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Oxidative Stress, Immunity, and Antioxidant Phytochemicals: From Bench Evidence to Clinical Relevance

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ABSTRACT

Oxidative stress and inflammation are tightly intertwined drivers of acute and chronic disease. Antioxidant phytochemicals-plant-derived polyphenols, carotenoids, organosulfur compounds and related small molecules-modulate redox balance and reprogram immune responses through multi-layered mechanisms that extend beyond simple radical scavenging. Preclinical models demonstrate that phytochemicals (for example, resveratrol, curcumin, quercetin, EGCG, lutein, sulforaphane) regulate Nrf2- and NF-κB-dependent transcription, restrain inflammasome activation, alter kinase signaling (MAPK, JAK-STAT), shape immune cell metabolism and epigenetics, and interact with the gut microbiome to generate bioactive metabolites. Clinical translation has produced promising biomarker changes and condition-specific benefits, but large-scale, consistent clinical efficacy is limited by low oral bioavailability, heterogenous formulations, variable dosing, and incomplete mechanistic bridging (PK–PD). This review synthesizes current mechanistic and translational evidence, highlights clinical studies and limitations, and proposes priorities standardized preparations, PK–PD mapping, targeted patient selection, and microbiome-aware strategies to move antioxidant phytochemicals from bench to bedside.

Keywords: Antioxidant phytochemicals, Oxidative stress, Immune modulation, Nrf2 / NF-κB signaling, Translational pharmacology

INTRODUCTION

Reactive oxygen and nitrogen species (ROS/RNS) are unavoidable byproducts of aerobic life. At physiological levels they act as second messengers in host defense, cellular signaling, and resolution of inflammation; when excessive or poorly contained they damage biomolecules and perpetuate maladaptive inflammation [1]. The immune system both generates oxidants (to kill microbes) and is modulated by redox state; thus oxidative stress is both cause and consequence of dysregulated immunity in conditions ranging from infection and sepsis to metabolic and neurodegenerative disease [2]. Understanding how dietary and botanical antioxidants influence this redox–immune axis is essential for rational translational development. Recent syntheses summarize the biochemical and pathophysiological foundations linking free radicals, oxidative damage, and human disease.

2. Major phytochemical classes with immune relevance

Dietary phytochemicals represent a broad spectrum of plant-derived molecules that exert immunomodulatory activity through antioxidant and signaling mechanisms [3]. These compounds can be grouped according to their structural families and bioactive properties.

Polyphenols form the largest and most extensively studied class. This group includes flavonoids such as quercetin and luteolin, catechins like epigallocatechin gallate (EGCG) from green tea, and stilbenes such as resveratrol [4]. Polyphenols are known to modulate immune signaling networks, influencing macrophage polarization, T cell differentiation, and dendritic cell function [5]. Their ability to reduce pro-inflammatory cytokine production and support regulatory pathways demonstrates their importance in balancing immune responses. Beyond their direct antioxidant activity, polyphenols can reprogram intracellular signaling pathways, making them attractive candidates for preventing or treating chronic inflammatory diseases [6].

Curcuminoids, represented most prominently by curcumin from turmeric, have gained recognition for their pleiotropic effects on immune function. Curcumin can inhibit nuclear factor-kappa B (NF-κB) activation, suppress inflammasome assembly, and regulate kinase signaling pathways including JAK/STAT and MAPK [7]. These actions have been observed in models of arthritis, metabolic inflammation, and neurodegeneration. Curcuminoids

not only mitigate inflammatory cascades but also influence the resolution phase by encouraging anti-inflammatory mediator production and enhancing tissue repair [8]. Their wide-ranging actions underscore the therapeutic interest in curcuminoids for disorders characterized by oxidative stress and chronic inflammation.

Carotenoids such as β-carotene, lutein, and lycopene are lipophilic molecules that incorporate into cell membranes where they exert stabilizing effects [9]. Their presence reduces membrane susceptibility to oxidative damage and helps maintain barrier function in mucosal tissues. Carotenoids are also implicated in visual health and photoprotection, but their immune relevance extends to the regulation of oxidative signaling within phagocytes and the modulation of inflammatory mediator release [10]. Epidemiological data suggest that higher carotenoid intake correlates with improved immune resilience and reduced infection risk [11].

