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Functional Food Bioactives at the Host-Pathogen Interphase: Biochemical Mechanisms and Implications for Disease Prevention and Health

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Abstract

Background: The rising burden of infectious and chronic diseases has renewed interest in functional food-derived bioactive compounds with preventive and therapeutic relevance. Phytochemicals, naturally occurring non-nutritive compounds found in fruits, vegetables, legumes, herbs, cereals, and medicinal plants, are increasingly recognized as important modulators of host defense, microbial ecology, immune homeostasis, and metabolic resilience. Their functions extend beyond antioxidant activity to direct regulation of host-pathogen interactions.

Objective: This review examines the role of phytochemicals in disease prevention through the lens of nutritional biochemistry, with emphasis on their influence at the host-pathogen interface. It highlights mechanistic pathways through which phytochemicals modulate immune signaling, microbiota composition, epithelial barrier integrity, inflammation, oxidative stress, and pathogen virulence.

Methods: A structure narrative review was conducted using literature published between 2020 and 2026 retrieved from major scientific databases, including PubMed, Scopus, Web of Science, ScienceDirect and Google Scholar. Relevant experimental, clinical, epidemiological, and translational studies on phytochemicals, host-pathogen interactions, immune regulation, gut microbiota, oxidative stress, and disease prevention were critically screened and synthesized thematically to highlight major biochemical mechanisms and preventive health implications.

Results: Accumulating evidence shows that phytochemicals such as polyphenols, flavonoids, terpenoids, alkaloids, glucosinolates, carotenoids, and organosulfur compounds regulate key molecular pathways involved in disease prevention. These include nuclear factor erythroid 2-related factor 2 activation, nuclear factor-kappa B suppression, gut microbiota remodeling, quorum sensing inhibition, pathogen membrane disruption, and cytokine modulation. Phytochemicals also improve host tolerance to infection while reducing susceptibility to metabolic and inflammatory disorders.

Conclusion: Phytochemicals occupy a strategic position in disease prevention by linking nutrition, metabolism, immunity, and microbial control. Understanding their biochemical roles at the host-pathogen interphase strengthens the case for functional food-based preventive strategies and precision nutrition in modern healthcare.

Novelty of the Review: This review provides an integrated functional food science perspective on bioactives at the host-pathogen interphase, an area that remains insufficiently explored in existing literature. Unlike conventional review that examine phytochemicals mainly as antioxidants or

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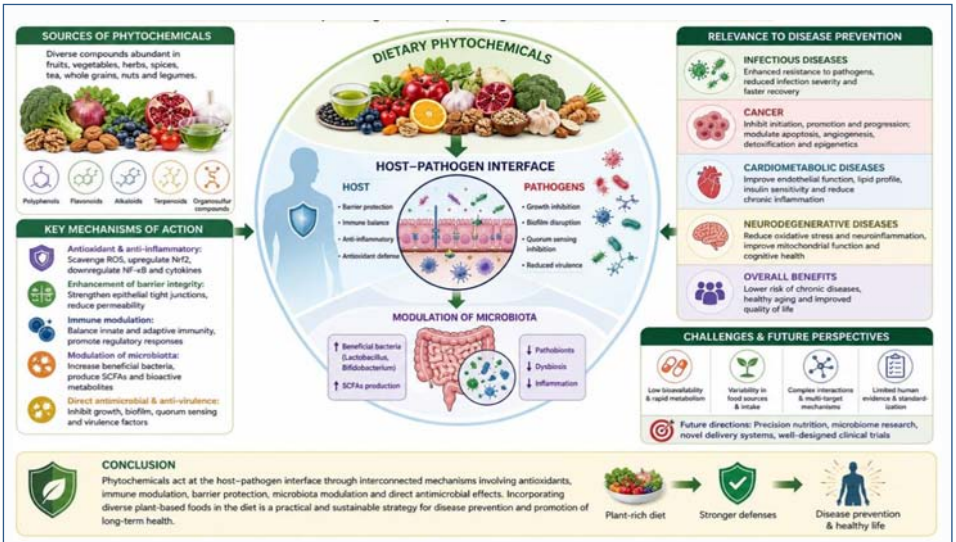
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isolated therapeutic agents, the present study highlights their interconnected roles in immune regulation, microbiota regulation, epithelial barrier protection, antimicrobial activity, and cellular signalling within a unified host-pathogen framework.

Keywords: Functional Food; Bioactives; e Host-Pathogen Interphase; Biochemical Mechanisms; Disease Prevention; Oxidative Stress; Anti-Inflammatory Activity



Graphical Abstract:

Introduction

The relationship between diet and disease has moved beyond the classical focus on macronutrients and essential micronutrients. Attention has increasingly shifted toward phytochemicals, a diverse group of plant-derived compounds that, although not required for basic survival, exert profound biological effects in humans [1]. These compounds are now understood as active participants in cellular signaling, metabolic regulation, and immune defense, placing them at the centre of modern nutritional biochemistry. Their relevance becomes even more apparent when viewed at the interface where the host encounters pathogenic organisms [2].

The host-pathogen interphase represents a dynamic environment in which microbial invasion, host defense, and metabolic responses are tightly interconnected. At this boundary, epithelial barriers, immune cells, and resident microbiota interact continuously with external agents. Disruption of this balance may lead to infection, chronic inflammation, or metabolic dysfunction. Phytochemicals influence this delicate equilibrium through multiple mechanisms, including modulation of oxidative stress, regulation of inflammatory signaling pathways, alteration of microbial composition, and interference with pathogen survival strategies [2].

Recent advances have revealed that phytochemicals act not merely as antioxidants, as once widely assumed, but as regulators of gene expression and intracellular signaling [3]. Compounds such as flavonoids, polyphenols, and terpenoids have been shown to influence transcription factors, including nuclear factor-kappa B and nuclear factor erythroid 2-related factor 2, thereby shaping immune responses and cellular resilience [4]. These interactions are particularly important in the context of infectious diseases, where excessive inflammation may be as damaging as the pathogen itself.

Another critical dimension is the interaction between phytochemicals and the gut microbiota. The gastrointestinal tract serves as a major site of host–pathogen interaction, and its microbial inhabitants play a central role in maintaining health. Phytochemicals can act as substrates for microbial metabolism, leading to the production of bioactive metabolites that further influence host physiology [5]. At the same time, they can suppress pathogenic microbes and support beneficial species, thereby reinforcing colonization resistance [5, 6].

