127, 129]. Individuals with a UM-A metabotype produce urolithin (Uro)-A, although those in UM-B category produce Uro-B and a

metabolite called isourolithin-A, and sometimes produce Uro-A [128]. Supplementation may provide a viable means to harness urolithin's health benefits for those unable to naturally produce it [130].

The microbial metabolite Uro-A has the highest level of biological activity among all urolithins and is of great scientific interest in the field of aging [125,128]. Uro-A has significant anti-inflammatory and antioxidative effects. Uro-A has also been shown to act by altering signaling in multiple pathways (AKT/mTORr, TLR3, NF-κB/STAT1, ERK/MAPK, and Nrf2) and reduce the expression of proinflammatory microRNAs and cytokines, minimize oxidative stress by lowering ROS and superoxide concentrations, and protect against DNA damage, sometimes at relatively low doses (eg, 1 μM) [131]. Uro-A, can promote healthy skeletal muscles during age-associated muscle decline, improve cardiac and skeletal muscle function in human models of heart failure (when given at concentrations achievable in a clinic), and may reduce the effect of mitochondrial dysfunction that occurs with cardiac aging and disease [132]. Preclinical studies have also demonstrated that Uro-A significantly enhances recovery from diminished physical and cognitive functions associated with age, along with mitigating muscle wasting and brain damage. These effects are accompanied by a reduction in aging-related molecules like advanced glycation end-products and a decrease in neuronal apoptosis, suggesting a protective benefit against brain damage [133]. A study in patients with Parkinson disease found those with a diverse microbiome (capable of producing urolithins) exhibit a less severe disease stage [134]. Other studies suggest Uro-B may promote learning and memory. Together these works underscore a potential microbial-mediated therapeutic avenue for neurodegenerative disease treatment [135]. Concurrent treatments with Uro-A and metformin, in a type 2 diabetes mellitus model, significantly reduced fasting blood glucose concentrations and enhanced cognitive abilities, and downregulating inflammatory markers [136]. In conditions of osteoarthritis, Uro-A administration in aging mice protected against systemic bone loss and improved bone mineral density [137]. Uro-A and Uro-B treatments also alleviated some negative effects of a high-fat diet, protecting against weight gain, dyslipidemia, and dysbiosis, with Uro-A being more effective [138]. In summary, there is a diverse set of literature that suggests Uro-A, and also Uro-B, may be beneficial to promote healthy aging but, more research in this field is needed as the cytotoxic effects of urolithins across different cell lines present a controversial and complex picture.

Urolithins have also been associated with potential health benefits for the gut like maintaining intestinal mucosa integrity [139]. Potential also exists for urolithins in treating inflammatory bowel diseases, as a study in a colitis model showed treatment with Uro-A and its synthetic analog UAS03 had therapeutic and preventative efficacy through the activation of AhR and Nrf2 pathways [140]. In colonic cells Uro-A and Uro-B have also been shown to inhibit prostaglandin E2 production, whereas ellagic acid had no effect. It is also worth noting that consumption of foods containing ellagic acid, like walnuts, changed microbial community structure and bacterial richness in participants [141].

Equol from daidzein

S-equol (referred to as equol in this paper) is a phytoestrogen and isoflavone formed by intestinal bacteria from daidzein, or its glucoside daidzin, following the consumption of soybeans or other legumes [142]. Based on clinical trials, only 20%–70% of human participants produce equol from soy products or daidzein, as its production relies on the gut microbiota [142,143]. Many equol-producing microbes belong to the family Coriobacteriaceae (including species such as *Adlercreutzia equolifaciens, Slackia isoflavoniconvertens*, and *Slackia equolifaciens*), but many species from other families have also been discovered like *Bifidobacterium breve, Streptococcus intermedius, Bacteroides ovatus,* and *Ruminococcus productus* [142,144]. To date, equol production has been shown to be influenced by genetics, lifestyle, gender, and dietary habits [145,146]. Age-related diseases like stroke can also affect the capacity to produce equol by decreasing the abundance of bacteria that can metabolize daidzein. Supplements are an alternative source for equol, especially in individuals who do not eat soy or who do not produce equol [147].

Research spanning over 40 years in cell culture, animal models, and human studies has established that soy isoflavones, and equol, promote healthy aging, although some controversy still exists [142,145,146,148]. Several clinical trials, demonstrated that the equol-producing status of an individual was critical for participants to obtain the benefits associated with soy isoflavones [149]. Equol supplements have been shown, mostly in the context of clinical trials focused on menopause, to improve hot flashes, skin health, vaginal health, metabolic health, and protect from bone mineral loss [147]. Equol has great affinity for estrogen receptors, antiandrogenic activity, and antioxidant properties [142,145,146,148]. Isoflavones, including equol, also affect signaling pathways like NF-κB and promote cardiovascular and skin health [150]. Isoflavones, and in particular equol, have vasodilatory properties, and equol was shown to improve arterial stiffness and atherosclerosis [151]. The potential antidiabetic and neuroprotective effects of isoflavones, including their role in reducing cognitive decline and dementia were also examined [152]. Equol may also promote bone mineral density in women through mechanisms involving the estrogen receptor or other pathways [148]. Consumption of soy foods and their isoflavones have also been inversely associated with the development of cancers including breast and prostate cancers [148,153]. A cancer clinical trial showed that S-equol supplements were well-tolerated and decreased cell proliferation in patients with triple-negative breast cancer [154]. There is a need to expand this work and additionally test whether equol supplementation can help reduce cancer incidence.

Sulforaphane from glucoraphanin

Sulforaphane (SFN) is an isothiocyanate, a bioactive sulfur-containing compound made from glucoraphanin found in cruciferous vegetables like broccoli. Glucoraphanin is metabolized by gut bacteria (e.g. *Bacteroides thetaiotaomicron*), which cleaves glucose to produce SFN [155]. Other factors like presence of myrosinase and epithiospecifier protein enzymes, cooking conditions, and pH of the environment play important roles in SFN production and absorption [50,156]. Glucoraphanin can also be converted to SFN-nitrile by bacteria including *Lactococcus lactis* KF147 and *Lactobacillus plantarum* KW30 [155]. This is significant because SFN-nitrile is biologically inert and its production may decrease the efficacy of cruciferous vegetable consumption [157]. These data highlight that the composition of an individual's

microbiota may directly affect the bioavailability of SFN, particularly when cruciferous vegetables are cooked, and likely contributes to high concentrations of interindividual variation in isothiocyanate concentrations observed in clinical trials [158].

SFN has been shown in *Caenorhabditis elegans* and *Drosophila* models to promote longevity and healthspan [159,160]. SFN is best known for promoting healthspan through its cancer chemopreventive properties [50]. For example, in multiple cancer models, SFN treatment has been shown to block cancer initiation by modulating the Nrf2 pathway and increasing the clearance of carcinogens at concentrations that are achievable by eating broccoli sprouts [161]. After cancer initiation, SFN can inhibit tumor growth, beneficially alter expression of epigenetic enzymes, induce apoptosis, and inhibit metastasis [162,163]. SFN treatment, in rodent models, was associated with healthier aging by slowing the progression of neurodegenerative diseases, reduced serum triglycerides and total cholesterol, alleviated nonalcoholic fatty liver disease, protected against cardiovascular dysfunction, and improved neurologic outcomes after ischemic stroke [164,165]. Clinical trials, which often use broccoli sprouts as a concentrated source of SFN, found significantly lowered LDL cholesterol concentrations, and among type 2 diabetics, broccoli sprouts improved markers of oxidative stress and insulin resistance [166]. SFN intake has also been linked to improved cognitive functions, like processing speed and working memory in older adults, and reduced depressive symptoms in cardiac patients [167]. SFN may also be beneficial for those with conditions involving inflammation, such as people with seasonal allergies and asthma, and may protect against muscle injury and *Helicobacter pylori* infection [168]. Although there are likely multiple mechanisms by which SFN contributes to these positive outcomes, the common mechanisms identified include reduced inflammation, induction of the Nrf2 pathway, and beneficial changes in cell signaling cascades [169].

Recent work also suggest that SFN may promote healthy aging by positively influencing the gut microbiota. Two months of SFN treatment (supplemented in diet at 442.5 mg/kg) restored the gut microbe in old mice to mimic that found in young animals [170]. In addition, in rodent models, SFN supplementation, or consumption of broccoli sprouts, protected the gut from the development of ulcerative colitis and Crohn disease and was associated with improved NF-κB and Nrf2 signaling, improved gut barrier integrity, and decreased inflammation [171]. SFN treatment also reversed or improved gut dysbiosis triggered through chemical agents known to cause ulcerative colitis or bladder cancer [172]. Taken together, these data show that SFN can protect gut integrity but more work is needed to test this in a clinical setting and with SFN rich foods. It is also worth noting that consumption of cruciferous vegetables at concentrations achievable in diet, or SFN treatment, can shift the gut microbiota, including changes in the Firmicutes/Bacteroidetes ratio or increasing *Bacteroides fragilis* abundance [173].

