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Viktorija Maksimova is an associate professor in pharmaceutical botany and pharmacognosy at the Department of applied pharmacy, Faculty of Medical Sciences at the University of Goce Delcev in Shtip, North Macedonia. She is a Master of Pharmacy and defended her PhD thesis in the topic of Antioxidative and cytotoxic effect of capsicinoids, in 2016 at the same University. Currently, she's working on medicinal plants, and she is interested in researching small bioactive molecules as a novel superior antioxidant and cytotoxic agents among polyphenols and alkaloids. Recently she has become interested in studying plant bioactive molecules as NRF2 modulators.

# Piperine as a natural derived NRF2 stimulator in prevention or therapy of ROS induced diseases


**Background:** Piperine is the major alkaloid represented in *Piper nigrum* (black pepper) showing different pharmacological properties that are still extensively studied. Piperine's ability to activate the protein expression levels of NRF-2 and HO-1 and inhibit the protein expression levels of Keap-1, is directly influencing the antioxidative capacity of the cells and ROS homeostasis.

**Results:** Activation of NRF2 by piperine has triggered an antioxidant response cell system (HO-1, GSH, CAT, SOD) scavenging ROS, and decreasing lipid peroxidation in colon cancer cells. These results indicate that piperine may be an effective molecule in prophylactic aims of colon carcinogenesis by targeting the NF-κB/NRF-2/Keap-1/HO-1 pathway. The novel effects of piperine in attenuating the oxidative stress in lung epithelial cells were shown recently. Treatment with piperine enhanced the NRF2 expression and reversed changes induced by cigarette smoke extract. Increased NRF2 levels promoted anti-inflammatory effect in the same cells. Piperine has shown protective effects against Aβ-induced neuronal damage and oxidative stress, in the SH-SY5Y cell model. Activation of NRF2 pathway can also lead to inhibition of LPS-induced inflammatory response in microglial cells. In addition, a novel piperine derivative, HJ105, obtained through structure-based design and optimization was revealed in 2021, as a potent small molecule for treatment of Alzheimer disease. This structure promoted effective suppression of Keap1-NRF2 complex formation, and additional neuroprotective mechanisms of HJ105 underlying apoptotic cell death, oxidative stress response and neuro-inflammation.

**Conclusion:** Piperine and even more its derivatives are attracting increasing attention for their anti-apoptotic, anti-inflammatory, anti-antioxidant, cytoprotective and cognitive enhancing effects.