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How Polyphenols Contribute To Optimal Health and Immune Response

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Introduction

There is no question scientific testing shows that a diet full of natural foods is our best defense against pathogens. Contained within these plants are phytochemicals. One class of phytochemicals are polyphenols. They are a large group of heterogeneous compounds characterized by hydroxylated phenyl moieties, and are found mostly in plants, including fruits, vegetables, nuts, seeds, and cereals, as well as natural nutraceuticals such as SMPL72 fulvic mineral liquid, or beverages such as tea, coffee and wine [1].

Polyphenols have become an intense focus of research due to their potential benefits to health, particularly in relation to the prevention of cancer [2, 3] and cardiovascular diseases [4, 5].

Their suggested beneficial effects are anticarcinogenic [6, 7], antiatherogenic [8, 9], antiulcer [10], antithrombotic [11, 12], anti-inflammatory [13, 14], antiallergenic [15, 16], anticoagulant [17], immune modulating [18], antimicrobial [19, 20], vasodilatory [21], and analgesic activities [22].

To achieve these health benefits, polyphenols require in situ processing by the gut microbiota to be transformed into a potentially more bioactive, low-molecular-weight metabolite [23]. Faria et al. (2014) reviewed that total polyphenol absorption in the small intestine is relatively low (5%–10%) in comparison to other macro- or micronutrients. The remaining 90%–95% of polyphenols transit to the large intestinal lumen and accumulate in the millimolar range. From the lumen, together with conjugates excreted from bile, they are exposed to the enzymatic activities of the gut microbiota [24]. The microbiota that colonize the distal regions of the colon represent the highest concentration of microorganisms found in human body, as well as the most diverse [25]. It is known that the human gut has an ecosystem of around 10^{13} – 10^{14} bacterial cells, an estimate 10 times that of human somatic cells [26]. In addition, the aggregate microbial genome (i.e., microbiome) is predicted to contain more than three million genes, or 150 times more than human genes [27].

The reciprocal relationship between polyphenols and gut microbiota may contribute to host health benefits. The need to clarify the molecular mechanisms underlying the observed prebiotic enrichment of beneficial bacteria and antimicrobial activities against gut pathogenic bacteria is apparent [23, 29–33].

Commensals residing in the gut may improve health by protecting against gastrointestinal disorders and pathogens, processing nutrients, reducing serum cholesterol, strengthening intestinal epithelial tight cell junctions, producing antibodies, increasing mucus secretion and modulating intestinal immune response through cytokine stimulus [34, 35].

Furthermore, the gut microbiota bio-transforms polyphenols into metabolites that may have greater biological activity than their precursor structures [23]. In short,

the gut microbiota is essential for the maintenance of intestinal homeostasis and overall optimal human health [28].

Gut Health, Inflammation and Immunity

Gut microbiota (GM) plays several crucial roles in host physiology and influences several relevant functions. In more than one respect, it can be said that “you feed your microbiota and it feeds you”[36].

GM diversity is affected by diet. Our GM influences metabolic and immune functions of the host's physiology. Consequently, an imbalance of GM, or dysbiosis, may be the cause or at least may lead to the progression of various pathologies such as infectious diseases, gastrointestinal cancers, inflammatory bowel disease, and even obesity and diabetes. Therefore, GM is an appropriate target for nutritional interventions to improve health.

For this reason, phytochemicals, such as polyphenols (e.g. fulvic acids) that can influence GM have recently been studied as adjuvants for the treatment of obesity, inflammatory diseases and overall immune health.

Phytochemicals include prebiotics and probiotics, as well as several chemical compounds such as polyphenols and derivatives, carotenoids, and thiosulfates. The largest group of these comprises polyphenols, which can be subclassified into four main groups:

1. flavonoids (including eight subgroups)
2. phenolic acids (such as curcumin)
3. stilbenoids (such as resveratrol)
4. lignans

Once nutrients and nutraceuticals (e.g. polyphenols) have been incorporated into the body, the gut environment is essential in maintaining homeostasis; in this sense, like GM, the surface of the intestinal mucous membrane plays a fundamental role in the preservation of homeostasis. Consequently, the correct functioning of its permeability is of great importance [36].

