**BIOCHEMICAL MECHANISMS OF NUTRACEUTICAL COMPOUNDS: MORE THAN ANTIOXIDANTS**

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Regular consumption of nutraceutical compounds found ubiquitously in plants has been associated with a reduced risk of a number of oxidative stress related chronic diseases. Their protective/preventive role has often been ascribed to their antioxidant/radical scavenger activity. But their in vitro measured antioxidant capacity is simply an index of sensitivity to oxidation rather than of protection obtained in vivo. In fact, the concentrations of the antioxidants in cells or plasma are very low, and the reaction rates of phytochemicals with free radical species are insignificant in comparison to the reaction rates of formation of these harmful compounds. As a free radical scavenger mechanism cannot be substantiated on a kinetic basis in vivo, what then accounts for the nutraceutical effect of these compounds? Many of the so-called 'antioxidants' provide cellular and tissue protection against oxidative damage by inducing endogenous antioxidant defences and acting as modulators of intracellular signaling pathways. Phytochemicals act to produce an additive increase in electrophilic signaling that results in the induction of protective enzymes and increased nucleophilic compounds, resulting in a more reductive/electrophilic environment, referred as "nucleophilic tone" (1) defined as the overall potential cellular adaptive response to oxidative challenge brought by electrophiles.

The mechanisms underpinning the increase of the nucleophilic tone involve the MAPK and PI3K /Akt signaling cascades, and the Nrf2/ARE/EpRE system. The MAPK signaling pathway has a central role in regulating cell growth and survival, and in the transcriptional activation of COX-2. Nrf2 acts as a cytoplasmic "switch" to activate a battery of cytoprotective genes especially those of the Phase II detoxification enzymes. One more biochemical target of nutraceuticals is the non-enzymatic glycation of proteins and the generation of so called advanced glycation end products (AGEs). Although AGE formation is increased in diabetes, AGEs are formed by normal metabolic processes during aging. AGEs content in the organism is not only due to the rate of their formation but also by the rate of their removal by the glyoxalase system (Glo) I and II. Certain polyphenols have been proposed to counteract AGE formation both in vivo and in vitro by inducing the Glo system. Furthermore, receptors for AGEs, such as RAGE, have also been recognized to play an important role in the activation of NFκB and subsequent transcription of many proinflammatory genes.

In particular, nutraceutical compounds as quercetin, the main polyphenol of the western diet, abundant in apples and onions, may prevent cell damage by inducing multiple cytoprotective pathways (2-4), and sulforaphane, derived from the hydrolysis of the Cruciferous vegetables glucosinolates, is able to modulate the expression of genes and proteins related to the Nrf2/Phase II detoxification and inflammatory pathways (5-7) and to detoxify AGEs (8).

But individual nutraceuticals can have greater or lesser effects on specific Nrf2- and inflammation-related genes in various tissues and experimental models. Therefore, only using a combination of nutraceuticals it would be possible to modulate the greatest diversity of Nrf2- and inflammation

related genes in the greatest number of tissues to achieve the most dramatic protective effects against oxidative damage, toxicants, and inflammation, and to provide the most robust preventive/protective and anti-aging benefits.

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