Organosulfur compounds and glucosinolate derivatives represent another important group. Sulforaphane from cruciferous vegetables and allicin-related compounds from garlic are notable examples. These molecules act as electrophiles capable of activating adaptive stress responses, most prominently through the Nrf2 pathway [12]. By upregulating cytoprotective and detoxifying enzymes, organosulfur compounds enhance the cellular defense machinery while modulating innate immune functions such as natural killer (NK) cell activity and phagocytosis [12]. Together with the other groups, they highlight how structurally diverse phytochemicals converge on immune regulation.

Collectively, phytochemicals act not only through their parent structures but also through metabolites generated by host and microbial enzymes [13]. These biotransformed products often display altered bioactivity, thereby contributing significantly to systemic immunomodulation.

3. Mechanistic pathways linking phytochemicals to immune regulation

The immunological impact of phytochemical antioxidants arises from interconnected mechanisms that go beyond the classical notion of radical scavenging.

Although many phytochemicals possess chemical groups capable of neutralizing reactive oxygen and nitrogen species, physiological concentrations achieved through diet are often insufficient for bulk quenching. Instead, these compounds influence redox-sensitive signaling pathways, sometimes through mild pro-oxidant effects that trigger hormetic responses [14]. This hormesis induces endogenous protective pathways that strengthen cellular defenses and resilience.

A central mechanism involves activation of the transcription factor Nrf2, a master regulator of antioxidant and cytoprotective genes. Phytochemicals such as sulforaphane, curcumin, and resveratrol modify Nrf2's repressor Keap1 or activate upstream kinases, releasing Nrf2 to translocate into the nucleus [15]. The result is increased expression of enzymes like heme oxygenase-1, NAD(P)H quinone oxidoreductase, and glutathione synthesis enzymes, which collectively enhance cellular tolerance to oxidative stress and mitigate inflammation [16]. Simultaneously, many phytochemicals suppress the NF-κB pathway, which is central to the production of pro-inflammatory cytokines including tumor necrosis factor-α, interleukin-1β, and interleukin-6 [17]. By preventing degradation of the inhibitory protein IκB or interfering with upstream kinases, phytochemicals limit NF-κB activation. The coordinated upregulation of Nrf2 pathways and inhibition of NF-κB establishes a more balanced immune state by restraining excessive inflammation while sustaining protective responses [18].

Another crucial target is the NLRP3 inflammasome. Overactivation of this multiprotein complex drives pyroptosis and pathogenic release of IL-1β and IL-18 [19]. Compounds such as curcumin, quercetin, and resveratrol inhibit inflammasome priming and assembly through suppression of mitochondrial reactive oxygen species and interference with protein–protein interactions [20]. This reduces inflammasome-driven tissue damage in models of metabolic, neurodegenerative, and autoimmune disorders.

Phytochemicals also modulate other kinase pathways including MAPK and JAK/STAT, thereby altering proliferation and differentiation of immune cells [21]. Additionally, they influence epigenetic processes such as histone modifications and microRNA regulation, producing long-term changes in immune transcriptional programs [21]. On the metabolic front, they shift immune cell energy production away from glycolysis toward oxidative phosphorylation, favoring anti-inflammatory phenotypes such as regulatory T cells and M2 macrophages [22].

Finally, interaction with the gut microbiota represents an increasingly recognized mechanism. Complex polyphenols and glucosinolates are metabolized into smaller bioactive derivatives such as phenolic acids and urolithins [23]. These metabolites can reach systemic circulation and modulate immunity, while phytochemicals reciprocally influence microbial community composition and barrier integrity. This bidirectional relationship adds an important layer to the systemic immune effects of dietary phytochemicals

