Review of: "Tomatoes Unveiled: A Comprehensive Exploration from Cultivation to Culinary and Nutritional Significance"

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Potential competing interests: No potential competing interests to declare.

The development and progression of cancer are associated with the dysregulation of multiple pathways involved in cell proliferation and survival, as well as dysfunction in redox balance, immune response, and inflammation. The master antioxidant pathway, known as the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, regulates the cellular defense against oxidative stress and inflammation, making it a promising cancer prevention and treatment target. Cannabinoids have demonstrated anti-tumor and anti-inflammatory properties, affecting signaling pathways, including Nrf2. Increased oxidative stress following exposure to anti-cancer therapy prompts cancer cells to activate antioxidant mechanisms. This indicates the dual effect of Nrf2 in cancer cells—influencing proliferation and apoptotic processes and protecting against the toxicity of anti-cancer therapy. Therefore, understanding the complex role of cannabinoids in modulating Nrf2 might shed light on its potential implementation as an anti-cancer support. In addition, ample evidence has pointed to a close link between oxidative stress, mitochondrial dysfunction, and depression. Nuclear factor-erythroid 2-related factor-2 (Nrf2) is a master regulator of cellular redox homeostasis and affects mitochondrial function. Nrf2 holds promise for depression prevention and treatment. Moreover, anxiety-like behaviors induced by ethanol addiction/withdrawal in mice, associated with the NF-κB-mediated inflammatory signaling pathway and Nrf2-mediated antioxidative/antiinflammatory stress signaling pathways. Also, several studies reveal that nuclear factor erythroid 2-related factor 2 (Nrf2) regulates redox homeostasis and works as an anti-inflammatory in various degenerative disorders. Relevant to inflammatory damage and its therapeutics, experimental models suggest that redox active compounds, which have been shown to act via hormetic dose responses, are endowed with powerful anti-inflammatory effects, displaying endpoints of biomedical and clinical relevance. Thus, interplay and coordination of redox interactions and their interaction with endogenous and exogenous antioxidant defence systems is an emerging area of research interest in anti-inflammatory anti-degenerative therapeutics. Thus, stress-resistant cells in which the vitagene system has been induced could be the basis to uncover molecular modulators of adaptation, resistance, and cytoprotection as potential pharmacological targets for preventing spermatozoa degeneration. This reviewer is satisfied with the significance of this study, the care with which the study was performed, and the implications of the results for human health. Results presented are interesting, and the questions posed are of extremely high interest; thus, the paper does give adequate definitive information. Pending minor points, this paper can be accepted.

Minor concerns:

Emerging data suggests that Nrf2-regulated vitagenes are proteins capable of increasing stress resilience pathways in a wide range of human pathologies. As a result, stimulation of Nrf2-dependent resilience responses suggests an important new target for restoring redox equilibrium in the CNS. Given the relationship between the vitagene network and its possible biological relevance in the defense mechanisms against oxidative stress-driven degenerative diseases, authors should mention in the discussion appropriately this aspect (See and quote, please, Calabrese et al., 2010, Antiox. Redox Signal 13,1763; Calabrese et al., Nature Neurosci., 2007 8, 766; Calabrese V, et al., J. Neurosci Res. 2016 94:1588-1603. doi: 10.1002/jnr.23925; Mancuso, C., et al., Bilirubin as an endogenous modulator of neurotrophin redox signaling. J. Neurosci. Res. 86: 2235 - 2249, 2008; Platania CBM, et al., Biochem Pharmacol. 2020 May;175:113908. doi: 10.1016/j.bcp.2020.113908)