The global rise in non-communicable diseases, alongside persistent infectious threats, has intensified the search for preventive strategies that are safe, accessible, and sustainable. Dietary phytochemicals offer a promising approach because they operate at multiple biological levels, from molecular signaling to ecosystem-level interactions within the microbiome. Their ability to modulate both host defense and pathogen behavior distinguishes them from conventional pharmacological agents that often target a single pathway. This review explores the roles of phytochemicals in disease prevention through the framework of nutritional biochemistry at the host-pathogen interphase. It integrates current evidence from molecular, cellular, and clinical studies to provide a coherent understanding of how these compounds contribute to maintaining health and preventing disease.

Methodology

This review adopts a structured narrative approach to synthesize current evidence on the roles of functional food bioactives in disease prevention at the host-pathogen interface within the framework of functional food science. The methodology was designed to provide comprehensive coverage of recent advances in phytochemical research, host-microbiome interactions, immune regulation, and disease prevention mechanisms while maintaining translational relevance to public health and preventive nutrition.

Literature search strategy

A systematic search of peer-reviewed literature published between January 2020 and April 2026 was conducted using major scientific databases, including PubMed, Scopus, Web of Science, ScienceDirect and Google Scholar. Search terms were developed to capture key thematic areas and included combinations of the following keywords: "Phytochemicals," "polyphenols," "flavonoids," "terpenoids," "alkaloids," "gut microbiota," "Host-pathogen interface", "functional foods" "immune modulation," "oxidative stress", "anti-inflammatory activity" and "disease prevention." Boolean operators (AND, OR) were used to refine search outputs and improve specificity.

In addition to database searches, relevant reports and review articles from recognized international organizations and scientific bodies were examined to provide contextual information on nutrition, microbiome research, and chronic disease prevention. Reference lists of selected articles were also screened to identify additional relevant studies.

Inclusion and exclusion criteria

Studies were included if they met the following criteria:

(i) Published in English between 2020 and 2026;

(ii) Focused on phytochemicals, plant bioactive compounds, or dietary polyphenols relevant to disease prevention;

(iii) Investigated mechanisms associated with host-pathogen interactions, immune regulation, oxidative stress, inflammation, microbiota modulation, or metabolic regulation;

(iv) Included experimental, clinical, epidemiological, or translational findings relevant to functional food science.

Exclusion criteria included:

(i) Studies published before 2020 unless they provided essential foundational insights;

(ii) Articles lacking sufficient methodological detail or scientific relevance;

(iii) Opinion articles without supporting empirical evidence;

(iv) Studies unrelated to phytochemicals, disease prevention, or functional food science.

Data extraction and synthesis

Relevant data were extracted systematically from selected studies, including phytochemical classes, dietary sources, molecular mechanisms, biological activities, microbiota interactions, and disease prevention outcomes. Additional variables such as study design, population characteristics, and major biochemical findings were also considered where applicable.

The extracted evidence was synthesized thematically to provide an integrated understanding of how phytochemicals influence disease prevention at the host-pathogen interface. Emphasis was placed on mechanistic pathways involving immune modulation, oxidative stress regulation, antimicrobial activity, epithelial barrier protection, and microbiota-mediated effects. Recent and high-quality evidence was prioritized to ensure scientific relevance and contemporary applicability.

Quality assessment

The quality and relevance of selected studies were evaluated based on study design, methodological clarity, sample size, reproducibility of findings, and relevance to the review objectives. Greater emphasis was placed on peer-reviewed experimental studies, clinical investigations, high-impact review articles, and recent publications with clear mechanistic or translational significance. Studies with weak methodological rigor, insufficient data presentation, or unclear relevance to host-pathogen interactions and functional food science were interpreted cautiously during evidence synthesis.

Limitations of the methodology

This review has certain methodological limitations. As a narrative synthesis, the review may be subject to selection bias despite the structured search strategy employed. Variability in study design, photochemical composition, dosage, experimental models, and outcome measures across studies also limited direct comparison of findings. In addition, differences in bioavailability, dietary patterns, and gut microbiota composition among populations may influence the generalizability of reported effects. Although, recent literature was prioritized, some foundational studies published before 2020 were included where necessary to provide conceptual background.

Conceptual Framework: Host-Pathogen Interface in Functional Food Science

The host-pathogen interface is best understood as a biologically active boundary where host tissues, immune mechanisms, resident microbiota, and invading organisms engage in continuous interaction. This interface is not limited to a single anatomical site. It spans the gastrointestinal tract, respiratory mucosa, skin, and urogenital surfaces, each with distinct biochemical environments that influence susceptibility to disease. Nutritional biochemistry provides a useful framework for examining how dietary components, particularly phytochemicals, shape these interactions at molecular and cellular levels [7].

At the core of this interface lies the epithelial barrier, which serves both as a physical shield and as a signaling platform. Tight junction proteins, mucosal secretions, and antimicrobial peptides form the first line of defense against pathogens. Disruption of this barrier is often an early event in infection and inflammatory disorders. Phytochemicals contribute to barrier integrity by modulating pathways that regulate cell adhesion, oxidative balance, and inflammatory tone. For example, several plant-derived polyphenols have been shown to enhance tight junction stability and reduce epithelial permeability under inflammatory conditions [8].

Beyond the barrier, the innate immune system plays a central role in recognizing and responding to pathogens. Pattern recognition receptors such as Toll-like receptors detect microbial components and initiate signaling cascades that lead to cytokine production and immune activation. While this response is essential for pathogen clearance, excessive or prolonged activation may result in tissue damage. Phytochemicals help maintain balance by fine-tuning these signaling pathways. They can attenuate overactivation of pro-inflammatory mediators while preserving antimicrobial defense, thereby improving host tolerance to infection [9, 10].

A defining feature of the host–pathogen interface is the presence of the gut microbiota, a complex community of microorganisms that contributes to nutrient metabolism, immune education, and colonization resistance [11]. The microbiota competes with pathogens for nutrients and attachment sites, produces antimicrobial compounds, and shapes host immune responses. Dietary

