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Editorial

Quercetin: the Ultimate Anti-inflammatory Elixir?

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"Let food be thy medicine and medicine be thy food". Hippocrates—400 BC.

The endless quest for natural components owing potent anti-inflammatory effects is leading to an ever-expanding number of trials *in vivo* and *ex vivo*.

One of the most interesting innovations is exploring the herbal/dietary approach through nutraceuticals, a broad panel of nutrients having potent preventive and therapeutic effects.

This "run for a cure" is pushed forward by the worldwide epidemic trend of non-communicable diseases (notably cardiovascular diseases, obesity and metabolic syndrome, type 2 diabetes mellitus, and cancers). These disorders share several pathophysiological aspects, particularly with chronic inflammation as a common causative core and the potential therapeutic target.

In fact, the immune system dysregulation and inflammatory cascade are pathogenic factors, which are involved in the pathogenesis of a wide variety of illnesses; and chronic inflammatory diseases are considered as the most significant cause of death in the world today and the include non-communicable diseases and many auto-immune and/or neurodegenerative disorders.[1]

Many bioactive dietary components have therapeutic effects by targeting inflammatory pathways, and changing metabolic and genetic regulations. However, such dietary components may modulate glucose metabolism and activate the nuclear factor-κB (NF-κB) signaling to trigger inflammation through common pathway master switches.[2] A natural approach to control of these inflammatory pathways (through the so-called nutraceuticals) has evidenced that some nutrients (*via* specific nutritional management or diet) are cost-effective and potentially highly efficient, especially for some antioxidants.

Quercetin (Q) is a flavonoid antioxidant in the flavonoid group derived from polyphenolic secondary metabolites. The nutritional Q has a relatively increased bioavailability compared to other phytochemicals, and is found in appreciable amounts in a myriad of food like grapes, berries, cherries, apples, citrus fruits, red and common onions, buckwheat, kale, tomatoes, and figs.[3]

Q has proven to have a great potential in the prevention and treatment of different chronic diseases, and exerts health beneficial effects in a number of cellular and animal models, as well as in humans, through modulating the signaling pathways and gene expression. In addition, Q metabolites are found in systemic circulation after their consumption and can act as potent anti-inflammatory and antioxidant agents, contributing to the overall biological effects and health benefits of Q-rich diet or Q supplementation.[4,5]

In a recent research article published in the *Journal of Exploratory Research in Pharmacology*, Liao and Lin explored the role of Q in the changes in the levels of pro-/anti-inflammatory cytokines and other inflammation-related signaling events *in vitro* lipopolysaccharides-stimulated macrophages.[6]

This study revealed that Q decreased the levels of pro-inflammatory TNF-α production and increased anti-inflammatory IL-10 expression in murine macrophages. The investigators suggested that Q might inhibit the lipopolysaccharide-induced inflammation by suppressing the Toll-like receptor-2 (TLR2) expression and the signal transducer and activator of transcription 3 (STAT3) activation in activated macrophages.

It is well known that CD4+ and CD8+ T cells, B cells, dendritic cells, and macrophages are responsible for adaptive immunity and their functional balance is crucial for self-tolerance and defending against pathogenic invaders. Specifically, macrophages can be activated as pro-inflammatory I type macrophages to trigger an inflammation by producing pro-inflammatory cytokines, such as interleukin (IL)-1β, TNF-α, and IL-6. Macrophages can also be alternatively activated as II type macrophages to produce anti-inflammatory IL-10. Q is considered as one of the most potent flavonoids acting on inflammation and modifying immune responses: it has been previously reported that Q is an efficacious protective agent against LPS-induced inflammation in human peripheral blood mononuclear cells by inhibiting the LPS-induced TLR4/NF-kB signaling.[7]

The Liao and Lin's study focused on macrophages, which are major producers and responders of TNF-α.[6] The production of TNF usually precedes and promotes the subsequent release of inflammatory mediators (encompassing interleukins and type I interferons). Activated pro-inflammatory macrophages can also produce chemokines, lipid mediators, and antimicrobial peptides. This hyper-inflammatory response is often induced by danger signals, such as bacterial LPS.[8]

Q is also a renowned antioxidant: it is a potent scavenger of reactive oxygen species and reactive nitrogen species to reduce oxidative stress.[9] In addition, Q can inhibit the NF-κB signaling

Abbreviations: NF-κB, Nuclear Factor-κB; Q, Quercetin; TNF-α, Tumor Necrosis Factor-α; IL-10, Interleukin-10; TLR2, Toll-like receptor-2; STAT3, Signal transducer and activator of transcription 3; LPS, Lipopolysaccharids; TRAPS, TNF-Receptor Associated Periodic Syndrome.

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to reduce pro-inflammatory cytokine production. Indeed, the NF-κB signaling regulates multiple aspects of innate and adaptive immune responses and serves as an important mediator of inflammation by inducing the production of pro-inflammatory cytokines and chemokines.[9,10] The novel findings of Q increasing IL-10 production indicate that Q is potent in regulating the balance of pro-inflammatory and anti-inflammatory responses.

The anti-inflammatory properties of Q open a large window for regulating many other inflammatory processes, like the immune deficiencies (such as the STAT3 gain of function) or the peculiar autoinflammatory diseases (such as the TNF-Receptor Associated Periodic Syndrome, TRAPS) and even some chronic inflammatory diseases, like rheumatoid arthritis. However, the potential therapeutic effect of Q and its molecular mechanisms remain to be investigated.

Time is more than appropriate for such important laboratory findings to be translated into pharmaceutical (nutraceutical) products for clinical evaluation.

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Conflict of interest

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Declarations

The authors state no ethical or legal conflict involved in the manuscript, no form of academic misconduct involved in the manuscript, including but not limited to plagiarism, fabrication, falsification, or inappropriate authorship.

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