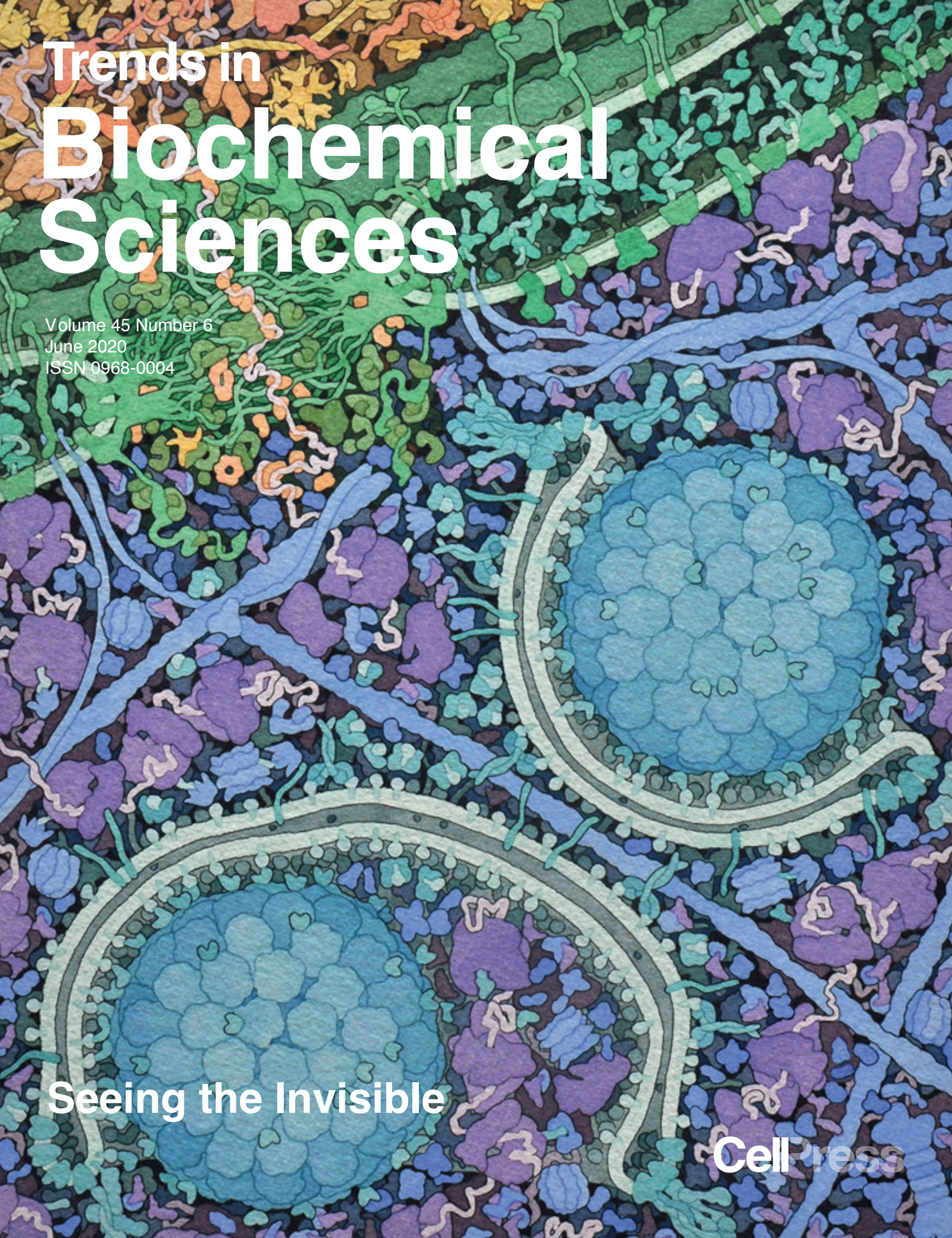
Trends in
Biochemical
Sciences
Volume 45 Number 6
June 2020
ISSN 0968-0004
Seeing the Invisible
CellPress

Trends in Biochemical Sciences

CellPress
REVIEWS

Opinion

# Phytochemicals as Prebiotics and Biological Stress Inducers

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**Phytochemicals in fruits and vegetables produce health benefits, but questions remain regarding their bioavailability, molecular targets, and mechanism of action. Here, we address these issues by considering the prebiotic and biological properties of phytochemicals. A fraction of phytochemicals consumed orally passes through the gut lumen, where it modulates the composition of the gut microbiota and maintains intestinal integrity. Phytochemicals and microbiota-derived metabolites that are absorbed by the organism comprise compounds that, at low doses, induce stress resistance mechanisms, including autophagy, DNA repair, and expression of detoxifying and antioxidant enzymes. We propose that these mechanisms improve cellular and organ function and can account for the promiscuous bioactivities of phytochemicals, despite their limited bioavailability and extremely varied chemical structures.**