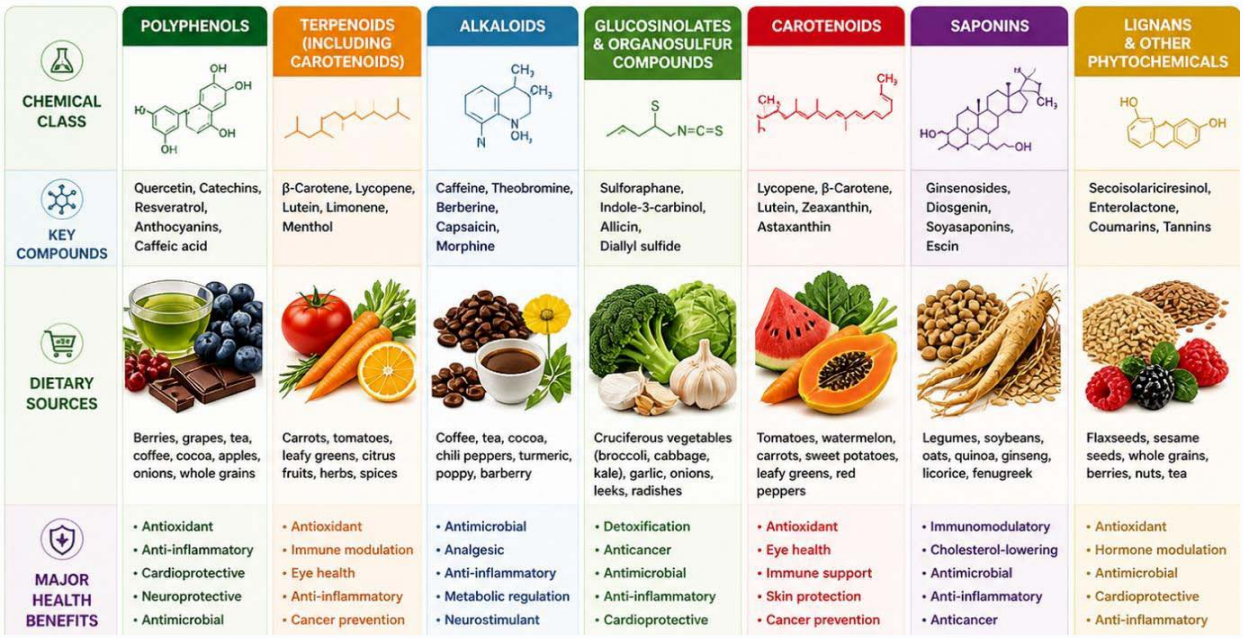


Figure 1: Classes of phytochemicals and their major health benefits.

phytochemicals interact closely with this microbial ecosystem. Many are poorly absorbed in their native form and reach the colon, where they are metabolized into smaller, bioactive compounds. These metabolites often exhibit enhanced biological activity and can influence both microbial composition and host physiology [12].

Another important aspect of this interface is pathogen adaptability. Pathogens do not merely invade; they respond to the host environment by altering gene expression, virulence factor production, and metabolic pathways [13]. Quorum sensing, a mechanism through which bacteria communicate and coordinate behavior, plays a key role in this adaptability. Emerging evidence suggests that certain phytochemicals can disrupt quorum sensing and inhibit virulence without necessarily killing the organism. This approach reduces selective pressure for resistance and represents a subtle but effective means of disease control [14].

Oxidative stress also defines the host–pathogen interaction. During infection, reactive oxygen and nitrogen species are generated as part of the host defense. While these molecules can damage pathogens, they may also harm host tissues if not properly regulated. Phytochemicals contribute to redox homeostasis by modulating antioxidant defense systems and influencing redox-sensitive signaling pathways. This dual role supports pathogen clearance while limiting collateral damage [15].

Taken together, the host–pathogen interface can be viewed as a network of interconnected systems rather than a simple point of contact. Phytochemicals operate within this network by influencing barrier function, immune signaling, microbial ecology, pathogen behavior, and redox balance. Understanding these interactions provides a foundation for exploring how diet can be strategically used to prevent disease and maintain physiological stability.

Classification and Dietary Sources of Major Phytochemicals

Phytochemicals comprise a large and structurally diverse group of plant-derived compounds. Their classification is commonly based on chemical structure and biosynthetic origin, which often correlates with their biological functions (Figure 1). Understanding these classes is important, as each group exhibits distinct biochemical properties that influence disease prevention at the host–pathogen interface.

Polyphenols

Polyphenols represent one of the most extensively studied groups of phytochemicals. They are broadly divided into flavonoids, phenolic acids, stilbenes, and lignans. These compounds are abundant in fruits, vegetables, tea, coffee, cocoa, and whole grains. Flavonoids, including quercetin, catechins, and anthocyanins, are particularly rich in berries, citrus fruits, onions, and green tea. Phenolic acids such as caffeic and ferulic acids are widely distributed in cereals and coffee, while stilbenes, notably resveratrol, are found in grapes and red wine [16, 17].

Polyphenols are recognized for their ability to modulate oxidative stress, inflammation, and microbial composition [18]. Their structural diversity allows interaction with multiple molecular targets, including enzymes, receptors, and transcription factors. Importantly, many polyphenols reach the colon where they undergo microbial transformation, producing metabolites with enhanced bioactivity [19].

Terpenoids

Terpenoids, also known as isoprenoids, constitute the largest class of phytochemicals, derived from five-carbon isoprene units. This group includes carotenoids, monoterpenes, diterpenes, and triterpenes. Carotenoids such as beta-carotene, lycopene, and lutein are found in carrots, tomatoes, leafy vegetables, and palm oil. Monoterpenes and sesquiterpenes are abundant in essential oils from herbs and spices such as mint, thyme, and ginger [20, 21].

These compounds play key roles in membrane stability, antioxidant defense, and immune modulation. Carotenoids, for example, are involved in quenching reactive oxygen species and

supporting epithelial integrity, while other terpenoids influence signaling pathways related to inflammation and cellular stress responses [22].

Alkaloids

Alkaloids are nitrogen-containing compounds with significant pharmacological activity. They are commonly found in plants such as cocoa, coffee, tea, and various medicinal herbs. Examples include caffeine, theobromine, and berberine. Although traditionally associated with toxicity at high doses, many alkaloids exhibit beneficial effects at dietary or controlled levels, including antimicrobial, anti-inflammatory, and metabolic regulatory actions [23, 24].

Berberine, for instance, has gained attention for its effects on glucose metabolism and gut microbiota modulation, while other alkaloids influence enzyme systems and cellular signaling relevant to host defense [25].

Glucosinolates and Organosulfur Compounds

Glucosinolates are sulfur-containing compounds predominantly found in cruciferous vegetables such as broccoli, cabbage, kale, and Brussels sprouts. Upon hydrolysis, they yield biologically active isothiocyanates, including sulforaphane. Organosulfur compounds are also abundant in allium vegetables such as garlic and onions, where compounds like allicin are formed [26, 27].

These phytochemicals are strongly linked to detoxification processes and antimicrobial activity. They modulate phase I and phase II detoxifying enzymes and influence redox-sensitive signaling pathways. Sulforaphane, in particular, is known to activate cytoprotective mechanisms that enhance cellular resilience against oxidative and inflammatory stress [28].

Carotenoids

Although classified under terpenoids, carotenoids are often discussed separately due to their nutritional significance. These pigments are responsible for the red, yellow, and orange colors of many fruits and vegetables. Dietary sources include carrots, sweet potatoes, tomatoes, and leafy greens. In addition to their role as provitamin A compounds, carotenoids contribute to immune function and protection against oxidative damage [29, 30].