Hesperetin from hesperidin

Hesperetin is a bioactive flavonoid made by intestinal bacteria following consumption of hesperidin, a polyphenol abundant in foods like sweet oranges, lemons, and orange juice [174]. Hesperidin reaches the colon without being absorbed earlier in the digestive tract due to its resistance to stomach and intestinal enzymes [175]. In the colon, specific microbiota convert hesperidin into hesperetin through enzymatic action, primarily involving bifidobacteria (e.g. *Bifidobacterium catenulatum*, *B pseudocatenulatum*, *B pseudocatenulatum* WC0403, and *B breve* WC0422) [176]. Hesperetin is absorbed into the bloodstream, is further metabolized (forms metabolites like hesperetin-7-O-glucuronide and hesperetin-3-sulfate), and crosses the BBB [177]. Bioavailability of hesperidin and hesperetin from foods and supplements is variable across clinical studies, but overall, these compounds are thought to have low bioavailability. Clinical trials are investigating optimal delivery methods and strategies to enhance their bioavailability include improving solubility and permeability [177].

Hesperetin has been associated with potential health benefits for the gut, including improving barrier functions and reducing inflammation, in both animal and in vitro studies. The composition of the gut microbiota has also been shown to be affected by treatment with hesperetin, hesperidin, hesperetin-7-O-glucoside, and dietary sources of these compounds [178]. In addition, these compounds can inhibit the growth of pathogenic microbes, reduce inflammation, stimulate SCFA production, and increase beneficial commensal bacteria (like *Lactobacillus* and *Bifidobacterium* species) [179]. In a recent study, increased SCFA production and an improvement in a biomarker of intestinal inflammation was found in persons with metabolic syndrome following 12 wk of supplementation with a citrus extract that was >80% hesperidin [180].

In animal studies, hesperetin treatment extended lifespan and mitigated symptoms of neurodegenerative diseases [181]. Hesperetin prolonged healthspan by decreasing the accumulation of age-related body fat, improving glucose homeostasis, and decreasing muscle aging. The mechanisms by which hesperetin protects from aging phenotypes include the increased expression of the prolongevity gene *CISD2*, modulation of Nrf2 and NF-κB, reduction in oxidative stress and inflammation, and prevention of protein aggregate formation associated with Alzheimer disease [182–184]. Hesperetin, hesperidin, and/or citrus flavones can also protect against senescence, promote skin rejuvenation, and protect against age-associated bone loss [175,185,186]. Consumption of citrus flavones is also associated with decreased risk of developing cancer and cardiovascular diseases, suggesting that metabolites derived from citrus, like hesperetin, could increase healthspan by preventing these conditions. Clinical evidence shows that hesperetin, hesperidin, and citrus juices enhance endothelial function, peripheral vasodilation, stimulate nitric oxide production, and reduce inflammation. Additionally, a 12-wk regimen of hesperidin supplementation has been found to lower triglyceride amounts, fasting glucose, blood pressure, and inflammation markers in individuals with metabolic syndrome or nonalcoholic fatty liver disease [187]. A clinical study on the antiaging effects of hesperetin on skin reported improved hydration and elasticity after 12 wk of topical application of a skincare product containing hesperetin and sodium cyclic lysophosphatidic acid [188]. Further clinical trials are necessary to determine broadly how well hesperetin promotes healthy aging, although existing studies indicate it may benefit cardiovascular health [189].

Additional microbial metabolites from phytochemicals that may promote healthy aging

There is a growing number of known microbial metabolites made from phytochemicals, which promote healthy aging. This

list includes naringenin, baicalein, capsiate, tetrahydrocurcumin, protocatechuic, hydroxytyrosol, enterodiol, and enterolactone. Although less is known about these metabolites than Uro-A, in vitro studies, animal studies, and a few clinical trials show that they have a wide array of potential benefits including properties that support cancer chemoprevention, cardioprotection, neuroprotection, improved skin health, and improved bone mineral density (Table 1). Many of these studies were completed with the microbial metabolite delivered in a purified form, so more work will be needed to establish if these benefits can be achieved by consuming foods. It is important to note that these metabolites may not be uniformly beneficial, as seen with enterodiol which has promising cancer chemoprevention potential, but has also been associated with a decrease in cognition among older women [190]. Although we have focused on the metabolites that may be beneficial in the context of preventing aging, microbial metabolites that promote aging also exist. The microbial metabolites described in Table 1 come from a diverse variety of plant-based foods, including some found in the Mediterranean diet and a root used in traditional Chinese medicine. This list also highlights that an individual's culture and food choices will play a strong role in determining which of these metabolites individuals may encounter and be able to produce.

There are a growing number of gnotobiotic and fecal transplant studies that establish the requirement of microbiota and microbial metabolism in the health-promoting effects of phytochemicals. New technologies including metabolomics and improved in vitro modeling of the GI tract (e.g. the SHIME (Simulator of Human Intestinal Microbial Ecosystem) model) are likely to lead to many new discoveries of microbial metabolites produced from phytochemicals that may promote healthy aging [191]. To facilitate these discoveries, there is a significant need to improve and expand metabolomics databases to contain a broader range of microbial metabolites. Likewise, new technologies that allow sampling of the microbiota in the intestine may provide greater capacity to understand what microbes are actively producing health-promoting metabolites from phytochemicals [192, 193]. There is also an exciting future for research focusing on the metabolic capacity of an individual's microbiota (ie, the metabolic pathways present) rather than focusing on the presence of specific taxa, as many different organisms in the microbiota often have similar capacities to metabolize phytochemicals [124]. As these discoveries are made, additional work will be needed to establish the bioactivity of new microbial metabolites, and clinical trials will be needed to test their efficacy for promoting healthspan and reducing disease burden.

Conclusion

Both diet and the gut microbiota can influence lifespan and healthspan by promoting healthy aging and preventing the development of age-related diseases. Phytochemicals in our diet play an important role in promoting gut health, healthy aging, and healthspan. These bioactive compounds exhibit multifaceted effects and collectively mitigate inflammation, nurture a diverse and healthy microbial composition, and shape resilient metabolic signaling which are foundational to a healthy gut and healthy aging. Importantly, the mitigation of dysbiosis and chronic inflammation, key hallmarks of aging, is a critical way by which diet can promote healthy aging. The gut microbiota also produces beneficial microbial metabolites from phytochemicals like Uro-A, equol, hesperetin and SFN. These, and a growing list of microbial metabolites, have potential to target the hallmarks of aging including mitochondrial dysfunction, cellular senescence, epigenetic alterations, genomic instability, chronic inflammation, and dysbiosis. Through these and other mechanisms, these beneficial microbial metabolites have promise for the prevention and, in some cases, treatment of age-related diseases including cancer, osteoporosis, neurodegeneration, and cardiovascular and metabolic diseases to improve healthspan. More trials are needed in diverse clinical populations, to discover the full potential of microbial metabolites produced from phytochemicals for health aging. In the application of how these microbial metabolites are used, it is important to consider that an individual's capacity to produce health-promoting microbial metabolites from food will be dependent on the specific bacteria present in the individual's gut microbiota.

Author contributions

The authors' responsibilities were as follows – EH, JFS: designed the research; LMB, PEJ, CPW, MH: conducted the research; LMB, PEJ, CPW, MH: wrote the paper; EH: had primary responsibility for final content; and all authors: read and approved the final manuscript.

Conflict of interest

EH reports financial support by United States Department of Agriculture National Institute of Food and Agriculture, Oregon Agricultural Experimental Station, National Institutes of Health, and Amway Research Fund to the Linus Pauling Institute and a relationship of board membership with Haleon Scientific Advisory Board, Vytology Scientific Advisory Board, and Amway Scientific Advisory Board.

Funding

This work was supported by the United States Department of Agriculture National Institute of Food and Agriculture (NIFA-2020-67001-31214), Oregon Agricultural Experimental Station (W5002; OR00735), National Institutes of Health (P30ES030287), as well as the Amway Research Fund to the Linus Pauling Institute. The content is the sole responsibility of the authors and does not necessarily represent the official views of the NIH, the USDA, or Amway. Supporting funding sources had no involvement in study design; collection, analysis, and interpretation of data; writing of the report; or have any restrictions regarding the submission of the report for publication.

References

[1] C. López-Otín, M.A. Blasco, L. Partridge, M. Serrano, G. Kroemer, Hallmarks of aging: an expanding universe, Cell. 186 (2) (2023) 243–278.
[2] T.S. Ghosh, F. Shanahan, P.W. O'Toole, The gut microbiome as a modulator of healthy ageing, Nat. Rev. Gastroenterol. Hepatol. 19 (9) (2022) 565–584.
[3] M. Kaeberlein, How healthy is the healthspan concept? Geroscience 40 (4) (2018) 361–364.
[4] Y. Sato, K. Atarashi, D.R. Plichta, Y. Arai, S. Sasajima, S.M. Kearney, et al., Novel bile acid biosynthetic pathways are enriched in the microbiome of centenarians, Nature 599 (7885) (2021) 458–464.