4. Immune cell–level effects: innate and adaptive immune systems

Phytochemical antioxidants exert diverse and cell-specific effects across both innate and adaptive immunity. In macrophages, compounds such as quercetin and curcumin attenuate the release of pro-inflammatory cytokines, including TNF-α and IL-6, while promoting a phenotypic switch from pro-inflammatory M1 macrophages to tissue-repairing M2 subsets [24]. This polarization is supported by metabolic reprogramming toward oxidative

phosphorylation, which enhances resolution of inflammation and tissue repair. Neutrophils, another frontline defense, respond to phytochemicals through tempered oxidative burst activity [25]. While excessive reactive oxygen species from neutrophils contribute to collateral tissue damage, polyphenols such as EGCG and resveratrol reduce this overactivation yet preserve phagocytic and antimicrobial competence, thereby improving the balance between microbial clearance and host protection [26].

Dendritic cells, which bridge innate and adaptive immunity, are also modulated by phytochemicals [26]. Flavonoids and curcuminoids can impair maturation and reduce expression of costimulatory molecules such as CD80 and CD86, thereby diminishing excessive T cell priming in inflammatory conditions [27,28]. This moderation prevents uncontrolled immune activation while still permitting antigen surveillance.

T lymphocytes are another critical target. Phytochemicals dampen hyperactive Th1 and Th17 effector responses, both implicated in autoimmunity and chronic inflammation [29]. At the same time, they promote regulatory T cell (Treg) differentiation and function, often through epigenetic changes and modulation of signaling pathways like STAT5 [29]. By influencing T cell metabolism, certain polyphenols enhance oxidative pathways that support tolerance-promoting phenotypes.

B lymphocytes show more variable responses. Some phytochemicals, such as resveratrol, enhance antibody generation under conditions like vaccination, suggesting adjuvant potential [33]. Others may suppress excessive B cell proliferation and antibody production in autoimmune settings [30]. These context-dependent outcomes highlight the need for dose- and disease-specific tailoring.

Natural killer (NK) cells, central to antiviral and antitumor defense, can have their cytotoxic potential enhanced by moderate doses of phytochemicals [31]. Resveratrol, sulforaphane, and quercetin have been shown to increase NK cell activity, potentially strengthening surveillance against virally infected or malignant cells [32].

5. Clinical evidence and translational challenges

Clinical trials investigating phytochemical antioxidants provide promising but inconsistent findings. For example, curcumin supplementation in patients with arthritis or inflammatory bowel disease has been associated with reduced symptom scores and lower inflammatory biomarkers [34]. Similarly, resveratrol has shown benefits in cardiovascular health by improving endothelial function and reducing circulating cytokines [35]. Quercetin and green tea catechins have been linked to enhanced antiviral defense and improved metabolic profiles [36]. Despite these encouraging signals, large-scale clinical translation remains hindered by several factors. A major limitation is poor oral bioavailability, as many phytochemicals undergo rapid metabolism and conjugation, leading to low plasma and tissue concentrations. Formulation strategies such as nanoparticle encapsulation, lipid carriers, and co-administration with bioenhancers like piperine are being developed to overcome this barrier [37]. Another challenge is variability in botanical extracts and supplements. Lack of standardization results in heterogeneous dosing and inconsistent outcomes across studies. Furthermore, phytochemicals exhibit pleiotropic actions, making it difficult to pinpoint mechanistic biomarkers that link exposure to clinical benefit. Trial designs are often short in duration, underpowered, or lacking appropriate mechanistic endpoints. Nevertheless, accumulating human data support the view that phytochemical antioxidants can beneficially modulate immune and redox pathways in specific populations. To move forward, translational research must focus on standardized preparations, pharmacokinetic–pharmacodynamic mapping, and patient stratification based on disease mechanisms or microbiome profiles. By addressing these gaps, phytochemicals may evolve into effective adjuvants or preventive strategies for immune-related disorders.

CONCLUSION

Antioxidant phytochemicals offer multi-targeted, biologically plausible routes to modulate the redox–immune interface. Strong preclinical evidence and early clinical signals warrant further translational investment, but success requires rigorous pharmacology, standardized preparations, and mechanism-linked clinical trials. If these hurdles are addressed, phytochemicals could become valuable adjuncts for immune modulation and disease prevention.

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