Emerging evidence suggests that carotenoids also influence cell signaling and gene expression, extending their role beyond simple antioxidant activity [31].

Saponins and other phytochemicals

Saponins are glycosylated compounds found in legumes, soybeans, and some herbs. They are known for their ability to interact with cell membranes and exhibit antimicrobial and immune-modulating properties. Other notable phytochemicals include tannins, lignans, and coumarins, each contributing uniquely to host defense and metabolic regulation [32, 33].

Lignans, present in seeds such as flaxseed, are converted by gut microbiota into enterolignans with estrogen-like activity, which may influence hormonal balance and disease risk. Tannins, widely distributed in tea and certain fruits, exhibit antimicrobial and antioxidant properties that are relevant to the host–pathogen interface [34].

Dietary patterns and phytochemical synergy

It is important to recognize that phytochemicals are rarely consumed in isolation. Whole diets rich in plant-based foods provide complex mixtures of these compounds, which often act synergistically. This synergy enhances their biological effects, as multiple phytochemicals can target different pathways simultaneously. Diets such as the Mediterranean diet and traditional plant-based diets have been associated with reduced risk of both infectious and non-communicable diseases, partly due to their high phytochemical content [35, 36].

In summary, the classification of phytochemicals reflects both their chemical diversity and their wide distribution in plant-based foods. Each class contributes uniquely to disease prevention, yet their combined effects within whole dietary patterns provide the most consistent health benefits. This diversity underpins their capacity to influence the host–pathogen interface at multiple levels, setting the stage for a deeper exploration of their molecular mechanisms.

Molecular Mechanisms of Phytochemicals in Disease Prevention

The biological effects of phytochemicals are best understood through the molecular pathways they influence. Rather than acting through a single mechanism, most phytochemicals interact with multiple cellular targets. This multi-target behavior is central to their effectiveness in disease prevention, particularly at the host–pathogen interface where oxidative stress, inflammation, immune signaling, and microbial activity converge.

Modulation of oxidative stress and redox signaling

Oxidative stress plays a dual role in host–pathogen interactions. While reactive oxygen species contribute to pathogen clearance, excessive accumulation damages host tissues and disrupts cellular homeostasis. Phytochemicals regulate this balance by influencing redox-sensitive pathways rather than acting only as direct antioxidants.

A key mechanism involves activation of the nuclear factor erythroid 2-related factor 2 pathway, which controls the expression of antioxidant and cytoprotective genes. Compounds such as flavonoids and isothiocyanates enhance this pathway, leading to increased production of enzymes such as glutathione S-transferase and heme oxygenase-1. This strengthens cellular defense against oxidative injury and supports tissue integrity during infection and inflammation [37, 38].

In parallel, phytochemicals can suppress excessive generation of reactive species by modulating mitochondrial function and enzyme systems such as NADPH oxidases. This controlled regulation of redox balance reduces collateral damage while preserving antimicrobial activity [39].

Regulation of inflammatory signaling pathways

Inflammation is a central component of disease pathogenesis, especially in infections and chronic disorders. Phytochemicals influence inflammatory responses by targeting key signaling pathways, most notably nuclear factor-kappa B. This transcription factor regulates the expression of pro-inflammatory cytokines, chemokines, and adhesion molecules.

Polyphenols such as quercetin, curcumin, and catechins have been shown to inhibit activation of nuclear factor-kappa B, thereby reducing the production of tumor necrosis factor-alpha, interleukin-6, and other mediators of inflammation [40, 41]. This

effect is particularly relevant in preventing chronic low-grade inflammation, which underlies many non-communicable diseases.

In addition to nuclear factor-kappa B, phytochemicals modulate mitogen-activated protein kinase pathways and other intracellular signaling networks. These interactions allow for fine control of immune responses, ensuring that inflammation remains effective against pathogens without becoming damaging to host tissues [42].

Modulation of immune function

Phytochemicals influence both innate and adaptive immunity. At the innate level, they affect the activity of macrophages, neutrophils, and natural killer cells. For example, certain flavonoids enhance phagocytic activity and improve pathogen clearance, while others regulate cytokine production to prevent excessive immune activation [43].

At the adaptive level, phytochemicals can influence T-cell differentiation and B-cell function. They may promote a balanced immune response by modulating the ratio of pro-inflammatory and regulatory T cells. This is important in maintaining immune tolerance and preventing immune-mediated tissue damage during infections [44].

Emerging evidence also suggests that phytochemicals can enhance antiviral defenses by influencing interferon signaling pathways. This has gained attention in recent years, particularly in the context of viral infections where immune modulation is critical [45].

Interaction with cell signaling and gene expression

Beyond their effects on inflammation and oxidative stress, phytochemicals directly influence gene expression and cellular signaling networks. They can act as ligands for nuclear receptors, modulate epigenetic mechanisms, and alter transcriptional activity.

Epigenetic regulation is a growing area of interest. Phytochemicals such as resveratrol and epigallocatechin gallate have been shown to influence DNA methylation and histone modification, leading to changes in gene expression patterns associated with disease prevention [46]. These modifications may have long-term effects on cellular function and disease susceptibility.

Phytochemicals also interact with signaling pathways involved in cell survival, apoptosis, and autophagy. By promoting controlled cell death in damaged or infected cells, they help maintain tissue homeostasis and limit the spread of pathogens [47].

Inhibition of pathogen growth and virulence

A distinguishing feature of many phytochemicals is their ability to interfere with pathogen survival without necessarily exerting strong bactericidal effects. This includes disruption of microbial cell membranes, inhibition of enzyme activity, and interference with nutrient acquisition.

Importantly, several phytochemicals target quorum sensing systems that regulate virulence factor expression in bacteria. By disrupting these communication pathways, they reduce the ability of pathogens to coordinate infection processes such as biofilm formation and toxin production [48, 49]. This approach limits pathogenicity while reducing the likelihood of resistance development.

In viral infections, phytochemicals may inhibit viral entry, replication, or assembly by interacting with viral proteins or host cell receptors. Although many of these findings are based on experimental models, they highlight the broad spectrum of phytochemical activity [50].

Maintenance of epithelial barrier integrity

The integrity of epithelial barriers is critical in preventing pathogen entry. Phytochemicals contribute to this function by regulating tight junction proteins and maintaining mucosal structure. They reduce inflammation-induced disruption of barrier function and support the production of protective mucus and antimicrobial peptides [51].

This effect is particularly important in the gastrointestinal tract, where barrier dysfunction is associated with increased susceptibility to infection and chronic inflammatory diseases. By preserving barrier integrity, phytochemicals reduce pathogen translocation and systemic inflammation [52].