[5] S. Pang, X. Chen, Z. Lu, L. Meng, Y. Huang, X. Yu, et al., Longevity of centenarians is reflected by the gut microbiome with youth-associated signatures, Nat. Aging. 3 (4) (2023) 436–449.
[6] L.M. DeVito, N. Barzilai, A.M. Cuervo, L.J. Niedernhofer, S. Milman, M. Levine, et al., Extending human healthspan and longevity: a symposium report, Ann. N.Y. Acad. Sci. 1507 (1) (2022) 70–83.
[7] F.B. Hu, Diet strategies for promoting healthy aging and longevity: an epidemiological perspective, J. Intern. Med. 295 (4) (2024) 508–531.
[8] G.M. Pes, M.P. Dore, F. Tsofliou, M. Poulain, Diet and longevity in the Blue Zones: a set-and-forget issue? Maturitas 164 (2022) 31–37.
[9] A.M. Armet, E.C. Deehan, A.F. O'Sullivan, J.F. Mota, C.J. Field, C.M. Prado, et al., Rethinking healthy eating in light of the gut microbiome, Cell Host Microbe 30 (6) (2022) 764–785.
[10] A.A. Johnson, B.W. English, M.N. Shokhirev, D.A. Sinclair, T.L. Cuellar, Human age reversal: fact or fiction? Aging Cell 21 (8) (2022) e13664.
[11] L.J. Dominguez, G. Di Bella, N. Veronese, M. Barbagallo, Impact of Mediterranean diet on chronic non-communicable diseases and longevity, Nutrients 13 (6) (2021) 2028.
[12] A. Cortés-Martín, M.V. Selma, F.A. Tomás-Barberán, A. González-Sarrías, J.C. Espín, Where to look into the puzzle of polyphenols and health? The postbiotics and gut microbiota associated with human metabotypes, Mol. Nutr. Food Res. 64 (9) (2020) e1900952.
[13] P.E. Jamieson, F. Carbonero, J.F. Stevens, Dietary (poly) phenols mitigate inflammatory bowel disease: Therapeutic targets, mechanisms of action, and clinical observations, Curr. Res. Food Sci. 6 (2023) 100521.
[14] T. Wilmanski, C. Diener, N. Rappaport, S. Patwardhan, J. Wiedrick, J. Lapidus, et al., Gut microbiome pattern reflects healthy ageing and predicts survival in humans, Nat. Metabolism. 3 (2) (2021) 274–286.
[15] T.S. Ghosh, F. Shanahan, P.W. O'Toole, Toward an improved definition of a healthy microbiome for healthy aging, Nat. Aging. 2 (11) (2022) 1054–1069.
[16] E.N. DeJong, M.G. Surette, D.M. Bowdish, The gut microbiota and unhealthy aging: disentangling cause from consequence, Cell Host Microbe 28 (2) (2020) 180–189.
[17] Z. Cao, N. Sugimura, E. Burgermeister, M.P. Ebert, T. Zuo, P. Lan, The gut virome: a new microbiome component in health and disease, EBioMedicine 81 (2022) 104113.
[18] L. Pu, S. Pang, W. Mu, X. Chen, Y. Zou, Y. Wang, et al., The gut mycobiome signatures in long-lived populations, Iscience 27 (8) (2024) 110412.
[19] R. Okumura, K. Takeda, Maintenance of intestinal homeostasis by mucosal barriers, Inflamm. Regen. 38 (2018) 5.
[20] F. Schreiber, I. Balas, M.J. Robinson, G. Bakdash, Border control: the role of the microbiome in regulating epithelial barrier function, Cells 13 (6) (2024) 477.
[21] H.E. Jakobsson, A.M. Rodríguez-Piñeiro, A. Schütte, A. Ermund, P. Boysen, M. Bemark, et al., The composition of the gut microbiota shapes the colon mucus barrier, EMBO Rep 16 (2) (2015) 164–177.
[22] L. Tatge, R. Solano Fonseca, P.M. Douglas, A framework for intestinal barrier dysfunction in aging, Nat. Aging. 3 (10) (2023) 1172–1174.
[23] N. Bosco, M. Noti, The aging gut microbiome and its impact on host immunity, Genes Immun. 22 (5–6) (2021) 289–303.
[24] D. Saavedra, A.L. Añé-Kourí, N. Barzilai, C. Caruso, K.-H. Cho, L. Fontana, et al., Aging and chronic inflammation: highlights from a multidisciplinary workshop, Immun. Ageing 20 (1) (2023) 25.
[25] R. Sharma, Emerging interrelationship between the gut microbiome and cellular senescence in the context of aging and disease: perspectives and therapeutic opportunities, Probiotics Antimicrob, Proteins 14 (4) (2022) 648–663.
[26] W.K. Mousa, F. Chehadeh, S. Husband, Microbial dysbiosis in the gut drives systemic autoimmune diseases, Front. Immunol. 13 (2022) 906258.
[27] S. Srivastava, The mitochondrial basis of aging and age-related disorders, Genes 8 (12) (2017) 398.
[28] K. Endres, K. Friedland, Talk to me—interplay between mitochondria and microbiota in aging, Int. J. Mol. Sci. 24 (13) (2023) 10818.
[29] S. Victorelli, H. Salmonowicz, J. Chapman, H. Martini, M.G. Vizioli, J.S. Riley, et al., Apoptotic stress causes mtDNA release during senescence and drives the SASP, Nature 622 (7983) (2023) 627–636.
[30] D.V. Chartoumpekis, A. Zaravinos, Y. Apidianakis, G. Lagoumintzis, Editorial: microbiota and mitochondria: impact on cell signaling, physiology, and disease, Front. Microbiol. 13 (2022) 1056499.
[31] M.X. Byndloss, E.E. Olsan, F. Rivera-Chávez, C.R. Tiffany, S.A. Cevallos, K.L. Lokken, et al., Microbiota-activated PPAR-γ signaling inhibits dysbiotic Enterobacteriaceae expansion, Science 357 (6351) (2017) 570–575.
[32] D.N. Jackson, A.L. Theiss, Gut bacteria signaling to mitochondria in intestinal inflammation and cancer, Gut Microbes 11 (3) (2020) 285–304.
[33] M. Boehme, K.E. Guzzetta, T.F. Bastiaanssen, M. Van De Wouw, G.M. Moloney, A. Gual-Grau, et al., Microbiota from young mice counteracts selective age-associated behavioral deficits, Nat. Aging. 1 (8) (2021) 666–676.
[34] G. Intili, L. Paladino, F. Rappa, G. Alberti, A. Plicato, F. Calabrò, et al., From dysbiosis to neurodegenerative diseases through different communication pathways: an overview, Biology 12 (2) (2023) 195.
[35] W. Zhang, D. Xiao, Q. Mao, H. Xia, Role of neuroinflammation in neurodegeneration development, Signal Transduct. Target Ther. 8 (1) (2023) 267.
[36] R. Solanki, A. Karande, P. Ranganathan, Emerging role of gut microbiota dysbiosis in neuroinflammation and neurodegeneration, Front. Neurol. 14 (2023) 1149618.
[37] L. Bravo, Polyphenols: chemistry, dietary sources, metabolism, and nutritional significance, Nutr. Rev. 56 (11) (1998) 317–333.
[38] L. Guo, H. Yao, W. Chen, X. Wang, P. Ye, Z. Xu, et al., Natural products of medicinal plants: biosynthesis and bioengineering in post-genomic era, Hortic. Res. 9 (2022) uhac223.
[39] H. Cheng, D. Zhang, J. Wu, J. Liu, Y. Zhou, Y. Tan, et al., Interactions between gut microbiota and polyphenols: a mechanistic and metabolomic review, Phytomedicine 119 (2023) 154979.
[40] N. Thevaranjan, A. Puchta, C. Schulz, A. Naidoo, J.C. Szamosi, C.P. Verschoor, et al., Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction, Cell Host Microbe 21 (4) (2017) 455–466.e4.
[41] M. Hämäläinen, R. Nieminen, P. Vuorela, M. Heinonen, E. Moilanen, Anti-inflammatory effects of flavonoids: genistein, kaempferol, quercetin, and daidzein inhibit STAT-1 and NF-kappaB activations, whereas flavone, isorhamnetin, naringenin, and pelargonidin inhibit only NF-kappaB activation along with their inhibitory effect on iNOS expression and NO production in activated macrophages, Mediators Inflamm 2007 (2007) 45673.
[42] S.S. Han, Y.-S. Keum, H.-J. Seo, K.-S. Chun, S.S. Lee, Y.-J. Surh, Capsaicin suppresses phorbol ester-induced activation of NF-κB/Rel and AP-1 transcription factors in mouse epidermis, Cancer Lett. 164 (2) (2001) 119–126.
[43] S.O. Kim, J.K. Kundu, Y.K. Shin, J.-H. Park, M.-H. Cho, T.-Y. Kim, et al., [6]-Gingerol inhibits COX-2 expression by blocking the activation of p38 MAP kinase and NF-κB in phorbol ester-stimulated mouse skin, Oncogene 24 (15) (2005) 2558–2567.
[44] H.S. Youn, J.Y. Lee, S.I. Saitoh, K. Miyake, K.W. Kang, Y.J. Choi, et al., Suppression of MyD88- and TRIF-dependent signaling pathways of toll-like receptor by (−)-epigallocatechin-3-gallate, a polyphenol component of green tea, Biochem. Pharmacol. 72 (7) (2006) 850–859.
[45] J.K. Lee, S.Y. Kim, Y.S. Kim, W.-H. Lee, D.H. Hwang, J.Y. Lee, Suppression of the TRIF-dependent signaling pathway of Toll-like receptors by luteolin, Biochem. Pharmacol. 77 (8) (2009) 1391–1400.
[46] H.S. Youn, J.Y. Lee, K.A. Fitzgerald, H.A. Young, S. Akira, D.H. Hwang, Specific inhibition of MyD88-independent signaling pathways of TLR3 and TLR4 by resveratrol: molecular targets are TBK1 and RIP1 in TRIF complex, J. Immunol. 175 (5) (2005) 3339–3346.
[47] F. He, X. Ru, T. Wen, NRF2, a transcription factor for stress response and beyond, Int. J. Mol. Sci. 21 (13) (2020) 4777.
[48] B.M. Dietz, Y.-H. Kang, G. Liu, A.L. Eggler, P. Yao, L.R. Chadwick, et al., Xanthohumol isolated from *Humulus lupulus* inhibits menadione-induced DNA damage through induction of quinone reductase, Chem. Res. Toxicol. 18 (8) (2005) 1296–1305.
[49] J.F. Stevens, J.S. Revel, C.S. Maier, Mitochondria-centric review of polyphenol bioactivity in cancer models, Antioxid. Redox Signal. 29 (16) (2018) 1589–1611.
[50] Y. Yagishita, J.W. Fahey, A.T. Dinkova-Kostova, T.W. Kensler, Broccoli or sulforaphane: is it the source or dose that matters? Molecules 24 (19) (2019) 3593.
[51] S. Wu, X. Liao, Z. Zhu, R. Huang, M. Chen, A. Huang, et al., Antioxidant and anti-inflammation effects of dietary phytochemicals: the Nrf2/NF-κB signalling pathway and upstream factors of Nrf2, Phytochemistry 204 (2022) 113429.