## Absorbed or Not? The Problem of Bioavailability

A diet rich in fruits and vegetables produces major health benefits, including increased lifespan and reduced incidence of chronic diseases such as cancer and cardiovascular and neurodegenerative diseases, as well as obesity and type 2 diabetes [1–3]. Epidemiological and experimental studies suggest that **phytochemicals** (see Glossary), including alkaloids, polyphenols, polysaccharides, and terpenoids, may be responsible for these health benefits [4–9]. While the benefits were attributed earlier to the phytochemicals' antioxidant properties, this possibility has been challenged by reports showing that the antioxidant effects do not correlate with the overall biological activity [10]. Moreover, systematic analysis of clinical trials indicates that high doses of antioxidants may actually increase mortality [11] and that phytochemical metabolites are usually found in plasma and tissues at concentrations more than 50-fold lower than endogenous antioxidants such as urate and bilirubin [12]. It thus remains unclear how phytochemicals may produce broad-range **bioactivities** resulting in health benefits, despite showing highly diverse chemical structures (Figure 1).

Another feature of phytochemicals that complicates explanations of their biological activity is their **bioavailability**, which is usually considered to be low. Humans can consume several grams of phytochemicals in the diet every day [13], but only a fraction of these compounds is absorbed into the circulation. For instance, only 16% of **resveratrol** consumed orally within food matrices is absorbed into the blood and excreted into urine 24 h following consumption, while the values for catechin and **quercetin** are even lower, at 2% and 5%, respectively [14]. Overall, the concentration of phytochemicals and their metabolites in the blood and tissues is usually in the low micromolar range [13]. While recent studies using more advanced detection methodologies indicate that as much as 80% of polyphenols may be absorbed into the human body [12,15,16], 90% of polyphenols from a cup of green tea are removed from the circulation within 8 hours, and a large degree of variation is observed between individuals [17].

## Highlights

Phytochemicals are molecules found in fruits, vegetables, and mushrooms that are widely consumed in the human diet.

Epidemiological studies indicate that phytochemicals may produce health benefits, but this possibility has been controversial until now due to the compounds' limited bioavailability and unclear mechanism of action.

Many phytochemicals can modulate the composition of the gut microbiota, thereby helping to maintain physiological functions without the need to be absorbed into the circulation.

Phytochemicals that do reach the circulation may produce health benefits by inducing stress resistance mechanisms, including autophagy, DNA repair, mitochondrial biogenesis, and expression of detoxifying and antioxidant enzymes.

Mechanisms of action involving the gut microbiota and stress resistance pathways can explain the broad bioactivities of phytochemicals, despite the limited bioavailability and highly varied chemical structures of these molecules.

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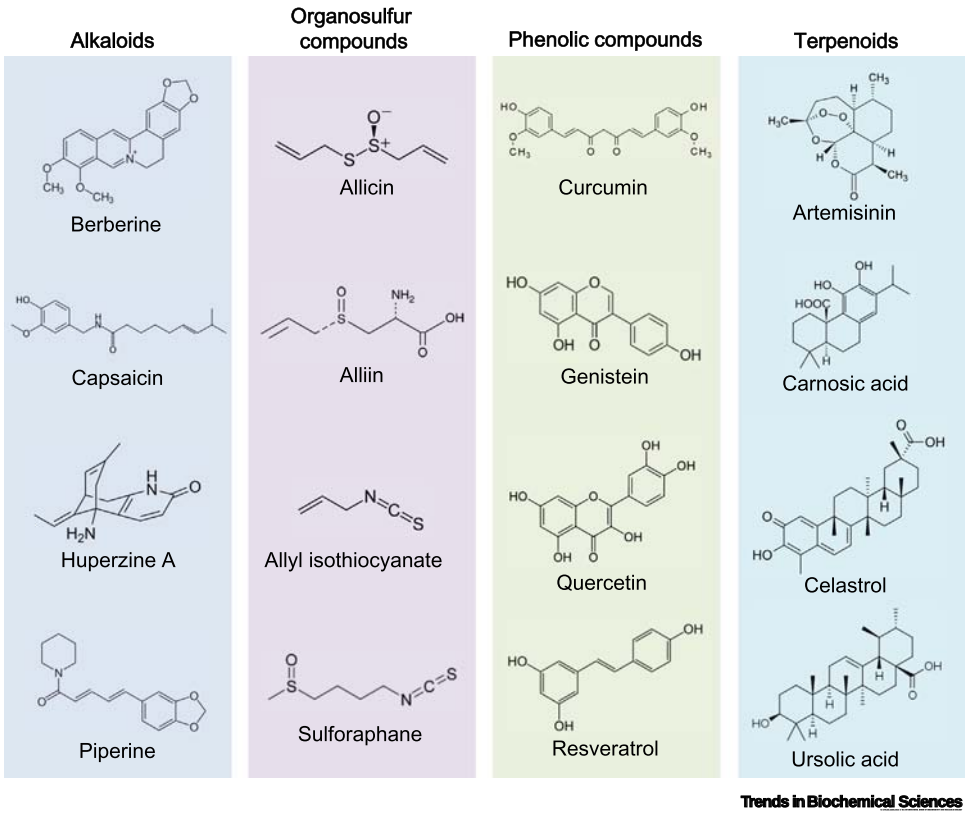