Several pathologies, as well as susceptibility to metabolic diseases, have been linked to alterations in the permeability of the intestinal barrier. Humans possess two interacting genomes: their own complete set of DNA and that of the microbiome genome (e.g. the entire genome of each of the multitude of microbes that colonize our small and large intestine) the majority of which resides in the gut, in the layer of mucin glycoproteins (mucus) produced by the cells called goblet cells [37].

The microbiome provides products such as vitamins and nutrients to human cells, thereby establishing a beneficial ecosystem for host physiology and preventing the proliferation of pathogens [38]. Thus, a symbiotic relationship is established between both genomes, through the expression of pattern recognition receptors (PRRs) that sense the presence of intestinal microbiota, through the microbe-associated molecular patterns (MAMPs).

This communication between the two genomes results in the accuracy of the mucosal barrier function, by regulating the production of its components: mucus, antimicrobial peptides, IgA and IL-22, facilitating homeostasis, and immune health [38-40]. Therefore, GM and the human host influence each other by exchanging their metabolic active molecules [41], working together, as a hologenome, to maintain mutual health [42].

Polyphenols and Cytokine Modulation

Cytokines are important mediator proteins, essential in networking communication for the immune system. Cytokines can be produced by lymphocytes (lymphokines), or monocytes (monokines) with pro-inflammatory and anti-inflammatory effects. Cytokines with chemotactic activities are termed chemokines. The equilibrium between pro-inflammatory cytokines (IL-1b, IL-2, TNFa, IL-6, IL-8, IFN-g . . .) and anti-inflammatory cytokines (IL-10, IL-4, TGFb) are thought to be an important parameter in immune response homeostasis and inflammation underlining many disease states [43].

In vivo and in vitro studies demonstrate that polyphenols affect macrophages by inhibiting multiple key regulators of inflammatory response such as the inhibition of TNFa, IL-1b, and IL-6 [44]. Flavonoids, as well, have an important anti-inflammatory effect by influencing cytokines' secretion. Several flavonoids are found to inhibit the expression of various pro-inflammatory cytokines and chemokines like TNFa, IL-1b, IL-6, IL-8, and MCP-1 (monocyte chemoattractant protein-1) in multiple cell types such as LPS-activated mouse primary macrophages, activated human mast cell line, activated human astrocytes, human synovial cells, and human peripheral blood mononuclear cells [45-50]. Modulation of inflammatory cytokines is one of many common mechanisms by which polyphenols in general exert their immunomodulatory effects.

Polyphenols, Inflammation, and Modulation of the NFkB Signaling Pathway
NF-kB or nuclear factor kappa-light-chain-enhancer of activated B cells is a complex protein that plays a key role in deoxyribonucleic acid (DNA) transcription, cytokine production and cell survival. It controls immune, inflammation, stress, proliferation and apoptotic responses of a cell to multiple stimuli [51].

The expression of a large number of genes involved in inflammation is controlled by NF-kB and the inhibition of NF-kB can be of a great benefit in controlling inflammatory conditions [52]. Several polyphenols modulate NF-kB activation and

reduce inflammation[53, 54]. For example, genistein or quercetin repress LPS-induced activation of NF- κ B in monocytes and reduces the inflammation by inhibiting NF- κ B activation upon adenosine monophosphate activated protein kinase stimulation in LPS-stimulated macrophages [55, 56]. Flavonoids can modulate NF- κ B activation cascade at early phases by affecting IKK activation and regulation of oxidant levels or at late phases by affecting binding of NF- κ B to DNA in T-cells [57]. Hydroxytyrosol, and resveratrol inhibit NF- κ B activation, and the expression of VCAM-1 in LPS-stimulated human umbilical vein endothelial cells [58].