[52] J.F. Stevens, C.S. Maier, The chemistry of gut microbial metabolism of polyphenols, Phytochem. Rev. 15 (3) (2016) 425–444.
[53] G.R. Gibson, R. Hutkins, M.E. Sanders, S.L. Prescott, R.A. Reimer, S.J. Salminen, et al., Expert consensus document: the International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics, Nat. Rev. Gastroenterol. Hepatol. 14 (8) (2017) 491–502.
[54] B. Chen, J. Luo, Y. Han, H. Du, J. Liu, W. He, et al., Dietary tangeretin alleviated dextran sulfate sodium-induced colitis in mice via inhibiting inflammatory response, restoring intestinal barrier function, and modulating gut microbiota, J. Agric. Food Chem. 69 (27) (2021) 7663–7674.
[55] L. Chen, B. Jiang, C. Zhong, J. Guo, L. Zhang, T. Mu, et al., Chemoprevention of colorectal cancer by black raspberry anthocyanins involved the modulation of gut microbiota and SFRP2 demethylation, Carcinogenesis 39 (3) (2018) 471–481.
[56] A.F. Cicero, F. Fogacci, M. Bove, M. Giovannini, C. Borghi, Impact of a short-term synbiotic supplementation on metabolic syndrome and systemic inflammation in elderly patients: a randomized placebo-controlled clinical trial, Eur. J. Nutr. 60 (2) (2021) 655–663.
[57] C.-L. Chan, R.-Y. Gan, N.P. Shah, H. Corke, Polyphenols from selected dietary spices and medicinal herbs differentially affect common food-borne pathogenic bacteria and lactic acid bacteria, Food Control 92 (2018) 437–443.
[58] J.A. Malik, M.A. Zafar, T. Lamba, S. Nanda, M.A. Khan, J.N. Agrewala, The impact of aging-induced gut microbiome dysbiosis on dendritic cells and lung diseases, Gut Microbes 15 (2) (2023) 2290643.
[59] J.B. Delehanty, B.J. Johnson, T.E. Hickey, T. Pons, F.S. Ligler, Binding and neutralization of lipopolysaccharides by plant proanthocyanidins, J. Nat. Prod. 70 (11) (2007) 1718–1724.
[60] K.T. Chung, Z. Lu, M.W. Chou, Mechanism of inhibition of tannic acid and related compounds on the growth of intestinal bacteria, Food Chem. Toxicol. 36 (12) (1998) 1053–1060.
[61] A. Moțățăianu, G. Șerban, S. Andone, The role of short-chain fatty acids in microbiota–gut–brain cross-talk with a focus on amyotrophic lateral sclerosis: a systematic review, Int. J. Mol. Sci. 24 (20) (2023) 15094.
[62] J. Schulthess, S. Pandey, M. Capitani, K.C. Rue-Albrecht, I. Arnold, F. Franchini, et al., The short chain fatty acid butyrate imprints an antimicrobial program in macrophages, Immunity 50 (2) (2019) 432–445.e7.
[63] N. Salazar, S. Arboleya, T. Fernández-Navarro, C.G. de Los Reyes-Gavilán, S. Gonzalez, M. Gueimonde, Age-associated changes in gut microbiota and dietary components related with the immune system in adulthood and old age: a cross-sectional study, Nutrients 11 (8) (2019) 1765.
[64] S. Saraswati, R. Sitaraman, Aging and the human gut microbiota—from correlation to causality, Front. Microbiol. 5 (2015) 764.
[65] R. Fellows, J. Denizot, C. Stellato, A. Cuomo, P. Jain, E. Stoyanova, et al., Microbiota derived short chain fatty acids promote histone crotonylation in the colon through histone deacetylases, Nat. Commun. 9 (1) (2018) 105.
[66] J.H. Cummings, E.W. Pomare, W.J. Branch, C.P. Naylor, G.T. Macfarlane, Short chain fatty acids in human large intestine, portal, hepatic and venous blood, Gut 28 (10) (1987) 1221–1227.
[67] H. Kim, K.A. Krenek, C. Fang, Y. Minamoto, M.E. Markel, J.S. Suchodolski, et al., Polyphenolic derivatives from mango (*Mangifera indica* L.) modulate fecal microbiome, short-chain fatty acids production and the HDAC1/AMPK/LC3 axis in rats with DSS-induced colitis, J. Funct. Foods. 48 (2018) 243–251.
[68] H. Xuan, A. Ou, S. Hao, J. Shi, X. Jin, Galangin protects against symptoms of dextran sodium sulfate-induced acute colitis by activating autophagy and modulating the gut microbiota, Nutrients 12 (2) (2020) 347.
[69] D. Amador-Noguez, K. Yagi, S. Venable, G. Darlington, Gene expression profile of long-lived Ames dwarf mice and Little mice, Aging Cell 3 (6) (2004) 423–441.
[70] S. Dong, M. Zhu, K. Wang, X. Zhao, L. Hu, W. Jing, et al., Dihydromyricetin improves DSS-induced colitis in mice via modulation of fecal-bacteria-related bile acid metabolism, Pharmacol. Res. 171 (2021) 105767.
[71] Y.-D. Wang, W.-D. Chen, D. Yu, B.M. Forman, W. Huang, The G-protein-coupled bile acid receptor, Gpbar1 (TGR5), negatively regulates hepatic inflammatory response through antagonizing nuclear factor kappa light-chain enhancer of activated B cells (NF-κB) in mice, Hepatology 54 (4) (2011) 1421–1432.
[72] R.M. Gadaleta, B. Oldenburg, E.C. Willemsen, M. Spit, S. Murzilli, L. Salvatore, et al., Activation of bile salt nuclear receptor FXR is repressed by pro-inflammatory cytokines activating NF-κB signaling in the intestine, Biochim. Biophys. Acta. 1812 (8) (2011) 851–858.
[73] T. Inagaki, A. Moschetta, Y.-K. Lee, L. Peng, G. Zhao, M. Downes, et al., Regulation of antibacterial defense in the small intestine by the nuclear bile acid receptor, Proc. Natl. Acad. Sci. U.S.A. 103 (10) (2006) 3920–3925.
[74] F. Liu, X. Wang, D. Li, Y. Cui, X. Li, Apple polyphenols extract alleviated dextran sulfate sodium-induced ulcerative colitis in C57BL/6 male mice by restoring bile acid metabolism disorder and gut microbiota dysbiosis, Phytother. Res. 35 (3) (2021) 1468–1485.
[75] X. Sun, Y. Zhang, G. Cheng, T. Zhu, Z. Zhang, L. Xiong, et al., Berberine improves DSS-induced colitis in mice by modulating the fecal-bacteria-related bile acid metabolism, Biomed. Pharmacother. 167 (2023) 115430.
[76] J.M. Benson, D.M. Shepherd, Dietary ligands of the aryl hydrocarbon receptor induce anti-inflammatory and immunoregulatory effects on murine dendritic cells, Toxicol. Sci. 124 (2) (2011) 327–338.
[77] D. Dodd, M.H. Spitzer, W. Van Treuren, B.D. Merrill, A.J. Hryckowian, S.K. Higginbottom, et al., A gut bacterial pathway metabolizes aromatic amino acids into nine circulating metabolites, Nature 551 (7682) (2017) 648–652.
[78] S. Ruiz-Ruiz, S. Sanchez-Carrillo, S. Ciordia, M.C. Mena, C. Méndez-García, D. Rojo, et al., Functional microbiome deficits associated with ageing: chronological age threshold, Aging Cell 19 (1) (2020) e13063.
[79] C. Yang, Y. Du, A. Zhao, L. Liu, D. Ren, P. Niu, et al., Dietary turmeric consumption alleviates ulcerative colitis via restoring tryptophan metabolism and alleviating gut microbiota dysbiosis in mice, J. Agric. Food Chem. 70 (48) (2022) 15213–15224.
[80] S. Riemschneider, M. Hoffmann, U. Slanina, K. Weber, S. Hauschildt, J. Lehmann, Indol-3-carbinol and quercetin ameliorate chronic DSS-induced colitis in C57BL/6 mice by AhR-mediated anti-inflammatory mechanisms, Int. J. Environ. Res. Public Health. 18 (5) (2021) 2262.
[81] D.E. Williams, Indoles derived from glucobrassicin: cancer chemoprevention by indole-3-carbinol and 3, 3'-diindolylmethane, Front. Nutr. 8 (2021) 734334.
[82] Z. Chen, R. Hou, S. Gao, D. Song, Y. Feng, Baicalein inhibits proliferation activity of human colorectal cancer cells HCT116 through downregulation of Ezrin, Cell. Physiol. Biochem. 49 (5) (2018) 2035–2046.
[83] J. Song, M. Li, N. Kang, W. Jin, Y. Xiao, Z. Li, et al., Baicalein ameliorates cognitive impairment of vascular dementia rats via suppressing neuroinflammation and regulating intestinal microbiota, Brain Res. Bull. 208 (2024) 110888.
[84] D. Saul, J. Kling, R. Kosinsky, D. Hoffmann, M. Komrakova, M. Wicke, et al., Effect of the lipoxygenase inhibitor baicalein on muscles in ovariectomized rats, J. Nutr. Metab. 2016 (1) (2016) 3703216.
[85] A. Vijayakumar, H.B. Sarveswari, S. Vasudevan, K. Shanmugam, A.P. Solomon, P. Neelakantan, Baicalein inhibits *Streptococcus mutans* biofilms and dental caries-related virulence phenotypes, Antibiotics 10 (2) (2021) 215.
[86] L. Pan, K.-S. Cho, I. Yi, C.-H. To, D.F. Chen, C.-W. Do, Baicalein, baicalin, and wogonin: protective effects against ischemia-induced neurodegeneration in the brain and retina, Oxid. Med. Cell. Longev. 2021 (1) (2021) 8377362.
[87] R. Dong, L. Li, H. Gao, K. Lou, H. Luo, S. Hao, et al., Safety, tolerability, pharmacokinetics, and food effect of baicalein tablets in healthy Chinese subjects: a single-center, randomized, double-blind, placebo-controlled, single-dose phase I study, J. Ethnopharmacol. 274 (2021) 114052.
[88] C. Kang, B. Wang, K. Kaliannan, X. Wang, H. Lang, S. Hui, et al., Gut microbiota mediates the protective effects of dietary capsaicin against chronic low-grade inflammation and associated obesity induced by high-fat diet, mBio 8 (3) (2017) e00470, 17.
[89] H.-S. Chae, C.L. Cantrell, I.A. Khan, R.L. Jarret, S.I. Khan, Capsiate-rich fraction of *Capsicum annuum* induces muscular glucose uptake, ameliorates rosiglitazone-induced adipogenesis, and exhibits activation of NRs regulating multiple signaling pathways, J. Agric. Food Chem. 71 (47) (2023) 18395–18404.
[90] Z. Guan, X. Jin, Z. Guan, S. Liu, K. Tao, L. Luo, The gut microbiota metabolite capsiate regulate SLC2A1 expression by targeting HIF-1α to inhibit knee osteoarthritis-induced ferroptosis, Aging Cell 22 (6) (2023) e13807.