Phytochemicals and Gut Microbiota Modulation

The gut microbiota forms a central component of the host–pathogen interface. It is a dense and metabolically active community that influences digestion, immune development, epithelial integrity, and resistance to infection. Disturbances in this microbial ecosystem, often described as dysbiosis, are associated with increased susceptibility to infectious diseases, chronic inflammation, and metabolic disorders. Phytochemicals play a significant role in shaping the composition and function of this ecosystem, thereby contributing to disease prevention.

Bidirectional interaction between phytochemicals and microbiota

A defining feature of many dietary phytochemicals is their limited absorption in the upper gastrointestinal tract. As a result, substantial amounts reach the colon, where they encounter gut microbiota. Microorganisms metabolize these compounds into smaller phenolic acids and other derivatives that often exhibit enhanced bioavailability and biological activity [53, 54]. This transformation extends the functional impact of phytochemicals beyond their native forms.

At the same time, phytochemicals influence microbial composition by selectively promoting beneficial species while inhibiting pathogenic ones. This bidirectional relationship creates a dynamic system in which diet and microbiota continuously shape each other [55].

Selective promotion of beneficial microorganisms

Several phytochemicals act in a manner similar to prebiotics by supporting the growth of beneficial bacteria such as Lactobacillus and Bifidobacterium species. Polyphenol-rich foods, including fruits, tea, and cocoa, have been shown to increase the abundance of these microbes, which are associated with improved gut health and immune function [56, 57].

These beneficial bacteria contribute to the production of short-chain fatty acids such as butyrate, acetate, and propionate. These metabolites play important roles in maintaining epithelial integrity, regulating immune responses, and providing energy to colonocytes. Butyrate, in particular, strengthens tight junctions and reduces inflammation, thereby enhancing resistance to pathogen invasion [58].

Suppression of pathogenic microorganisms

In addition to promoting beneficial microbes, phytochemicals can inhibit the growth and activity of pathogenic organisms. This effect

may occur through direct antimicrobial action or through indirect mechanisms such as competition for nutrients and ecological niches.

Polyphenols, tannins, and certain alkaloids have been shown to disrupt bacterial cell membranes, interfere with enzyme activity, and reduce the expression of virulence factors. These actions limit the ability of pathogens to colonize and establish infection within the host [59, 60].

Moreover, by enhancing the growth of commensal bacteria, phytochemicals strengthen colonization resistance, a process in which the existing microbiota prevents the establishment of harmful organisms. This is particularly relevant in the prevention of gastrointestinal infections.

Microbial metabolites and host signaling

The interaction between phytochemicals and microbiota leads to the production of a wide range of metabolites that influence host physiology. These include phenolic metabolites, short-chain fatty acids, and secondary bile acids. Many of these compounds act as signaling molecules that regulate immune responses, inflammation, and metabolic pathways.

For example, microbial metabolites derived from polyphenols can modulate the activity of immune cells and influence cytokine production. They may also interact with receptors such as G protein-coupled receptors, linking microbial activity to host metabolic regulation [61, 62].

This metabolic interplay highlights the importance of considering not only the original phytochemical compounds but also their transformation products when evaluating their biological effects.

Influence on gut barrier function

The gut microbiota and phytochemicals work together to maintain the integrity of the intestinal barrier. Beneficial microbes stimulated by phytochemicals contribute to mucus production and tight junction stability, while phytochemicals themselves directly modulate epithelial cell function.

This combined effect reduces intestinal permeability and prevents translocation of pathogens and toxins into systemic circulation. A stable barrier is essential for preventing both local and systemic inflammation, which are key drivers of many diseases [63].

Modulation of immune responses *via* microbiota

The gut microbiota plays a critical role in shaping the immune system, and phytochemicals indirectly influence immunity through their effects on microbial composition. Changes in microbiota induced by phytochemicals can alter the balance between pro-inflammatory and anti-inflammatory immune responses.

For instance, increased production of short-chain fatty acids is associated with the expansion of regulatory T cells, which help maintain immune tolerance and prevent excessive inflammation. At the same time, suppression of pathogenic bacteria reduces immune activation triggered by microbial toxins [64].

This indirect pathway of immune modulation complements the direct effects of phytochemicals on immune cells, creating a coordinated system of host defense.

Dietary patterns and microbial diversity

Diets rich in plant-based foods provide a wide range of phytochemicals that support microbial diversity. Greater diversity is generally associated with improved resilience of the microbiota and better health outcomes. In contrast, diets low in plant content and high in processed foods are linked to reduced diversity and increased disease risk [65].

Traditional diets, including those rich in whole grains, legumes, fruits, and vegetables, consistently show beneficial effects on microbiota composition. These dietary patterns provide a continuous supply of phytochemicals that sustain a balanced microbial ecosystem [65, 66].

Phytochemicals in Immune Regulation and Inflammation Control

Effective disease prevention depends on a balanced immune response that can eliminate pathogens without causing excessive tissue damage. This balance is tightly regulated through complex signaling networks involving immune cells, cytokines, and biochemical mediators. Phytochemicals contribute to this regulation by acting on both innate and adaptive immune systems, as well as on the inflammatory pathways that connect them. Their role is particularly important at the host-pathogen interface, where immune activation must be both rapid and controlled.

Modulation of innate immune responses

The innate immune system provides the first line of defense against invading pathogens. Cells such as macrophages, neutrophils, and dendritic cells recognize microbial components through pattern recognition receptors and initiate inflammatory responses. Phytochemicals influence these early events by modulating receptor signaling and downstream pathways.

Polyphenols and flavonoids have been shown to regulate Toll-like receptor signaling, thereby controlling the production of pro-inflammatory cytokines. This modulation helps prevent excessive activation that could lead to tissue injury while preserving the capacity to respond to infection [67, 68]. In macrophages, certain phytochemicals enhance phagocytic activity and improve microbial clearance, while others suppress the release of inflammatory mediators such as nitric oxide and prostaglandins [69].

Natural killer cells, which are important in antiviral defense, are also influenced by phytochemicals. Some compounds enhance their cytotoxic activity, thereby improving the elimination of infected cells [70].

Regulation of adaptive immunity

Adaptive immunity provides specificity and memory in the immune response. Phytochemicals influence the differentiation and function of T and B lymphocytes, which are central to this system. They can modulate the balance between different T helper cell subsets, including Th1, Th2, Th17, and regulatory T cells.

Maintaining this balance is critical, as excessive Th1 or Th17 responses are associated with chronic inflammation, while insufficient responses may impair pathogen clearance. Phytochemicals such as curcumin, resveratrol, and epigallocatechin gallate have been shown to promote regulatory T cell activity while limiting pro-inflammatory T cell responses [71, 72]. This contributes to immune tolerance and reduces the risk of immune-mediated damage.