Figure 1. Chemical Structures of Phytochemicals. Phytochemicals are classified into the families of alkaloids, organosulfur compounds, phenolic compounds, and terpenoids. Alkaloids, such as capsaicin in chili and piperine in black pepper, harbor nitrogen-containing functional groups and usually have a bitter or pungent taste. Organosulfur compounds contain sulfur-containing functional groups and are found in vegetables such as broccoli, garlic, and onions. Polyphenols are part of a large family of organic compounds containing phenol groups; the largest intake of polyphenols in the human diet probably comes from coffee and tea, but it also comes from red wine and fruits. Terpenoids such as artemisinin and celastrol from the Asian plants *Artemisia annua* and thunder god vine, respectively, are fragrant compounds originating from the condensation of isoprene monomers, often forming multicyclic compounds.

Yet, it has recently become clear that phytochemicals do not need to be absorbed to produce beneficial effects [18,19] (Figure 2). Through examples provided here, we present a model in which phytochemicals produce health benefits in two major ways: the nonabsorbed fraction of phytochemicals promotes intestinal functions and acts as a **prebiotic**, while the absorbed part induces stress resistance mechanisms that improve cellular and organ functions.

## Feed the Gut Microbiota Before It Feeds Itself

Plant and fungal compounds can produce various beneficial effects on the gut microbiota. The phytochemicals berberine, catechin, quercetin, and resveratrol enrich beneficial bacteria in the gut, including *Akkermansia*, *Bifidobacterium*, and *Lactobacillus*, and reduce the levels of opportunistic bacteria, including *Escherichia* and *Enterococcus* [18,19]. Similarly, a polyphenol-rich cranberry extract, which produces antidiabetic, anti-inflammatory, and weight-loss effects in obese mice, increases the levels of *Akkermansia muciniphila* [20]. Moreover, polysaccharide phytochemicals may induce the growth of beneficial bacteria that produce metabolites such as **short-chain fatty acids**, which in turn induce various beneficial effects on the host, including reduced appetite, insulin resistance, lipid accumulation, and inflammation [2].

## Glossary

**Autophagy:** cellular process in which dysfunctional or unnecessary macromolecules and organelles are targeted for degradation by inclusion within double-membrane vesicles and fusion with lysosomes; exercise, caloric restriction, intermittent fasting, some pharmaceutical drugs, and phytochemicals can improve cellular function by activating this recycling process.

**Bioactivities:** beneficial or detrimental effects of a substance on the body.

**Bioavailability:** proportion of a substance consumed orally that enters biological fluids and can exert an effect on the body. Substances that are modified or metabolized by the gut microbiota may also be absorbed and have bioactivities *in vivo*.

**Curcumin:** phenolic compound found in turmeric spice, widely used to prepare curry dishes in Asian cuisine.

**Hormesis:** biphasic dose response produced by stress on living organisms and characterized by beneficial effects at low doses and detrimental effects produced at high doses; interventions that may produce hormetic responses include exercise, caloric restriction, intermittent fasting, and phytochemical intake.

**Lipopolysaccharides (LPSs):** endotoxins found in the cell wall of gram-negative bacteria that produce a proinflammatory response in the body; high doses of these compounds in the blood can induce lethal septic shock, while low doses are associated with chronic inflammation.

**Metabolic endotoxemia:** systemic, proinflammatory condition caused by translocation into the blood of lipopolysaccharides originating from gram-negative bacteria in the gut microbiota; also called 'leaky gut syndrome,' this condition is believed to be involved in the pathogenesis of various chronic diseases, including cardiovascular disease, obesity, and type 2 diabetes.

**Phytochemicals:** plant compounds that do not usually contribute to primary metabolism in plants; these compounds represent secondary metabolites produced in response to stress, such as temperature shock, excess sunlight, or contact with insects. (Compounds derived from mycelium and mushrooms are also considered in this category in the present work, although, technically,

More specifically, our group showed that polysaccharides derived from the fungi *Ganoderma lucidum* and *Hirsutella sinensis* produce anti-inflammatory, antidiabetic, and antiobesity effects in high-fat diet (HFD)-fed mice by modulating the gut microbiota [21,22]. Levels of *Roseburia*, *Eubacterium*, and *Parabacteroides*, which are associated with an anti-inflammatory profile, were increased by the polysaccharides, while detrimental gram-negative species such as *Escherichia*, *Enterococcus*, and *Oscillibacter* were reduced. Notably, the health benefits produced by the polysaccharides could be reproduced by transplantation of the gut microbiota of phytochemical-treated animals into HFD-fed mice, confirming that the gut microbiota mediated the health benefits of the phytochemicals [21,22].