[91] G. Salvio, M. Petrelli, S. Paolini, V. Baldini, C. Sbaffi, S. Basili, et al., Gender-specific effects of capsiate supplementation on body weight and bone mineral density: a randomized, double-blind, placebo-controlled study in slightly overweight women, J. Endocrinol. Invest. 46 (7) (2023) 1415–1422.
[92] V.E.L. de Moura E Silva, J.M. Cholewa, R. Jäger, N.E. Zanchi, M.C. de Freitas, R.C. de Moura, et al., Chronic capsiate supplementation increases fat-free mass and upper body strength but not the inflammatory response to resistance exercise in young untrained men: a randomized, placebo-controlled and double-blind study, J. Int. Soc. Sports Nutr. 18 (1) (2021) 50.
[93] X. Wang, X. Wu, G. Meng, S. Bian, Q. Zhang, L. Liu, et al., Consumption of chilies and sweet peppers is associated with lower risk of sarcopenia in older adults, Aging (Albany NY) 13 (6) (2021) 9135–9142.
[94] T. Yuan, Z. Yin, Z. Yan, Q. Hao, J. Zeng, L. Li, et al., Tetrahydrocurcumin ameliorates diabetes profiles of db/db mice by altering the composition of gut microbiota and up-regulating the expression of GLP-1 in the pancreas, Fitoterapia 146 (2020) 104665.
[95] B. Scazzocchio, L. Minghetti, M. D'Archivio, Interaction between gut microbiota and curcumin: a new key of understanding for the health effects of curcumin, Nutrients 12 (9) (2020) 2499.
[96] Y. Pan, Y. Zhang, J. Yuan, X. Ma, Y. Zhao, Y. Li, et al., Tetrahydrocurcumin mitigates acute hypobaric hypoxia-induced cerebral oedema and inflammation through the NF-κB/VEGF/MMP-9 pathway, Phytother. Res. 34 (11) (2020) 2963–2977.
[97] A. Rajeswari, M. Sabesan, Inhibition of monoamine oxidase-B by the polyphenolic compound, curcumin and its metabolite tetrahydrocurcumin, in a model of Parkinson's disease induced by MPTP neurodegeneration in mice, Inflammopharmacology 16 (2) (2008) 96–99.
[98] X. Chen, Q. Xie, Y. Zhu, J. Xu, G. Lin, S. Liu, et al., Cardio-protective effect of tetrahydrocurcumin, the primary hydrogenated metabolite of curcumin in vivo and in vitro: induction of apoptosis and autophagy via PI3K/AKT/mTOR pathways, Eur. J. Pharmacol. 911 (2021) 174495.
[99] P. Asawanonda, S.-O. Klahan, Tetrahydrocurcuminoid cream plus targeted narrowband UVB phototherapy for vitiligo: a preliminary randomized controlled study, Photomed, Laser Surg 28 (5) (2010) 679–684.
[100] J. Tan, R. Hu, J. Gong, C. Fang, Y. Li, M. Liu, et al., Protection against metabolic associated fatty liver disease by protocatechuic acid, Gut Microbes 15 (1) (2023) 2238959.
[101] X. Yang, X. Sun, F. Zhou, S. Xiao, L. Zhong, S. Hu, et al., Protocatechuic acid alleviates dextran-sulfate-sodium-induced ulcerative colitis in mice via the regulation of intestinal flora and ferroptosis, Molecules 28 (9) (2023) 3775.
[102] X.-L. Tang, J.-X. Liu, W. Dong, P. Li, L. Li, C.-R. Lin, et al., Cardioprotective effect of protocatechuic acid on myocardial ischemia/reperfusion injury, J. Pharmacol. Sci. 125 (2) (2014) 176–183.
[103] A. Dong, C.-W. Lin, C.E. Echeveste, Y.-W. Huang, K. Oshima, M. Yearsley, et al., Protocatechuic acid, a gut bacterial metabolite of black raspberries, inhibits adenoma development and alters gut microbiome profiles in Apcmin/+ mice, J. Cancer Prev. 27 (1) (2022) 50–57.
[104] S. Shin, S.H. Cho, D. Park, E. Jung, Anti-skin aging properties of protocatechuic acid in vitro and in vivo, J. Cosmet. Dermatol. 19 (4) (2020) 977–984.
[105] C.A. Curry, Chemoprotective effects of flaxseed lignans enterodiol and enterolactone in non-transformed colonocytes, Texas A&M University, College Station, Texas, 2015.
[106] E. Corsini, M. Dell'Agli, A. Facchi, E. De Fabiani, L. Lucchi, M.S. Boraso, et al., Enterodiol and enterolactone modulate the immune response by acting on nuclear factor-κB (NF-κB) signaling, J. Agric. Food Chem. 58 (11) (2010) 6678–6684.
[107] J. Alwerdt, E.G. Valdés, M. Chanti-Ketterl, B.J. Small, J.D. Edwards, The relationship between phytoestrogens and speed of processing, Menopause 23 (8) (2016) 911–918.
[108] A. Pan, J. Sun, Y. Chen, X. Ye, H. Li, Z. Yu, et al., Effects of a flaxseed-derived lignan supplement in type 2 diabetic patients: a randomized, double-blind, cross-over trial, PLoS One 2 (11) (2007) e1148.
[109] K.D. Setchell, N.M. Brown, L. Zimmer-Nechemias, B. Wolfe, P. Jha, J.E. Heubi, Metabolism of secoisolariciresinol-diglycoside the dietary precursor to the intestinally derived lignan enterolactone in humans, Food Funct 5 (3) (2014) 491–501.
[110] I. Ikonomidis, K. Katogiannis, C. Chania, N. Iakovis, M. Tsoumani, A. Christodoulou, et al., Association of hydroxytyrosol enriched olive oil with vascular function in chronic coronary disease, Eur. J. Clin. Invest. 53 (7) (2023) e13983.
[111] P. Nardiello, D. Pantano, A. Lapucci, M. Stefani, F. Casamenti, Diet supplementation with hydroxytyrosol ameliorates brain pathology and restores cognitive functions in a mouse model of amyloid-β deposition, J. Alzheimers Dis. 63 (3) (2018) 1161–1172.
[112] L. Sun, C. Luo, J. Liu, Hydroxytyrosol induces apoptosis in human colon cancer cells through ROS generation, Food Funct. 5 (8) (2014) 1909–1914.
[113] F. Velotti, R. Bernini, Hydroxytyrosol interference with Inflammaging via modulation of inflammation and autophagy, Nutrients 15 (7) (2023) 1774.
[114] R. Takeda, T. Koike, I. Taniguchi, K. Tanaka, Double-blind placebo-controlled trial of hydroxytyrosol of Olea europaea on pain in gonarthrosis, Phytomedicine 20 (10) (2013) 861–864.
[115] X. Zeng, Y. Zheng, Y. He, J. Zhang, W. Peng, W. Su, Microbial metabolism of naringin and the impact on antioxidant capacity, Nutrients 14 (18) (2022) 3765.
[116] N. Oršolić, J. Nemrava, Ž. Jeleč, M. Kukolj, D. Odeh, B. Jakopović, et al., Antioxidative and anti-inflammatory activities of chrysin and naringenin in a drug-induced bone loss model in rats, Int. J. Mol. Sci. 23 (5) (2022) 2872.
[117] F. Naeini, Z. Namkhah, H. Tutunchi, S.M. Rezayat, S. Mansouri, M. Yaseri, et al., Effects of naringenin supplementation on cardiovascular risk factors in overweight/obese patients with nonalcoholic fatty liver disease: a pilot double-blind, placebo-controlled, randomized clinical trial, Eur. J. Gastroenterol. Hepatol. 34 (3) (2022) 345–353.
[118] R. Cao, X. Wu, H. Guo, X. Pan, R. Huang, G. Wang, et al., Naringin exhibited therapeutic effects against DSS-induced mice ulcerative colitis in intestinal barrier–dependent manner, Molecules 26 (21) (2021) 6604.
[119] T.H. Khan, M.A. Ganaie, K.M. Alharthy, H. Madkhali, B.L. Jan, I.A. Sheikh, Naringenin prevents doxorubicin-induced toxicity in kidney tissues by regulating the oxidative and inflammatory insult in Wistar rats, Arch. Physiol. Biochem. 126 (4) (2020) 300–307.
[120] Z. Namkhah, F. Naeini, S. Mahdi Rezayat, Mehdi Yaseri, S. Mansouri, M. Javad Hosseinzadeh-Attar, Does naringenin supplementation improve lipid profile, severity of hepatic steatosis and probability of liver fibrosis in overweight/obese patients with NAFLD? A randomised, double-blind, placebo-controlled, clinical trial, Int. J. Clin. Pract. 75 (11) (2021) e14852.
[121] S. Galluzzi, R. Zanardini, C. Ferrari, S. Gipponi, I. Passeggia, M. Rampini, et al., Cognitive and biological effects of citrus phytochemicals in subjective cognitive decline: a 36-week, randomized, placebo-controlled trial, Nutr. J. 21 (1) (2022) 64.
[122] S.R. Milligan, J.C. Kalita, A. Heyerick, H. Rong, L. De Cooman, D. De Keukeleire, Identification of a potent phytoestrogen in hops (*Humulus lupulus* L.) and beer, J. Clin. Endocrinol. Metab. 84 (6) (1999) 2249–2252.
[123] C.L. Miranda, V.D. Elias, J.J. Hay, J. Choi, R.L. Reed, J.F. Stevens, Xanthohumol improves dysfunctional glucose and lipid metabolism in diet-induced obese C57BL/6J mice, Arch. Biochem. Biophys. 599 (2016) 22–30.
[124] I. Rowland, G. Gibson, A. Heinken, K. Scott, J. Swann, I. Thiele, et al., Gut microbiota functions: metabolism of nutrients and other food components, Eur. J. Nutr. 57 (1) (2018) 1–24.
[125] A.H. Kuerec, X.K. Lim, A.L. Khoo, E. Sandalova, L. Guan, L. Feng, et al., Targeting aging with urolithin A in humans: a systematic review, Ageing Res. Rev. 100 (2024) 102406.
[126] C.E. Iglesias-Aguirre, R. García-Villalba, D. Beltrán, M.D. Frutos-Lisón, J.C. Espín, F.A. Tomás-Barberán, et al., Gut bacteria involved in ellagic acid metabolism to yield human urolithin metabotypes revealed, J. Agric. Food Chem. 71 (9) (2023) 4029–4035.
[127] M. Xia, Z. Hua, Y. Zhao, G. Zhang, X. Hou, G. Yang, et al., Improvement of urolithin A yield by in vitro cofermentation of *Streptococcus thermophilus* FUA329 with human gut microbiota from different urolithin metabotypes, J. Agric. Food Chem. 72 (6) (2024) 3008–3016.
[128] F. He, Y. Bian, Y. Zhao, M. Xia, S. Liu, J. Gui, et al., In vitro conversion of ellagic acid to urolithin A by different gut microbiota of urolithin metabotype A, Appl. Microbiol. Biotechnol. 108 (1) (2024) 1–14.
[129] C.E. Iglesias-Aguirre, A. González-Sarrías, A. Cortés-Martín, M. Romo-Vaquero, L. Osuna-Galisteo, J.J. Cerón, et al., In vivo administration of