B cell function is also influenced, with some phytochemicals enhancing antibody production and improving humoral immunity. This effect is relevant in both infection control and vaccine

responsiveness [73].

Control of cytokine production

Cytokines serve as key mediators of communication within the immune system. Their balanced production is essential for effective defense without excessive inflammation. Phytochemicals regulate cytokine networks by influencing transcription factors and signaling pathways involved in their expression.

Many phytochemicals suppress pro-inflammatory cytokines such as tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-6, while promoting anti-inflammatory cytokines such as interleukin-10 [74]. This shift toward an anti-inflammatory profile helps limit tissue damage during infection and chronic disease.

The regulation of cytokine storms, which are characterized by uncontrolled cytokine release, has attracted attention in recent years. Evidence suggests that certain phytochemicals may help attenuate these responses by modulating key signaling pathways, including nuclear factor-kappa B and Janus kinase-signal transducer and activator of transcription pathways [75].

Interaction with inflammatory signaling pathways

Inflammatory signaling pathways integrate immune responses with cellular stress signals. Among these, nuclear factor-kappa B and mitogen-activated protein kinase pathways are central regulators of inflammation. Phytochemicals act on these pathways at multiple levels.

Curcumin, quercetin, and other polyphenols inhibit activation of nuclear factor-kappa B, reducing the transcription of genes involved in inflammation. At the same time, they modulate mitogen-activated protein kinase signaling, influencing processes such as cell proliferation, apoptosis, and cytokine production [76, 77].

In addition, phytochemicals can activate pathways that promote resolution of inflammation. This includes the stimulation of antioxidant responses through nuclear factor erythroid 2-related factor 2, which indirectly reduces inflammatory signaling by limiting oxidative stress [78].

Influence on chronic low-grade inflammation

Chronic low-grade inflammation is a common underlying factor in many non-communicable diseases, including cardiovascular disease, diabetes, and cancer. Unlike acute inflammation, which is protective, chronic inflammation persists over time and contributes to tissue damage and disease progression.

Dietary phytochemicals play a significant role in reducing this form of inflammation. Regular consumption of phytochemical-rich foods has been associated with lower levels of inflammatory biomarkers such as C-reactive protein and pro-inflammatory cytokines [79]. This effect is attributed to the combined action of multiple compounds acting on different pathways.

The ability of phytochemicals to reduce chronic inflammation also enhances resistance to infections, as a balanced immune system is better equipped to respond effectively to pathogens.

Integration with microbiota-mediated immunity

The effects of phytochemicals on immune regulation are closely linked to their influence on the gut microbiota. Microbial metabolites, particularly short-chain fatty acids, play a key role in shaping immune responses. These metabolites promote the development of regulatory T cells and suppress inflammatory pathways.

By enhancing the production of these metabolites through microbiota modulation, phytochemicals indirectly contribute to immune balance. This integration of direct and indirect mechanisms highlights the complexity of their role in immune regulation [80].

Direct Antimicrobial and Anti-virulence Activities of Phytochemicals

Beyond their roles in host regulation, many phytochemicals exert direct effects on microorganisms. These actions range from inhibition of microbial growth to more subtle interference with virulence mechanisms. Unlike conventional antimicrobials that often target a single pathway, phytochemicals tend to act on multiple microbial structures and processes. This multi-target activity is particularly valuable in the context of rising antimicrobial resistance.

Disruption of microbial cell structure and function

A common mechanism of antimicrobial action among phytochemicals is the disruption of microbial cell membranes. Polyphenols, terpenoids, and certain alkaloids can interact with lipid bilayers, altering membrane permeability and leading to leakage of cellular contents. This compromises microbial viability and reduces the ability of pathogens to establish infection [81, 82].

In addition to membrane effects, phytochemicals may interfere with intracellular targets. They can inhibit key enzymes involved in metabolic pathways, protein synthesis, and nucleic acid replication. For example, flavonoids have been shown to inhibit bacterial DNA gyrase and topoisomerase, thereby limiting replication [83]. These combined effects contribute to broad-spectrum antimicrobial activity.

Inhibition of biofilm formation

Biofilms are structured communities of microorganisms embedded in a self-produced extracellular matrix. They provide protection against host defenses and antimicrobial agents, making infections difficult to treat. Phytochemicals have demonstrated the ability to prevent biofilm formation and disrupt established biofilms.

Compounds such as catechins, tannins, and essential oil components interfere with the adhesion of microbes to surfaces and inhibit the production of extracellular polymeric substances required for biofilm stability [84, 85]. This effect enhances susceptibility of pathogens to both host immune responses and antimicrobial agents.

Interference with Quorum sensing

Quorum sensing is a communication system that allows microorganisms to coordinate gene expression based on population density. This system regulates key virulence factors, including toxin production, motility, and biofilm formation. Targeting quorum sensing offers a strategy to control infection without directly killing the pathogen.

Several phytochemicals have been identified as quorum sensing inhibitors. These compounds disrupt signaling molecules or their receptors, thereby preventing coordinated expression of virulence genes. For instance, certain flavonoids and phenolic acids reduce the production of signaling molecules in bacterial species, leading to decreased pathogenicity [86, 87].

This approach reduces selective pressure for resistance, as it does not rely on bactericidal activity. Instead, it weakens the pathogen, allowing the host immune system to clear the infection more

effectively.

Antiviral mechanisms

Phytochemicals also exhibit antiviral activity through multiple mechanisms. They can interfere with viral entry into host cells by blocking receptor binding or membrane fusion. Some compounds inhibit viral replication by targeting viral enzymes such as polymerases and proteases.

Polyphenols, including epigallocatechin gallate and resveratrol, have been shown to inhibit replication of various viruses in experimental models. These effects are often mediated through interactions with viral proteins or modulation of host cell pathways required for viral replication [88, 89].

In addition, certain phytochemicals enhance host antiviral defenses by promoting interferon responses and strengthening innate immunity. This dual action, targeting both the virus and the host, contributes to their overall effectiveness.

Antifungal and antiparasitic effects

Fungal and parasitic infections remain significant contributors to global disease burden. Phytochemicals have demonstrated activity against a range of fungi and parasites through mechanisms similar to those observed in antibacterial action.

They may disrupt fungal cell membranes by interacting with ergosterol, inhibit spore germination, and interfere with metabolic pathways essential for growth. In parasitic organisms, phytochemicals can affect energy metabolism, enzyme activity, and structural integrity [90, 91].

These effects highlight the broad-spectrum potential of phytochemicals as agents that can act across different classes of pathogens.

Synergistic interactions with conventional therapies

An important aspect of phytochemical activity is their ability to enhance the effectiveness of conventional antimicrobial agents. Synergistic interactions have been observed where phytochemicals increase microbial sensitivity to antibiotics or reduce resistance mechanisms.