Phytochemicals that pass through the gut may produce health benefits in other ways. They reduce the detrimental effects of excess food and fat intake by inhibiting intestinal enzymes, reducing absorption of energy-dense nutrients, and favoring the excretion of secondary bile acids [2,23]. Moreover, by providing food substrates for colonic bacteria, phytochemicals, such as polysaccharides, prevent the proliferation of bacteria that degrade the intestinal mucus to obtain energy, thereby protecting the intestinal mucosa from erosion, infection, and inflammation. In the absence of phytochemicals and dietary fiber, the proliferation of mucus-degrading bacteria may compromise the intestinal barrier, leading to translocation of bacterial **lipopolysaccharides** (LPSs) into the blood, a condition called **metabolic endotoxemia** [24]. By maintaining intestinal integrity and preventing endotoxemia, polysaccharides and other phytochemicals may help prevent the development of cardiovascular disease, type 2 diabetes, and obesity [18,25]. Moreover, phytochemicals can reduce the detrimental effects of metabolites derived from a high-protein diet, such as ammonia, indoles, and hydrogen sulfide, which have been associated with the development of insulin resistance and type 2 diabetes [26].

While it remains to be determined to what extent the effects of phytochemicals and their metabolites are due to the gut microbiota or to other effects on intestinal homeostasis, it is apparent that these mechanisms can account for many bioactivities produced by these compounds, without the need for the compounds to reach the circulation. In this sense, phytochemicals produce many beneficial bioactivities by acting as prebiotics and improving various physiological functions that have been shown to depend on proper functioning of the gut and its microbiota (Figures 2 and 3).

## Is There Anything They Cannot Do? The Promiscuous Activity of Phytochemicals

### Broad Bioactivities

In addition to modulating physiological function via the gut, phytochemicals can produce a surprisingly broad range of effects. For instance, resveratrol has been described to produce antioxidant, anti-inflammatory, antidiabetic, antiobesity, cardioprotective, liver-protective, neuroprotective, and anticancer effects in experimental models [27]. Similar broad-range bioactivities have been described for other phytochemicals, such as artemisinin [28], berberine [29], **curcumin** [30], quercetin [31], sulforaphane [32], and ursolic acid [33] (Figure 1). The same phenomenon is observed for phytochemical-rich plant extracts. For example, a recent description of *Cissampelos* plants describes analgesic, anti-inflammatory, antiallergic, antidepressant, neuroprotective, anticancer, antioxidant, hepatoprotective, and antidiabetic activities [34]. Similar broad-range bioactivities have been reported for herbs such as chamomile [35] and green tea [36] and for spices that include turmeric [37] and garlic [38]. Some of these effects can be attributed to modulation of gut microbiota and maintenance of gut homeostasis, but one may wonder how these compounds can produce so many diverse bioactivities, despite their highly varied chemical structures (Figure 1).

Compared with vitamins and minerals, which are absorbed via specific transporters and according to the body's needs, phytochemicals are similar to **xenobiotic compounds** in the sense that none of

these are from the kingdom of fungi and have also been called 'fungochemicals.')

**Prebiotic:** a compound that promotes the growth of beneficial bacteria in the gut. These compounds are generally poorly digested and absorbed by the host but are available as a source of nutrients and energy to colonic bacteria.

**Proteostasis:** cellular processes activated to maintain homeostasis when proteins denaturate, aggregate, or become nonfunctional; these processes include regulated protein translation, molecular chaperones, and protein degradation pathways involving the proteasome and autophagy.

**Quercetin:** a flavonoid polyphenol found in many fruits, vegetables, and grains.

**Resveratrol:** a stilbenoid polyphenol found in grapes, berries, peanuts, and red wine.

**Short-chain fatty acids:** small fatty acids including acetate, butyrate, and propionate that are derived from polysaccharides by the gut microbiota; these molecules produce beneficial effects on the host, including reduced appetite, inflammation, and insulin resistance.

**Xenobiotic compounds:** molecules that are foreign to the human body and are actively metabolized, conjugated to increase their solubility in water, and excreted into the urine or bile. Common examples include environmental toxins and pharmaceutical drugs.

**Xenohormesis:** term used to describe the possibility that animals and humans may have evolved to sense unfavorable environmental conditions by reacting to compounds produced by plants under conditions of stress.