gut bacterial consortia replicates urolithin metabotypes A and B in a non-urolithin-producing rat model, Food Funct 14 (6) (2023) 2657–2667.
[130] A. Singh, D. D'Amico, P.A. Andreux, G. Dunngalvin, T. Kern, W. Blanco-Bose, et al., Direct supplementation with urolithin A overcomes limitations of dietary exposure and gut microbiome variability in healthy adults to achieve consistent levels across the population, Eur. J. Clin. Nutr. 76 (2) (2022) 297–308.
[131] W.-C. Huang, C.-J. Liou, S.-C. Shen, S. Hu, J.C. Chao, C.-Y. Hsiao, et al., Urolithin A inactivation of TLR3/TRIF signaling to block the NF-κB/STAT1 axis reduces inflammation and enhances antioxidant defense in poly (I: C)-induced RAW264.7 cells, Int. J. Mol. Sci. 23 (9) (2022) 4697.
[132] S. Liu, J. Faitg, C. Tissot, D. Konstantopoulos, R. Laws, G. Bourdier, et al., Urolithin A induces cardioprotection and enhanced mitochondrial quality during natural aging and heart failure, bioRxiv (2023), 2023.08. 22.554375.
[133] M. Zhang, X. Tang, B. Mao, Q. Zhang, J. Zhao, W. Chen, et al., Inhibition of the NF-κB and mTOR targets by urolithin A attenuates d-galactose-induced aging in mice, Food Funct 14 (23) (2023) 10375–10386.
[134] M. Romo-Vaquero, E. Fernández-Villalba, A.-L. Gil-Martinez, L. Cuenca-Bermejo, J.C. Espín, M.T. Herrero, et al., Urolithins: potential biomarkers of gut dysbiosis and disease stage in Parkinson's patients, Food Funct 13 (11) (2022) 6306–6316.
[135] X. Liu, Y. Liu, J. Liu, H. Zhang, C. Shan, Y. Guo, et al., Correlation between the gut microbiome and neurodegenerative diseases: a review of metagenomics evidence, Neural Regen. Res. 19 (4) (2024) 833–845.
[136] Y. Xiao, K. Li, J. Bian, H. Liu, X. Zhai, E. El-Omar, et al., Urolithin A attenuates diabetes-associated cognitive impairment by ameliorating intestinal barrier dysfunction via N-glycan biosynthesis pathway, Mol. Nutr. Food Res. 66 (9) (2022) e2100863.
[137] H. Tao, Y. Tao, C. Yang, W. Li, W. Zhang, X. Li, et al., Gut metabolite urolithin A inhibits osteoclastogenesis and senile osteoporosis by enhancing the autophagy capacity of bone marrow macrophages, Front. Pharmacol. 13 (2022) 875611.
[138] A.O. Abdulrahman, M.Y. Alzubaidi, M.S. Nadeem, J.A. Khan, I.A. Rather, M.I. Khan, Effects of urolithins on obesity-associated gut dysbiosis in rats fed on a high-fat diet, Int. J. Food Sci. Nutr. 72 (7) (2021) 923–934.
[139] T. Meroño, G. Peron, G. Gargari, R. González-Domínguez, A. Miñarro, E. Vegas-Lozano, et al., The relevance of urolithins-based metabotyping for assessing the effects of a polyphenol-rich dietary intervention on intestinal permeability: a post-hoc analysis of the MaPLE trial, Food Res. Int. 159 (2022) 111632.
[140] M. Ma, Y. Wang, S. Fan, Y. Huang, X. Su, C. Lu, Urolithin A alleviates colitis in mice by improving gut microbiota dysbiosis, modulating microbial tryptophan metabolism, and triggering Ahr activation, J. Agric. Food Chem. 71 (20) (2023) 7710–7722.
[141] F.A. Tomás-Barberán, R. García-Villalba, A. González-Sarrías, M.V. Selma, J.C. Espín, Ellagic acid metabolism by human gut microbiota: consistent observation of three urolithin phenotypes in intervention trials, independent of food source, age, and health status, J. Agric. Food Chem. 62 (28) (2014) 6535–6538.
[142] B. Mayo, L. Vázquez, A.B. Flórez, Equol: a bacterial metabolite from the daidzein isoflavone and its presumed beneficial health effects, Nutrients 11 (9) (2019) 2231.
[143] K.D. Setchell, S.P. Borriello, P. Hulme, D. Kirk, M. Axelson, Nonsteroidal estrogens of dietary origin: possible roles in hormone-dependent disease, Am. J. Clin. Nutr. 40 (3) (1984) 569–578.
[144] T. Ueno, S. Uchiyama, Identification of the specific intestinal bacteria capable of metabolising soy isoflavone to equol, Ann. Nutr. Metab. 45 (Suppl) (2001) 114.
[145] S.A. Aboushanab, S.M. Khedr, I.F. Gette, I.G. Danilova, N.A. Kolberg, G.A. Ravishankar, et al., Isoflavones derived from plant raw materials: bioavailability, anti-cancer, anti-aging potentials, and microbiome modulation, Crit. Rev. Food Sci. Nutr. 63 (2) (2023) 261–287.
[146] K.D. Setchell, The history and basic science development of soy isoflavones, Menopause 24 (12) (2017) 1338–1350.
[147] L.-R. Chen, N.-Y. Ko, K.-H. Chen, Isoflavone supplements for menopausal women: a systematic review, Nutrients 11 (11) (2019) 2649.
[148] A. Fatima, M.S. Khan, M.W. Ahmad, Therapeutic potential of equol: a comprehensive review, Curr. Pharm. Des. 26 (45) (2020) 5837–5843.
[149] K. Hayashi, H. Yamaguchi, H. Amaoka, T. Takahara, S. Kunisa, N. Tamai, et al., Equol-producing status affects exercise training-induced improvement in arterial compliance in postmenopausal women, J. Appl. Physiol. 130 (3) (2021) 827–835.