For example, some phytochemicals inhibit efflux pumps, which are used by bacteria to expel antimicrobial agents. By blocking these pumps, they increase intracellular concentrations of antibiotics, improving their efficacy [92]. Others may disrupt biofilms, allowing better penetration of antimicrobial drugs.

This synergy offers a promising approach to addressing antimicrobial resistance, as it allows lower doses of conventional drugs while maintaining therapeutic effectiveness.

Selectivity and reduced resistance pressure

A notable advantage of phytochemicals is their relative selectivity. Many compounds preferentially target pathogenic organisms while sparing beneficial microbiota. This contrasts with broad-spectrum antibiotics, which can disrupt microbial balance and contribute to dysbiosis.

Furthermore, because phytochemicals often act on multiple targets, the likelihood of pathogens developing resistance is reduced. This multi-target approach complicates the ability of microorganisms to adapt through single genetic changes [93].

Phytochemicals in the Prevention of Major Diseases

The preventive effects of phytochemicals become most evident when examined across major disease categories. Their ability to act on oxidative stress, inflammation, immune balance, and microbial dynamics allows them to influence both infectious and non-communicable diseases. This section integrates current evidence on how phytochemicals contribute to the prevention of key disease groups through mechanisms already discussed.

Infectious diseases

Phytochemicals play a dual role in infectious disease prevention by enhancing host defense and directly limiting pathogen activity. Through modulation of immune responses, they improve the capacity of the host to detect and eliminate pathogens while reducing excessive inflammation that may worsen disease outcomes.

Polyphenols and flavonoids have demonstrated broad antimicrobial and antiviral activities. They interfere with pathogen entry, replication, and virulence, while also supporting epithelial barrier integrity. For example, catechins and related compounds have been shown to reduce viral replication and enhance antiviral immune signaling pathways [94, 95]. Similarly, organosulfur compounds from garlic exhibit antibacterial and antifungal properties that limit microbial colonization [96].

In addition, phytochemicals influence the gut microbiota, strengthening colonization resistance against enteric pathogens. This is particularly relevant in regions where infectious diseases remain a major public health concern. By maintaining a balanced microbial ecosystem, phytochemicals reduce susceptibility to infections and support recovery [97].

Cancer prevention

Cancer development is closely linked to chronic inflammation, oxidative stress, and dysregulated cell signaling. Phytochemicals target these processes at multiple stages, including initiation, promotion, and progression of tumor development.

Many phytochemicals act as modulators of cell cycle regulation and apoptosis. Compounds such as curcumin, resveratrol, and epigallocatechin gallate promote programmed cell death in abnormal cells while sparing normal cells. They also inhibit angiogenesis and metastasis by regulating signaling pathways involved in cell proliferation and migration [98, 99].

Another important mechanism is the activation of detoxification systems. Glucosinolates and their derivatives enhance the activity of phase II detoxifying enzymes, facilitating the removal of carcinogens. At the same time, phytochemicals modulate epigenetic processes, influencing gene expression patterns associated with cancer risk [100].

Epidemiological studies consistently show that diets rich in fruits, vegetables, and whole plant foods are associated with reduced cancer incidence. This protective effect is attributed, in part, to the combined action of diverse phytochemicals present in these diets [101].

Cardiometabolic diseases

Cardiovascular diseases and metabolic disorders such as type 2 diabetes are major contributors to global morbidity and mortality. These conditions are characterized by chronic inflammation, oxidative stress, endothelial dysfunction, and metabolic imbalance.

Phytochemicals address these underlying factors through multiple mechanisms.

Flavonoids and polyphenols improve endothelial function by enhancing nitric oxide bioavailability and reducing oxidative stress. This leads to improved vascular relaxation and reduced blood pressure [102]. They also inhibit lipid oxidation, a key step in the development of atherosclerosis.

In metabolic regulation, phytochemicals influence glucose homeostasis and insulin sensitivity. Compounds such as berberine and certain polyphenols modulate pathways involved in glucose uptake and lipid metabolism. These effects contribute to improved glycemic control and reduced risk of metabolic syndrome [103].

Furthermore, the anti-inflammatory properties of phytochemicals reduce chronic low-grade inflammation associated with obesity and metabolic disorders. Their interaction with the gut microbiota also plays a role in regulating energy balance and metabolic function [104].

Neurodegenerative diseases

Neurodegenerative disorders, including Alzheimer's and Parkinson's diseases, are associated with oxidative stress, neuroinflammation, and accumulation of misfolded proteins. Phytochemicals offer neuroprotective effects through their ability to cross the blood-brain barrier and influence neuronal signaling.

Polyphenols such as flavonoids and stilbenes have been shown to reduce oxidative damage in neural tissues and modulate inflammatory responses in the brain. They also influence signaling pathways involved in neuronal survival, synaptic plasticity, and cognitive function [105, 106].

In addition, phytochemicals may inhibit the aggregation of proteins such as beta-amyloid, which is implicated in neurodegenerative disease progression. Their effects on mitochondrial function further support neuronal health by maintaining energy production and reducing oxidative stress [107].

Emerging evidence also highlights the role of the gut–brain axis in neurodegeneration. By modulating the gut microbiota, phytochemicals indirectly influence brain function and may reduce neuroinflammation through microbial metabolites [108].

Integrated perspective across disease categories

Although these disease categories are often considered separately, they share common underlying mechanisms, including oxidative stress, inflammation, immune dysregulation, and microbial imbalance. Phytochemicals act on these shared pathways, providing a unifying approach to disease prevention.

Their ability to function at multiple biological levels distinguishes them from many conventional interventions. Rather than targeting a single disease endpoint, phytochemicals support overall physiological balance, reducing the risk of diverse conditions simultaneously.

Challenges, Bioavailability, and Future Perspectives

Despite the wide range of beneficial effects attributed to phytochemicals, several limitations affect their translation from experimental findings to consistent clinical outcomes. These challenges relate mainly to bioavailability, variability in dietary intake, complexity of biological interactions, and gaps in human evidence. Addressing these issues is essential for advancing the role of phytochemicals in disease prevention within a nutritional biochemistry framework.

Bioavailability and biotransformation

One of the most significant challenges is the generally low and variable bioavailability of many phytochemicals. After ingestion, these compounds undergo extensive digestion, metabolism, and transformation before reaching systemic circulation. Factors such as chemical structure, food matrix, and interaction with other dietary components influence their absorption and distribution.

Polyphenols, for instance, are often present as glycosides or complex polymers that are poorly absorbed in the small intestine. They reach the colon where they are metabolized by gut microbiota into smaller compounds with improved bioavailability and biological activity [109, 110]. This dependence on microbial metabolism introduces variability, as differences in microbiota composition among individuals can lead to different metabolic outcomes.

