# Review of: "Targeting Alzheimer's disease hallmarks with the Nrf2 activator Isoeugenol"

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Potential competing interests: No potential competing interests to declare.

Alzheimer's disease (AD) is considered as the most common cause of dementia in elderly population. While the exact mechanism of AD has not been discovered, emerging literature suggests that natural compunds endowed with neuroprotective potential have multifaceted effects that reduce AD pathologies, even in old mice. In keeping with emerging finding, modulation of cellular resilience mechanisms induced by low levels of stressors represents a novel approach for the development of therapeutic strategies, and in this context, neuroprotective effects of a wide range of polyphenol compounds have been demonstrated in several in vitro and in vivo studies. Mushrooms have been used in traditional medicine for many years and have been associated with a long list of therapeutic properties, including antitumor, immunomodulatory, antioxidant, antiviral, antibacterial, and hepatoprotective effects. Recent studies have strikingly indicated the presence of polyphenols in nutritional mushrooms and demonstrated their protective effects in different models of neurodegenerative disorders in humans and rats ( D'Amico R et al., Antioxidants 2021, 10(6):898. doi: 10.3390/antiox10060898). Consistently, accumulation of misfolded proteins or perturbation of calcium homeostasis leads to endoplasmic reticulum (ER) stress and is linked to the pathogenesis of neurodegenerative diseases. Hence, understanding the ability of neuronal cells to cope with chronic ER stress is of fundamental interest. Interestingly, several brain areas uphold functions that enable them to resist challenges associated with neurodegeneration. NF-E2-related factor 2 (NRF2) plays a crucial role in the maintenance of cellular homeostasis by regulating various enzymes and proteins that are involved in the redox reactions utilizing sulfur. While substantial impacts of NRF2 on mitochondrial activity have been described, the precise mechanism by which NRF2 regulates mitochondrial function is still not fully understood. 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 reserach interest in anti-inflammatory anti-degenerative therapeutics. In addition, emerging finding underscores the wide portfolio of adaptive responses of neuronal cells to chronic oxidative as well as reductive stress. Thus, stress-resistant neuronal cells in which the vitagene system has been induced could be the basis to uncover molecular modulators of adaptation, resistance, and neuroprotection as potential pharmacological targets for preventing neurodegeneration. This reviewer is satisfied with the significance of this study, the care in 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:

Given the relationship between vitagene network, Mushroom nutritional approach and their possible biological relevance in the defense mechanisms against oxidative stress-driven degenerative diseases, Authors can 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; Scuto M, et al., Nutrients. 2019 11:2417. doi: 10.3390/nu11102417; Mancuso C., et al., J. Neurosci. Res 2008, 86: 2235 – 22491 ; D'Amico R et al., Antioxidants 2021, 10(6):898. doi: 10.3390/antiox10060898).