[150] K. Prokopidis, M. Mazidi, R. Sankaranarayanan, B. Tajik, A. McArdle, M. Isanejad, Effects of whey and soy protein supplementation on inflammatory cytokines in older adults: a systematic review and meta-analysis, Br. J. Nutr. 129 (5) (2023) 759–770.
[151] X. Zhang, C.V. Veliky, R.L. Birru, E. Barinas-Mitchell, J.W. Magnani, A. Sekikawa, Potential protective effects of equol (soy isoflavone metabolite) on coronary heart diseases—from molecular mechanisms to studies in humans, Nutrients 13 (11) (2021) 3739.
[152] A. Sekikawa, W. Wharton, B. Butts, C.V. Veliky, J. Garfein, J. Li, et al., Potential protective mechanisms of S-equol, a metabolite of soy isoflavone by the gut microbiome, on cognitive decline and dementia, Int. J. Mol. Sci. 23 (19) (2022) 11921.
[153] I. Boutas, A. Kontogeorgi, C. Dimitrakakis, S.N. Kalantaridou, Soy isoflavones and breast cancer risk: a meta-analysis, In Vivo 36 (2) (2022) 556–562.
[154] K.I. Lathrop, V.G. Kaklamani, A.J. Brenner, R. Li, A. Nazarullah, S. Hackman, et al., Novel estrogen receptor beta agonist S-equol decreases tumor proliferation in patients with triple negative breast cancer (TNBC), J. Clin. Oncol. 38 (15_suppl) (2020) 560.
[155] J.A. Bouranis, L.M. Beaver, E. Ho, Metabolic fate of dietary glucosinolates and their metabolites: a role for the microbiome, Front. Nutr. 8 (2021) 748433.
[156] J.W. Fahey, S.L. Wehage, W.D. Holtzclaw, T.W. Kensler, P.A. Egner, T.A. Shapiro, et al., Protection of humans by plant glucosinolates: efficiency of conversion of glucosinolates to isothiocyanates by the gastrointestinal microflora, Cancer Prev. Res. (Phila). 5 (4) (2012) 603–611.
[157] N.V. Matusheski, R. Swarup, J.A. Juvik, R. Mithen, M. Bennett, E.H. Jeffery, Epithiospecifier protein from broccoli (*Brassica oleracea* L. ssp. italica) inhibits formation of the anticancer agent sulforaphane, J. Agric. Food Chem. 54 (6) (2006) 2069–2076.
[158] J.A. Bouranis, L.M. Beaver, C.P. Wong, J. Choi, S. Hamer, E.W. Davis, et al., Sulforaphane and sulforaphane-nitrile metabolism in humans following broccoli sprout consumption: inter-individual variation, association with gut microbiome composition, and differential bioactivity, Mol. Nutr. Food Res. 68 (4) (2024) e2300286.
[159] Z. Qi, H. Ji, M. Le, H. Li, A. Wieland, S. Bauer, et al., Sulforaphane promotes *C. elegans* longevity and healthspan via DAF-16/DAF-2 insulin/IGF-1 signaling, Aging (Albany NY) 13 (2) (2021) 1649–1670.
[160] K. Trinh, K. Moore, P.D. Wes, P.J. Muchowski, J. Dey, L. Andrews, et al., Induction of the phase II detoxification pathway suppresses neuron loss in *Drosophila* models of Parkinson's disease, J. Neurosci. 28 (2) (2008) 465–472.
[161] A.T. Dinkova-Kostova, J.W. Fahey, R.V. Kostov, T.W. Kensler, KEAP1 and done? Targeting the NRF2 pathway with sulforaphane, Trends Food Sci. Technol. 69 (B) (2017) 257–269.
[162] B. Abbaoui, C.R. Lucas, K.M. Riedl, S.K. Clinton, A. Mortazavi, Cruciferous vegetables, isothiocyanates, and bladder cancer prevention, Mol. Nutr. Food Res. 62 (18) (2018) e1800079.
[163] C. Cao, H. Wu, S.N. Vasilatos, U. Chandran, Y. Qin, Y. Wan, et al., HDAC5–LSD1 axis regulates antineoplastic effect of natural HDAC inhibitor sulforaphane in human breast cancer cells, Int. J. Cancer. 143 (6) (2018) 1388–1401.
[164] N.M. Shawky, G.S. Shehatou, G.M. Suddek, N.M. Gameil, Comparison of the effects of sulforaphane and pioglitazone on insulin resistance and associated dyslipidemia, hepatosteatosis, and endothelial dysfunction in fructose-fed rats, Environ. Toxicol. Pharmacol. 66 (2019) 43–54.
[165] G. Schepici, P. Bramanti, E. Mazzon, Efficacy of sulforaphane in neurodegenerative diseases, Int. J. Mol. Sci. 21 (22) (2020) 8637.
[166] C.N. Armah, C. Derdemezis, M.H. Traka, J.R. Dainty, J.F. Doleman, S. Saha, et al., Diet rich in high glucoraphanin broccoli reduces plasma LDL cholesterol: evidence from randomised controlled trials, Mol. Nutr. Food Res. 59 (5) (2015) 918–926.
[167] R. Nouchi, Q. Hu, T. Saito, N.Y.D.S. Kawata, H. Nouchi, R. Kawashima, Brain training and sulforaphane intake interventions separately improve cognitive performance in healthy older adults, whereas a combination of these interventions does not have more beneficial effects: evidence from a randomized controlled trial, Nutrients 13 (2) (2021) 352.
[168] K. Sato, H. Kihara, Y. Kumazawa, K. Tatara, Oral chronic sulforaphane effects on heavy resistance exercise: implications for inflammatory and muscle damage parameters in young practitioners, Nutrition 90 (2021) 111266.