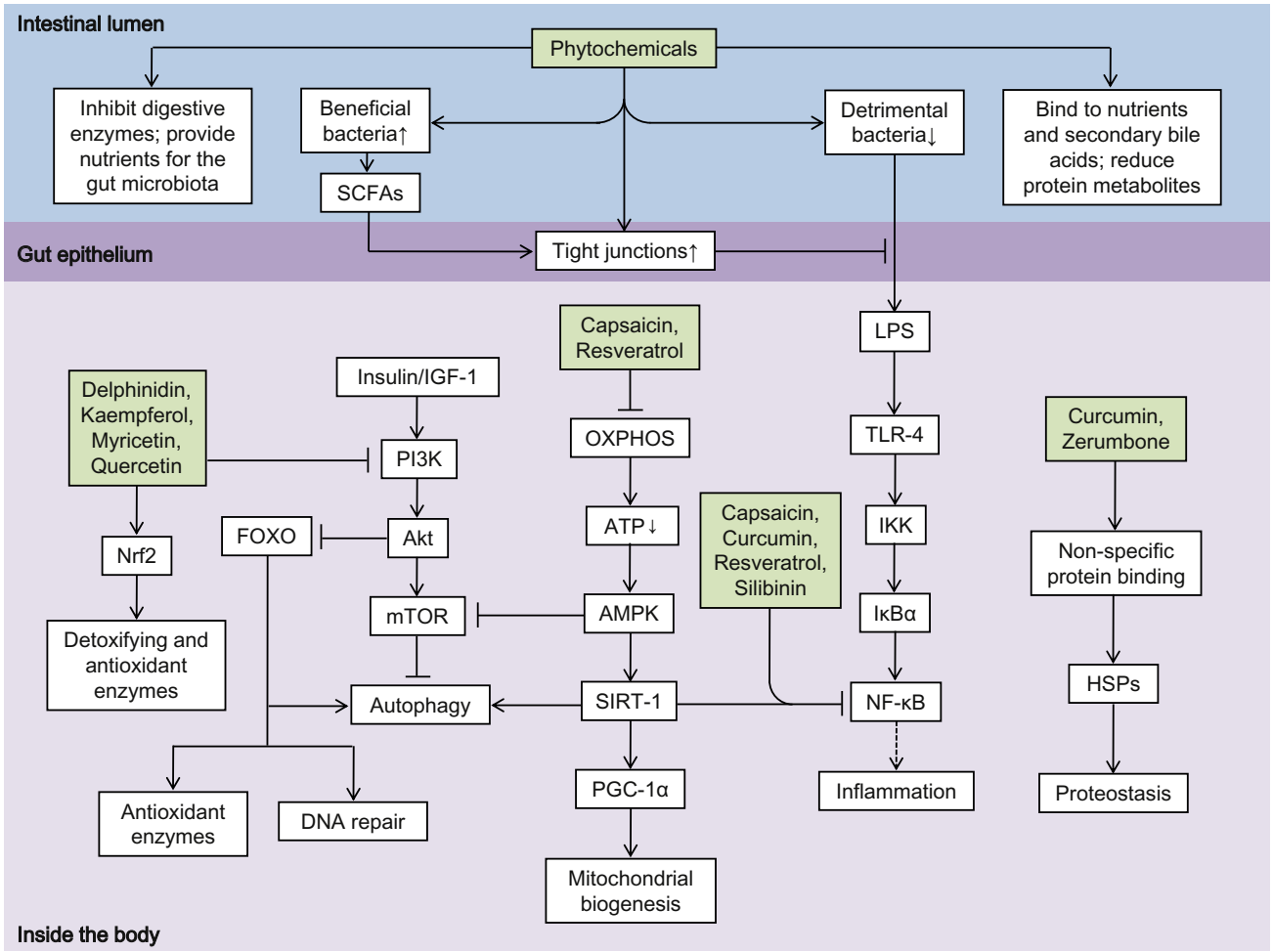


Figure 2. Mechanism of Action of Phytochemicals in the Human Body. Phytochemicals consumed in the diet are partially absorbed, and a significant fraction goes through the gut lumen, where it can modulate gut microbiota composition and improve gut barrier integrity by activating tight junction expression. The fraction of phytochemicals absorbed in the body represents exogenous compounds that induce stress resistance mechanisms. Examples are shown of phytochemicals (green boxes) that affect cellular and physiological reactions (white boxes). Modulation of these reactions induces cellular stress and an overcompensation reaction to maintain homeostasis, producing a hormetic response that improves cellular function, helps to prevent chronic diseases, and prolongs lifespan. Abbreviations: ATP, adenosine triphosphate; AMPK, 5′-adenosine monophosphate–activated protein kinase; FOXO, forkhead box O; HSPs, heat shock proteins; IGF-1, insulin-like growth factor-1; Iκβα, inhibitor of κB, alpha; IKK, inhibitor of κB kinase; LPS, lipopolysaccharide; mTOR, mammalian target of rapamycin; Nrf2, nuclear factor erythroid 2–related factor 2; OXPHOS, oxidative phosphorylation chain; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; PI3K, phosphoinositide 3-kinase; SIRT-1, sirtuin-1; SCFAs, short-chain fatty acids; TLR-4, Toll-like receptor-4.

these compounds are required for physiological reactions. While these compounds reach tissues and organs at concentrations in the high nanomolar to low micromolar range, as compared with micromolar to millimolar range for most vitamins and minerals, these concentrations can be sufficient to induce biological activities [13]. In fact, the bioavailability of phytochemicals is comparable to that of many pharmaceutical drugs taken orally, including statins and anticancer compounds [39,40].

In our view, the promiscuous bioactivities of phytochemicals and plant extracts indicate that, following their absorption into the body, they act via central pathways that affect different cellular and physiological functions.