In addition, rapid metabolism in the liver and intestinal cells may limit the concentration of active compounds in target tissues. This has led to increasing interest in delivery systems that enhance stability and absorption, including nanoformulations, encapsulation techniques, and food-based carriers [111].

Variability in dietary intake and food composition

The intake of phytochemicals varies widely depending on dietary habits, cultural practices, and food availability. Even within the same food, phytochemical content can differ due to factors such as plant variety, growing conditions, processing, and storage.

For example, the concentration of polyphenols in fruits and vegetables may be influenced by ripeness, environmental stress, and post-harvest handling. Processing methods such as heating or drying can either reduce or enhance the availability of certain compounds [112].

This variability makes it difficult to establish standardized intake levels or to compare results across studies. It also complicates the design of dietary recommendations aimed at maximizing phytochemical benefits.

Complexity of mechanisms and interactions

Phytochemicals act through multiple pathways and often interact with each other as well as with other dietary components. While this multi-target action is advantageous for disease prevention, it also introduces complexity in understanding their precise mechanisms.

Synergistic effects among different phytochemicals can enhance biological activity, but these interactions are not always predictable. In some cases, compounds may compete for absorption or metabolic pathways, reducing their effectiveness [113].

Furthermore, the interplay between phytochemicals, microbiota, and host metabolism creates a network of interactions that is difficult to dissect using conventional experimental approaches. Systems biology and integrative research methods are increasingly being used to address this complexity.

Limitations of current evidence

Although a large body of in vitro and animal research supports the health benefits of phytochemicals, human studies remain limited in number and often show inconsistent results. Differences in study

design, dosage, duration, and population characteristics contribute to these inconsistencies.

Clinical trials frequently use isolated compounds at doses that may not reflect typical dietary intake, raising questions about real-world applicability. In addition, long-term studies are needed to establish the preventive effects of phytochemicals on chronic diseases [114].

Another limitation is the reliance on biomarkers rather than clinical endpoints in many studies. While biomarkers provide useful insights, they do not always translate directly into reduced disease risk.

Safety and dose considerations

While phytochemicals are generally considered safe when consumed as part of whole foods, high doses of isolated compounds may have adverse effects. For example, excessive intake of certain polyphenols or alkaloids can interfere with nutrient absorption or interact with medications.

This highlights the importance of considering dose, form, and context of consumption. Whole-food approaches, which provide balanced mixtures of phytochemicals, are often safer and more effective than high-dose supplementation [115].

Emerging approaches and future directions

Future research is moving toward a more personalized understanding of phytochemical effects. Advances in nutrigenomics and metabolomics are enabling the study of how individual genetic and metabolic profiles influence responses to dietary compounds. This approach, often referred to as precision nutrition, aims to tailor dietary recommendations to individual needs.

The role of the gut microbiota is also a major focus of current research. Understanding how microbial composition influences phytochemical metabolism may lead to targeted dietary strategies that enhance beneficial outcomes [116].

In addition, there is growing interest in integrating phytochemicals into functional foods and nutraceuticals. These products are designed to deliver bioactive compounds in forms that improve stability, bioavailability, and consumer acceptance.

Technological innovations, including nanotechnology and advanced delivery systems, offer promising solutions to the challenges of poor bioavailability. However, their safety and long-term effects require careful evaluation.

Translational implications

Bridging the gap between experimental research and practical application remains a key priority. This involves not only improving study design but also translating findings into clear dietary guidelines that are accessible and culturally relevant.

Public health strategies that promote increased consumption of phytochemical-rich foods, such as fruits, vegetables, legumes, and whole grains, remain a practical and effective approach. These strategies align with broader goals of sustainable nutrition and disease prevention.

Conclusion

Phytochemicals occupy a central position in the interface between nutrition, immunity, and microbial ecology. Their relevance in disease prevention is not explained by a single mechanism but by coordinated actions across multiple biological systems. At the host-pathogen interphase, they influence barrier integrity, immune signaling, microbial balance, oxidative stress regulation, and pathogen behavior. This integrated activity provides a biological basis for their broad protective effects across infectious and non-communicable diseases.

Evidence from recent studies indicates that phytochemicals act as modulators of cellular signaling pathways rather than simple antioxidant agents. Their influence on nuclear factor-kappa B, nuclear factor erythroid 2-related factor 2, mitogen-activated protein kinases, and other regulatory networks highlights their capacity to fine-tune inflammatory and stress responses. This regulation is essential in maintaining immune balance, where both insufficient and excessive responses can be harmful.

The interaction between phytochemicals and the gut microbiota further strengthens their role in disease prevention. Through microbial metabolism and selective modulation of microbial populations, phytochemicals extend their biological effects beyond the gastrointestinal tract. The resulting metabolites contribute to immune regulation, metabolic control, and reinforcement of epithelial barriers. This microbiota-mediated dimension represents a key pathway through which diet influences systemic health.

In infectious diseases, phytochemicals reduce pathogen virulence, limit microbial growth, and enhance host defense mechanisms. In chronic diseases such as cancer, cardiovascular disorders, metabolic syndrome, and neurodegenerative conditions, they act on shared pathological processes including oxidative stress, chronic inflammation, and dysregulated cell signaling. This convergence suggests that phytochemical's function more as systems-level modulators than isolated therapeutic agents.

Despite their potential, challenges remain in translating experimental findings into consistent clinical outcomes. Variability in bioavailability, differences in dietary intake, microbial diversity, and study design all contribute to inconsistencies in reported effects. Addressing these limitations will require more integrative research approaches, including systems biology, metabolomics, and well-designed long-term clinical studies.

Future perspectives point toward a more personalized understanding of phytochemical action. Advances in precision nutrition and microbiome research are likely to refine how these compounds are used in disease prevention strategies. In addition, development of improved delivery systems and functional foods may enhance their stability and effectiveness.

Overall, phytochemicals represent a key link between diet and health at the molecular level. Their ability to influence host defense, microbial ecology, and disease pathways positions them as important tools in preventive medicine. A dietary pattern rich in diverse plant-based foods remains the most practical and sustainable approach to harnessing these benefits in real-world settings.

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Data Availability

The datasets generated during or analyzed during the current

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Authors' Contribution

Conceptualization, UF and IPA; methodology, OC and IPA; Resources, All authors; data curation, IPA; writing-original draft preparation, UF, OC and PAI; writing-review and editing, NAP, EBO, AM and AS; supervision, SMH. All authors have read and agreed to the published version of the manuscript.

Competing Interest

The authors have no competing interests to declare that are relevant to the content of this article.

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