[169] Y. Zhang, Q. Wu, J. Liu, Z. Zhang, X. Ma, Y. Zhang, et al., Sulforaphane alleviates high fat diet-induced insulin resistance via AMPK/Nrf2/GPx4 axis, Biomed. Pharmacother. 152 (2022) 113273.
[170] S.-R. Jun, A. Cheema, C. Bose, M. Boerma, P.T. Palade, E. Carvalho, et al., Multi-omic analysis reveals different effects of sulforaphane on the microbiome and metabolome in old compared to young mice, Microorganisms 8 (10) (2020) 1500.
[171] J. Wu, S. Cui, X. Tang, Q. Zhang, Y. Jin, J. Zhao, et al., *Bifidobacterium longum* CCFM1206 promotes the biotransformation of glucoraphanin to sulforaphane that contributes to amelioration of dextran-sulfate-sodium-induced colitis in mice, J. Agric. Food Chem. 71 (2) (2023) 1100–1112.
[172] Y. Zhang, L. Tan, C. Li, H. Wu, D. Ran, Z. Zhang, Sulforaphane alter the microbiota and mitigate colitis severity on mice ulcerative colitis induced by DSS, AMB Express 10 (1) (2020) 119.
[173] Y. Wu, Y. Shen, Y. Zhu, J. Mupunga, L. Zou, C. Liu, et al., Broccoli ingestion increases the glucosinolate hydrolysis activity of microbiota in the mouse gut, Int. J. Food Sci. Nutr. 70 (5) (2019) 585–594.
[174] B. Singh, J.P. Singh, A. Kaur, N. Singh, Phenolic composition, antioxidant potential and health benefits of citrus peel, Food Res. Int. 132 (2020) 109114.
[175] A. Mas-Capdevila, J. Teichenne, C. Domenech-Coca, A. Caimari, J.M. Del Bas, X. Escoté, et al., Effect of hesperidin on cardiovascular disease risk factors: the role of intestinal microbiota on hesperidin bioavailability, Nutrients 12 (5) (2020) 1488.
[176] A. Amaretti, S. Raimondi, A. Leonardi, A. Quartieri, M. Rossi, Hydrolysis of the rutinose-conjugates flavonoids rutin and hesperidin by the gut microbiota and bifidobacteria, Nutrients 7 (4) (2015) 2788–2800.
[177] K. Wdowiak, J. Walkowiak, R. Pietrzak, A. Bazan-Woźniak, J. Cielecka-Piontek, Bioavailability of hesperidin and its aglycone hesperetin—compounds found in citrus fruits as a parameter conditioning the pro-health potential (neuroprotective and antidiabetic activity)—mini-review, Nutrients 14 (13) (2022) 2647.
[178] J. Zhang, H. Lei, X. Hu, W. Dong, Hesperetin ameliorates DSS-induced colitis by maintaining the epithelial barrier via blocking RIPK3/MLKL necroptosis signaling, Eur. J. Pharmacol. 873 (2020) 172992.
[179] E.A. Franzosa, A. Sirota-Madi, J. Avila-Pacheco, N. Fornelos, H.J. Haiser, S. Reinker, et al., Gut microbiome structure and metabolic activity in inflammatory bowel disease, Nat. Microbiol. 4 (2) (2019) 293–305.
[180] M. Maurer Sost, Y. Stevens, B. Salden, F. Troost, A. Masclee, K. Venema, Citrus extract high in flavonoids beneficially alters intestinal metabolic responses in subjects with features of metabolic syndrome, Foods 12 (18) (2023) 3413.
[181] W. Wang, L. Qu, Z. Cui, F. Lu, L. Li, F. Liu, Citrus flavonoid hesperetin inhibits α-synuclein fibrillogenesis, disrupts mature fibrils, and reduces their cytotoxicity: in vitro and in vivo studies, J. Agric. Food Chem. 71 (43) (2023) 16174–16183.
[182] Q. Dong, Z. Cui, X. Wu, L. Li, F. Lu, F. Liu, Natural flavonoid hesperetin blocks amyloid β-protein fibrillogenesis, depolymerizes preformed fibrils and alleviates cytotoxicity caused by amyloids, Food Funct 15 (8) (2024) 4233–4245.
[183] A.O. Adedara, G.N. Bressan, M.M. Dos Santos, R. Fachinetto, A.O. Abolaji, N.V. Barbosa, Antioxidant responses driven by hesperetin and hesperidin counteract Parkinson's disease-like phenotypes in *Drosophila melanogaster*, Neurotoxicology 101 (2024) 117–127.
[184] C.-H. Yeh, Z.-Q. Shen, T.-W. Wang, C.-H. Kao, Y.-C. Teng, T.-K. Yeh, et al., Hesperetin promotes longevity and delays aging via activation of Cisd2 in naturally aged mice, J. Biomed. Sci. 29 (1) (2022) 53.
[185] R. Naz, F. Saqib, S. Awadallah, M. Wahid, M.F. Latif, I. Iqbal, et al., Food polyphenols and type II diabetes mellitus: pharmacology and mechanisms, Molecules 28 (10) (2023) 3996.
[186] R. Novotná, D. Škařupová, J. Hanyk, J. Ulrichová, V. Křen, P. Bojarová, et al., Hesperidin, hesperetin, rutinose, and rhamnose act as skin anti-aging agents, Molecules 28 (4) (2023) 1728.
[187] Z. Yari, M. Movahedian, H. Imani, S.M. Alavian, M. Hedayati, A. Hekmatdoost, The effect of hesperidin supplementation on metabolic profiles in patients with metabolic syndrome: a randomized, double-blind, placebo-controlled clinical trial, Eur. J. Nutri. 59 (6) (2020) 2569–2577.
[188] Y.S. Sheen, H.Y. Huang, Y.H. Liao, The efficacy and safety of an antiaging topical serum containing hesperetin and sodium cyclic lysophosphatidic acid: a single-center clinical trial, J. Cosmet. Dermatol. 20 (12) (2021) 3960–3967.
[189] H. Takumi, H. Nakamura, T. Simizu, R. Harada, T. Kometani, T. Nadamoto, et al., Bioavailability of orally administered water-dispersible hesperetin and its effect on peripheral vasodilatation in human subjects: implication of endothelial functions of plasma conjugated metabolites, Food Funct 3 (4) (2012) 389–398.
[190] L.Q. Wang, Mammalian phytoestrogens: enterodiol and enterolactone, J. Chromatogr. B. Analyt. Technol. Biomed. Life Sci. 777 (1–2) (2002) 289–309.
[191] W.T. Kwa, S. Sundarajoo, K.Y. Toh, J. Lee, Application of emerging technologies for gut microbiome research, Singapore Med. J. 64 (1) (2023) 45–52.
[192] R. Del-Rio-Ruiz, D.R.R. da Silva, H. Suresh, H. Creasey, C. Asci, D.M. dos Santos, et al., Soft autonomous ingestible device for sampling the small-intestinal microbiome, Device 2 (2024) 100406.
[193] D. Shalon, R.N. Culver, J.A. Grembi, J. Folz, P.V. Treit, H. Shi, et al., Profiling the human intestinal environment under physiological conditions, Nature 617 (7961) (2023) 581–591.