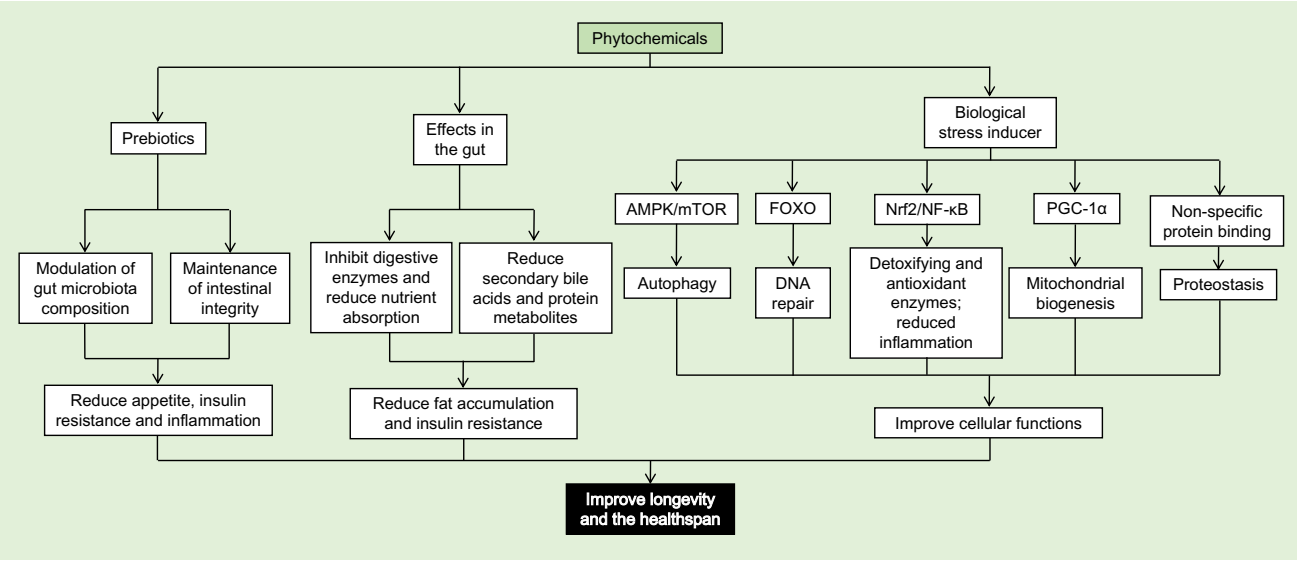


Figure 3. Flow Diagram of Phytochemicals' Mechanisms of Action. According to our proposed model, phytochemicals may improve cellular function and produce health benefits by acting as prebiotics and biological stress inducers, in addition to modulating intestinal function. Abbreviations: AMPK, 5′-adenosine monophosphate–activated protein kinase; FOXO, forkhead box O; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; Nrf2, nuclear factor erythroid 2–related factor 2; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α.

## Phytochemicals Maintain Gut Barrier Integrity

Once absorbed, some phytochemicals and their metabolites can activate the aryl hydrocarbon receptor (AhR) in intestinal epithelial cells, which improves gut barrier integrity by inducing the expression of tight junction proteins [41] (Figure 2). For example, urolithin A, a metabolite of polyphenols produced by the gut microbiota, binds to AhR nuclear factor erythroid 2–related factor 2 (Nrf2) and improves intestinal integrity in mice, thereby reducing inflammation and symptoms of toxin-induced colitis [41]. Absorbed phytochemicals can therefore improve gut barrier integrity and prevent the translocation of bacterial components such as LPS from the gut microbiota into the circulation.

## Induction of Detoxifying and Antioxidant Enzymes

Being similar to xenobiotic compounds, phytochemicals are actively metabolized and excreted by the body into the bile and urine [12]. Curcumin, tangeritin, and diosmin bind to AhR and induce expression of detoxifying enzymes such as the cytochrome P450 family and glutathione-*S*-transferases in the liver, lungs, and skin, which leads to modification of phytochemicals to render them water soluble and allow their excretion into urine [13,42]. Induction of detoxifying enzymes by phytochemicals is believed to contribute to the chemopreventive effects of fruits and vegetables against cancer by reducing the effects of exogenous carcinogens in the body [5,43]. However, several phytochemicals, such as luteolin and myricetin, are antagonists of AhR and may interfere with the detoxifying process [44].

Phytochemicals have traditionally been viewed as antioxidants, but evidence suggests that they may help to neutralize reactive oxygen species (ROS) indirectly by inducing expression of antioxidant enzymes. As such, phytochemicals such as quercetin, sulforaphane, and resveratrol activate the Nrf2 pathway and induce expression of antioxidant enzymes, including catalase and superoxide dismutase, which in turn neutralize ROS [45] (Figure 2). Activation of Nrf2 can also inhibit the transcription factor nuclear factor (NF)-κB, which may account for the anti-inflammatory effects of many phytochemicals [45].

### Activation of Autophagy and DNA Repair

**Autophagy** has emerged as a major cellular process that may improve cellular and organ functions and prevent chronic diseases by removing damaged proteins and organelles [46]. Many phytochemicals, such as 3′,4′,7-trihydroxyisoflavone, 5-deoxykaempferol, kaempferol, and delphinidin, inhibit phosphoinositide 3-kinase (PI3K) [43], a major negative regulator of autophagy (Figure 2). On the basis of analysis of X-ray crystallography, myricetin and quercetin bind directly to PI3K and inhibit its activity [47]. Similarly, phytochemicals such as berberine, curcumin, epicatechin, genistein, quercetin, monascin, naringin, salvianolic acid A, thujone, and tiliroside produce cellular changes that result in activation of 5′-adenosine monophosphate–activated protein kinase (AMPK) *in vivo*, which induces autophagy [48–50] (Figure 2). PI3K and other mitogen-activated kinases are also hyperactive in cancer cells, providing another mechanism for the chemopreventive effects of phytochemicals against cancer [43].