In summary, polyphenols can modulate NF- κ B activation cascade at different steps such as by affecting IKK activation and regulating of the oxidant levels or by affecting binding of NF- κ B to DNA leading to an important anti-inflammatory effect responsible for their potential value in treating chronic inflammatory conditions (Figure 1).

Polyphenols, Oxidative Stress, and Inflammation

Higher production of reactive oxygen species (ROS) is associated with oxidative stress and protein oxidation [59]. Subsequently inflammatory molecules and different inflammatory signals (i.e., peroxiredoxin2) are triggered by protein oxidations [60]. Furthermore, overproduction of ROS can prompt tissue injury that initiates the inflammatory process [61-65].

Therefore, the classical antioxidant actions of polyphenols undoubtedly contribute to their anti-inflammatory roles by interrupting the ROS-inflammation cycle (Figure 2). Polyphenols are known for their antioxidant activities; they scavenge a wide-ranging selection of ROS. Polyphenols can scavenge radicals and chelate metal ions, for example quercetin chelates iron ion [66]. They also inhibit multiple enzymes responsible of ROS generation [67]. In fact, free metal ions, as well as highly reactive hydroxyl radical release, is increased by the formation of ROS.

To the opposite, polyphenols are able to chelate metal ions like Fe²⁺, Cu²⁺, and free radicals which lead to a reduction of highly oxidizing free radicals in the body [68]. Transition metal ions, like Fe²⁺, Cu²⁺, Co²⁺, Ti³⁺, or Cr⁵⁺, results in OH $\cdot$ formation from H₂O₂ [69, 70]. Curcumin is able to chelate transition metal (Cu²⁺ and Fe²⁺) ions. Alike, EGCG and quercetin chelate Fe²⁺ (iron ion) [66]. Polyphenols like apocynin, resveratrol, and curcumin can inhibit NOX (NADPH oxidase) causing a reduction in the generation of O₂ $\cdot$ during infections consecutively in endothelial cells in THP1-monocytes [71-73].

Additionally, polyphenols can attenuate the mitochondrial ATP synthesis by blocking the mitochondrial respiratory chain and ATPase. As a result, ROS production is diminished. Curcumin [74], EGCG [75], phenolic acids [76], capsaicin [77], quercetins [78], anthocyanins [78], and resveratrol analogs [79] inhibit xanthine oxidase. Thus, they reduce ROS production.

Polyphenols affect the activity of cyclooxygenase, lipoxygenase, and NOS (nitric oxide synthase) as per found in macrophages [80]. These enzymes are known to metabolize arachidonic acid and their inhibition moderates the production of key mediators of inflammation (prostaglandins, leukotrienes, and NO . . .) [80].

Polyphenols exert the anti-inflammatory action by different mechanisms: radical scavenging, metal chelating, NOX inhibition, tempering the mitochondrial respiratory chain, inhibition of certain enzymes involved in ROS production, like xanthine oxidase and upregulation of endogenous antioxidant enzymes.

Conclusion

In conclusion, the vast number of published studies proved the immunomodulatory role of polyphenols in vivo and in vitro. Different underlying regulatory mechanisms are now well elucidated. These data highlighted here help demonstrate the promising role of polyphenols in prevention and therapy of diseases with underlining inflammatory conditions, including cancer, neurodegenerative diseases, obesity, type II diabetes, and cardiovascular diseases. It is generally believed that polyphenol activity is principally located in the gut where their immune-protective and anti-inflammatory activities are initiated and subsequently ensuring systemic anti-inflammatory effects. Since different polyphenols can have multiple intracellular targets, additional data is needed to determine the consequences of the interaction or the synergistic effects between multiple polyphenolic compounds or polyphenols and commonly used medications. Moreover, further in vivo and meta-analysis studies in humans are necessary to fully reveal the mechanisms of action of polyphenols in several physiological conditions in order to produce important insights into their prophylactic and therapeutic uses.

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