Clinical Summary

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Khan H, Sureda A, Belwal T, et al. Autoimmune Rev 2019;18(7):647-657.

Polyphenols Help Maintain Immune Equilibrium

Regulation of the immune response occurs through the collective actions of signaling pathways that direct innate and adaptive immune function. This review examines how dietary polyphenolic substances (quercetin, resveratrol, and others) affect immune signaling networks implicated in the development of autoimmune dysfunction.

Autoimmune conditions may affect up to 10% of the population, and genetic, lifestyle, epigenetic, and environmental factors dynamically impact risks for autoimmune issues. Autoimmunity involves the inappropriate generation of antibodies to components of the body at a systemic or organ-specific level, and can subsequently heighten risk for cancer and other diseases.

A common feature underlying autoimmunity is imbalanced activities or numbers of T-helper cell (Th cell) subsets combined with insufficient moderating influence from regulatory T cells (Tregs), which normally help preserve immune tolerance to 'self' immune markers. If this imbalance is not corrected, it can eventually result in overproduction of proinflammatory cytokines, activation of tissue enzymes, loss of self-tolerance, and the generation of autoantibodies. Activated T cells release chemical messengers that can expand or delimit adaptive as well as innate immune responses, including interleukins, interferons, cytokines, growth factors, and nuclear signaling factors (tumor necrosis factor, etc.).

Polyphenols are phytonutrients that are being studied for their influence at the innate/adaptive immune interface. Dietary polyphenols possess a considerable range of antioxidant potential, and additionally display beneficial antimicrobial, neuroprotective, metabolic, and cardiovascular properties. Those under research for immunomodulatory activity in autoimmunity include curcumin, quercetin, ginkgo flavonoids, epigallocatechin gallate (EGCG), apigenin, luteolin, resveratrol, hesperidin, anthocyanidins, fisetin, genistein, milk thistle flavonoids, and others. Their broad ability to downregulate the production of proinflammatory signaling molecules may aid balance among T-cell subsets, support intestinal integrity, and limit inappropriate generation of antibodies and destructive tissue enzymes.

This study examines the effects of polyphenols on signaling networks that control the initiation, expansion, and conclusion of the immune response. Specific messaging pathways examined include:

- The arachidonic acid pathway of eicosanoid lipid mediator metabolism (involving cyclooxygenases, lipoxygenases, and related enzymes)
- Epigenetic regulation of gene activation and silencing to alter the development and mobilization of immune cell lineages
- The nuclear factor-kappa B (NFκB) and mitogen-activated protein kinase (MAPK) systems influencing proinflammatory gene expression (for tumor necrosis factor, other cytokines, LOX, COX, etc.)
- The phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt) pathways modulating cellular energy metabolism and cytokine expression

According to these researchers:

“To maintain an effective immunological homeostasis, a balance between Th cell activation and Treg cells mediated suppression is required.”

“Each type of polyphenol targets different immune cells and, therefore, triggers a plethora of diverse intracellular signaling pathways that ultimately regulate the host’s immune response.”

Research Summary

In clinical and preclinical studies, polyphenols have displayed the ability to modulate functional immune balance and related genetic expression in the following ways:

- Clinical trials employing relatively high dosages of curcumin, quercetin, EGCG, or ginkgo extract have shown benefit in patients with autoimmune imbalance. Findings included alterations in key immune markers (IL-10, TNF, and IL-8), improvement in lipid and carbohydrate metabolism, heightened plasma antioxidant activity, and symptomatic amelioration in study subjects with ulcerative colitis, vitiligo, sarcoidosis, or multiple sclerosis.
- Numerous polyphenols (quercetin, resveratrol, anthocyanidins, luteolin, and others) have demonstrated strong inhibition of enzymes associated with proinflammatory prostaglandins, leukotrienes, and thromboxanes that can perpetuate an immune response and contribute to loss of self-tolerance. Studied enzymes include cyclooxygenases (COXs) and lipoxygenases (LOXs) as well as the initiator of the arachidonic acid cascade, phospholipase A2.
- Genomic function and consequent production of immune cells and immunomodulating proteins can be profoundly impacted by epigenetic modification of DNA and other chromosomal structures. Resveratrol, quercetin, curcumin, fisetin, and myricetin may alter cell life-and-death cycles through these mechanisms, and EGCG, curcumin, and resveratrol are known to influence epigenetic control of proinflammatory gene expression.

- The NFκB signaling network exerts significant genetic control over the production of reactive species as well as cytokines and chemokines (including interleukins, tumor necrosis factor-α, monocyte chemoattractant protein-1, and adhesion molecules). Polyphenols such as quercetin, resveratrol, genistein, EGCG, and those in olives have been seen to block NFκB activation and limit nuclear binding of NFκB-related messengers in a wide variety of immune cells and vascular, respiratory, and connective tissue cells.
- Polyphenols also influence messaging along the PI3K/Akt pathways that regulate cellular energy utilization and the genetic expression of IL-6, IL-17, IL-1β, and other cytokines strongly implicated in autoimmunity. Specific polyphenols investigated for these effects include resveratrol, quercetin, silibinin (from milk thistle), ellagic acid, and EGCG.
- MAPKs are specialized kinases that respond to stress signaling by invoking the inflammatory response, and affect immune cell development and inflammatory messenger expression. The activity of numerous MAPKs is moderated by polyphenols that include quercetin, resveratrol, catechins (esp. EGCG), luteolin, hesperidin, chrysin, kaempferol, and naringin.

NUTRITION CONCLUSION

Regular consumption of foods rich in quercetin, resveratrol, catechins, and other polyphenolic compounds—like peppers and other vegetables, berries and other fresh fruits, and buckwheat—represents a crucial dietary means of optimizing signaling between the innate and adaptive immune compartments. Dysfunctional messaging between adaptive and innate immune functions due to environmental, lifestyle, genetic, and epigenetic factors is implicated in the loss of self-tolerance that defines autoimmunity.