Autophagy can also be induced by reduced levels of cellular energy, because it occurs in skeletal muscle cells following intense exercise [51]. Resveratrol inhibits ATP synthase of the oxidative phosphorylation chain, resulting in reduced ATP production [52]. This in turn can activate AMPK and sirtuin-1 (SIRT-1), inhibit mammalian target of rapamycin (mTOR), and lead to induction of autophagy. Additionally, resveratrol inhibits cAMP-degrading phosphodiesterase, which leads to activation of SIRT-1 and peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), processes that are associated with reduced diet-induced obesity and insulin resistance, as well as improved muscle stamina and mitochondrial biogenesis, in mice [53] (Figure 2). Resveratrol also binds to and inhibits tyrosyl tRNA synthetase and leads to poly (ADP-ribose) polymerase 1 activation and DNA repair [54].

### Nonspecific Binding to Cellular Proteins

Another feature that contributes to the broad bioactivity of phytochemicals is their nonspecific binding to different proteins. For instance, curcumin, phenethyl isothiocyanate, and zerumbone bind to various cellular proteins and induce **proteostasis** by inducing a heat shock response and activation of the proteasome and autophagy [55,56] (Figure 2). Because these phytochemicals also induce Nrf2 and suppress expression of cyclooxygenases, the mechanisms described here contribute to explaining the antioxidative, anti-inflammatory, and chemopreventive effects of phytochemicals [57]. Furthermore, many phytochemicals, such as resveratrol, inhibit proinflammatory enzymes and mediators such as cyclooxygenases, leukotriene $A_4$ hydrolase, and NF-κB [43], which can reduce inflammation (Figure 2).

### Stress Resistance and Hormesis

As seen above, phytochemicals modulate nutrient- and energy-sensing effectors such as mTOR and AMPK, as well as stress resistance pathways involving SIRT-1, Nrf2, PGC-1α, and heat shock proteins [48,49,58–60]. We believe that by activating autophagy, mitochondrial biogenesis, and neutralization of ROS via expression of antioxidant enzymes (Figures 2 and 3), phytochemicals act systemically to improve cellular and organ functions in a manner similar to the health benefits produced by other forms of stress, such as physical exercise, caloric restriction, and intermittent fasting [48,49,58–61].

While some phytochemicals can activate cellular processes such as the expression of detoxifying and antioxidant enzymes [60], most phytochemicals may act by inhibiting their cellular targets (Figure 2), resulting in mild stress that improves organ function. The concept of **hormesis** has been used to explain the beneficial effects of mild stress on the human body. While stress produces toxic or detrimental effects at high doses, it is beneficial at low doses because it improves cellular function by inducing resistance and repair mechanisms [62–64] (Box 1). Notably,

Box 1. Too Much of a Good Thing

The public views substances derived from plants such as green tea, garlic, onions, and broccoli as safe because they are derived from foods that are consumed every day. However, many phytochemicals derived from wild plants, at low or high doses, have been used as poisons, including atropine, curare alkaloids, scopolamine, and strychnine. Phytochemicals found in common food can also be toxic. Fruits and vegetables commonly consumed by humans contain phytochemicals such as amygdalin (apple seeds), chaconine and solanine (potatoes), myristicin (nutmeg), and psoralen (lemon), which can be toxic or even lethal if consumed in high doses. In fact, it appears that phytochemicals can produce either beneficial or toxic effects, depending on the doses used. For example, capsaicin found in red chili pepper can both prevent and induce cancer in animal models [75]. Substances usually considered innocuous, such as ginkgo biloba, green tea, ginger, and saffron, can produce carcinogenic, nephrotoxic, neurotoxic, and hepatotoxic effects when given at high doses to laboratory animals [76]. Additionally, daily intake of a drink as innocuous as green tea at high doses (6 cups/day for 4 months) can produce liver toxicity in healthy humans [77].

the concept that many phytochemicals produce broad-range bioactivities by inducing stress resistance may be extended to the bioactivity of pharmaceutical drugs and dietary supplements such as aspirin, glucosamine, and metformin (Box 2).

## Hormesis or Xenohormesis? An Evolutionary Perspective

Most phytochemicals are secondary metabolites produced by plants to increase resistance to environmental stress or pathogens [65]. Thus, polyphenol levels increase in plants submitted to UV light, and these compounds protect the plant from oxidative stress. The fact that phytochemicals induce stress resistance in animals and humans led to the proposition that these mammalian organisms have evolved to sense unfavorable environmental conditions and protect themselves against the impending unfavorable environment [66]. This **xenohormesis** concept is based on the observation that the polyphenols butein, piceatannol, and resveratrol activate the SIRT-1 enzyme, resulting in prolonged longevity in model organisms [67,68]. However, it is still unclear if these compounds are direct agonists of the enzyme [69] or whether they induce SIRT-1 activity by acting on upstream targets [70,71].

The xenohormesis hypothesis has led to the proposal that animals and humans have lost the ability to synthesize compounds such as polyphenols or that endogenous compounds that activate SIRT-1 and other enzymes may soon be identified [72]. This view posits that there has been evolutionary pressure for animals and humans to sense stress compounds produced by plants in order to increase survival under unfavorable conditions. However,

Box 2. The Importance of Aging-Related Pathways

Some pharmaceutical drugs may produce a broad range of health benefits by activating stress resistance pathways in a manner similar to exercise, intermittent fasting, and phytochemical intake. For instance, aspirin and its prodrug salicylate, which are well known for their analgesic, anti-inflammatory, and antithrombotic effects via inhibition of cyclooxygenases and platelet aggregation, induce autophagy by inhibiting EP300 acetyltransferase activity [78] and by directly activating 5′-adenosine monophosphate–activated protein kinase [79]. Similarly, rapamycin and metformin induce autophagy and produce antiaging effects in model organisms, as do dietary supplements, including resveratrol, glucosamine, and trehalose [48,49,80].

Other compounds that may have broad bioactivities by activating stress resistance mechanisms such as autophagy include spermidine, hydroxycitrate, and 4,4′-dimethoxychalcone [81]. The autophagy-inducing effects produced by these compounds involve recycling of damaged proteins and organelles in a systemic manner in the body [82]. These effects are profound and go beyond the effects described, such as for aspirin on thrombosis or glucosamine on cartilage formation. Accordingly, epidemiological and clinical studies suggest that compounds such as glucosamine, metformin, and spermidine increase longevity in humans [83–85].

We believe that many pharmaceutical drugs and dietary supplements that prolong lifespan and improve the health span of animals or humans are likely to act by modulating nutrient-sensing and stress resistance pathways in the body. This hypothesis is in line with the model presented here regarding phytochemicals if we consider that these compounds (e.g., aspirin, glucosamine, metformin, spermidine) have been isolated or derived from plants or fungi.

it appears more likely that phytochemicals modulate stress resistance pathways in human cells, because these pathways are essential for survival and are conserved in insects, animals, and humans [61]. We believe that rather than invoking evolutionary pressure, the induction of stress resistance pathways in animals and humans following consumption of phytochemicals reflects a typical hormesis response, in which small doses of stress-inducing compounds produce health benefits due to overcompensation of homeostatic mechanisms in living organisms [62].

The short half-lives of phytochemicals, spanning from minutes to hours, are consistent with the mechanism of hormesis, which requires intermittent exposure to stress in order to produce beneficial effects, whereas continuous exposure may be detrimental [73]. As an analogy, exercise produces health benefits when performed intermittently, with periods of rest being required to develop the adaptive and protective response. In the model presented here, we propose that regular but intermittent consumption of phytochemicals maintains gut homeostasis and produces systemic hormetic stress, which together can account for the broad beneficial effects of fruits, vegetables, and mushrooms on human health (Figure 3).

## Concluding Remarks

The realization that phytochemicals act as prebiotics in the gut lumen and as biological stress inducers when absorbed into the body can explain some controversial observations regarding these molecules, including their limited bioavailability, highly varied structures, multiple cellular targets, promiscuous bioactivities, and toxicity at high doses. Ironically, the limited bioavailability of phytochemicals and the relatively low concentrations of metabolites detected *in vivo* may minimize toxicity and instead favor beneficial, hormetic effects. However, the effects of phytochemicals are likely to vary according to the composition of the gut microbiota and host genetic polymorphism, which affect absorption, detoxification, and overall bioactivities [74]. For these reasons, personalization of phytochemical use may be necessary to obtain optimal health benefits (see Outstanding Questions). We expect that further studies, ranging from gut microbiota and gene polymorphism analysis to clinical trials with plant-based diets and specific phytochemicals, will have significant impact on the fields of nutrition and medicine.

## Outstanding Questions

What is the influence of gut microbiota composition and host genetic polymorphism in the effects produced by dietary phytochemicals?

Can the frequency and quantity of fruit, vegetable, and mushroom consumption be personalized for individuals to maximize health benefits?

How can knowledge about the effects of phytochemicals and pharmacological drugs via hormesis be used to design better dietary interventions and medical treatments?

How does the capacity to maintain homeostasis influence the hormetic response produced by the diet or specific phytochemicals in aging individuals?

Can properly designed observational studies and clinical trials demonstrate the health benefits of phytochemicals, plant-based diets, and dietary supplements?

### Acknowledgments

The authors' work is supported by Primordia Institute of New Sciences and Medicine.

### Disclaimer Statement

Y.F.K. is president of Chang Gung Biotechnology. J.D.Y. is chairman of the board of Chang Gung Biotechnology. The authors have filed patents related to the preparation and use of natural health products, medicinal mushrooms, and probiotics.

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