

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

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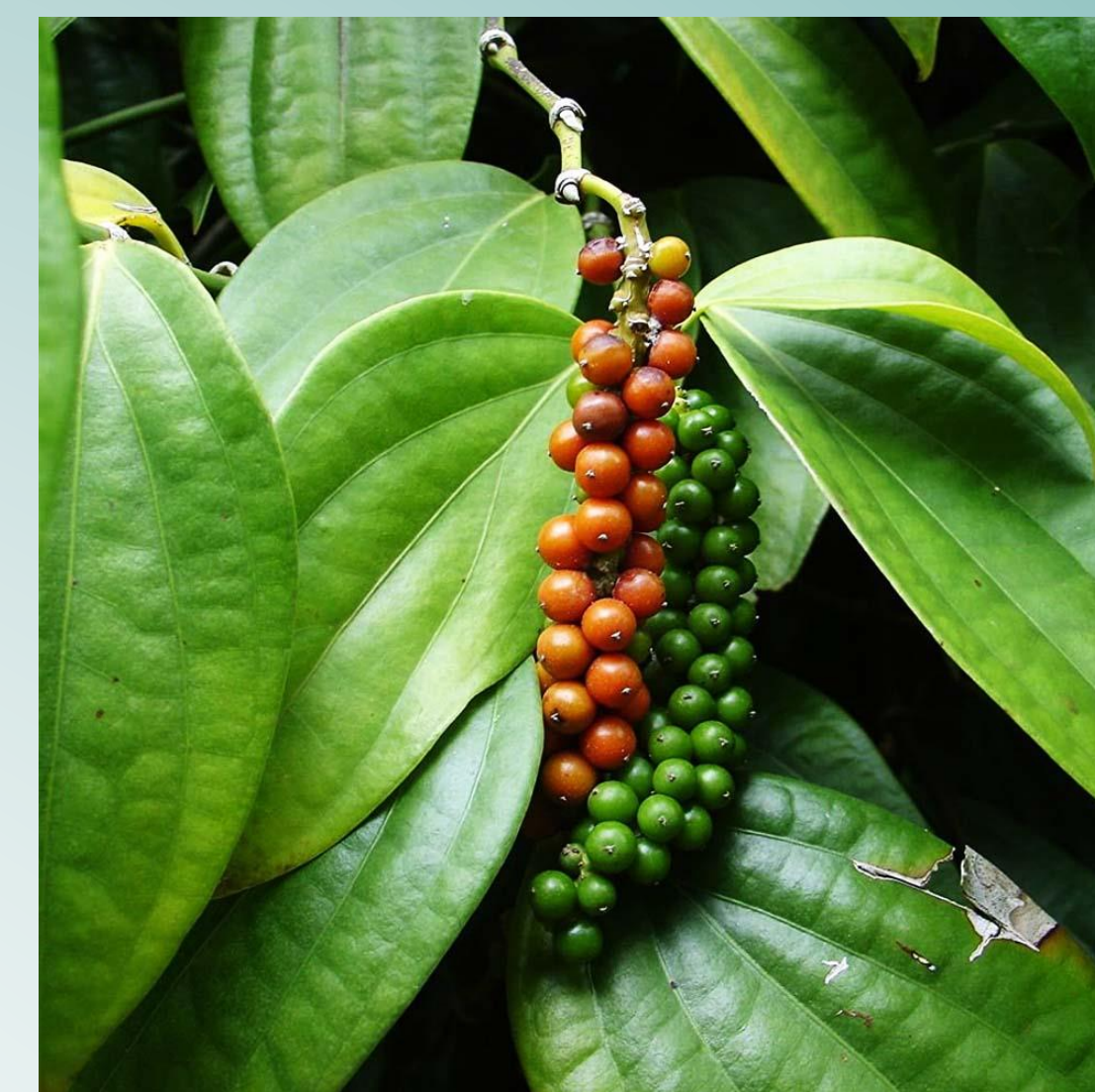
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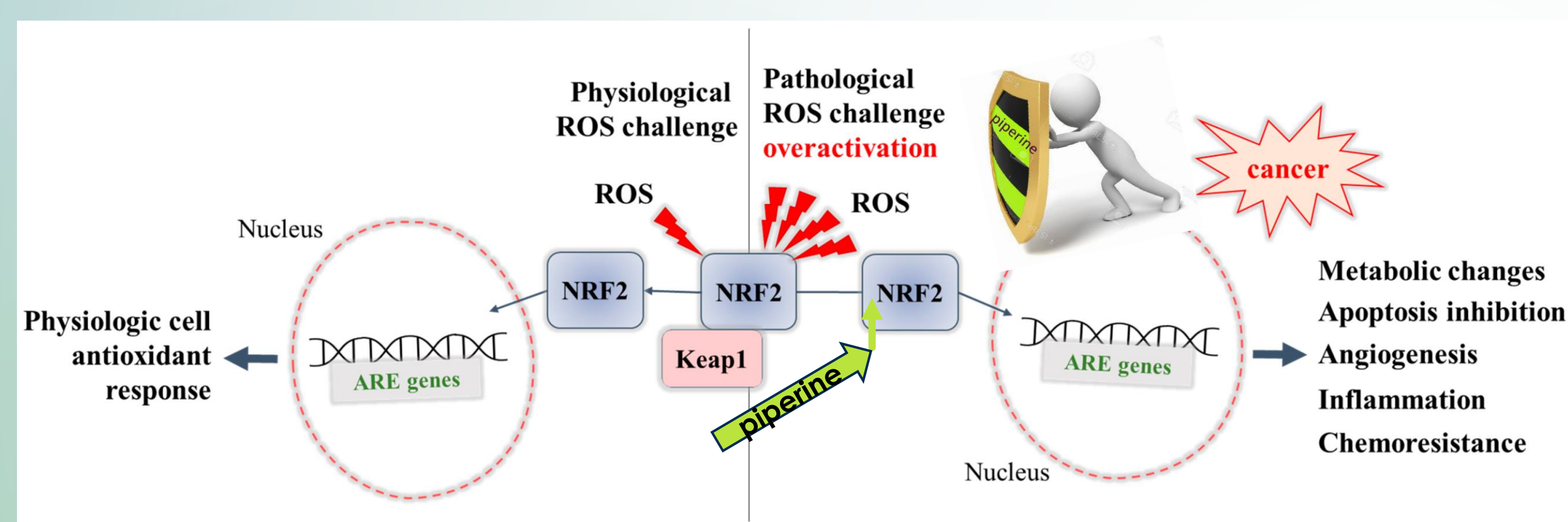
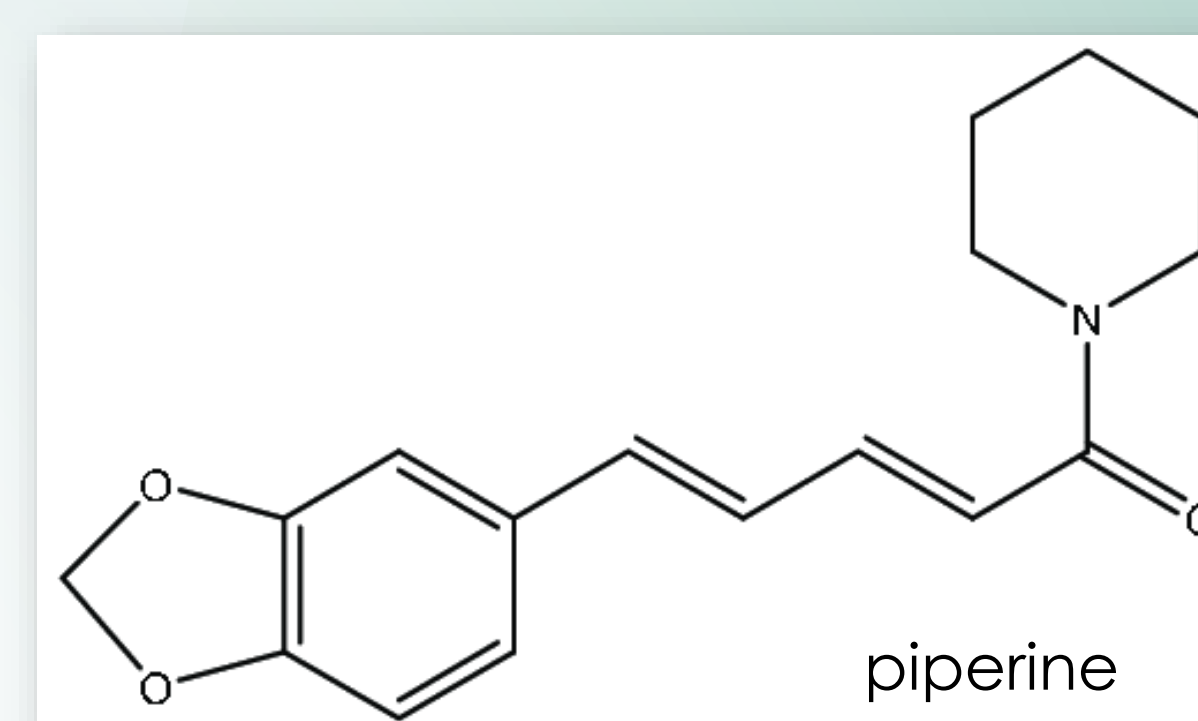
**Background:** Piperine is the major alkaloid represented in *Piper nigrum* (black pepper) showing different pharmacological properties that are still extensively studied.

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. The results published for piperine and its property for NRF2 activation indicate that piperine may be an effective molecule in prophylactic aims of colon carcinogenesis by targeting the NF- $\kappa$ B/NRF-2/Keap-1/HO-1 pathway.



*Piper nigrum* L



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 A $\beta$ -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.

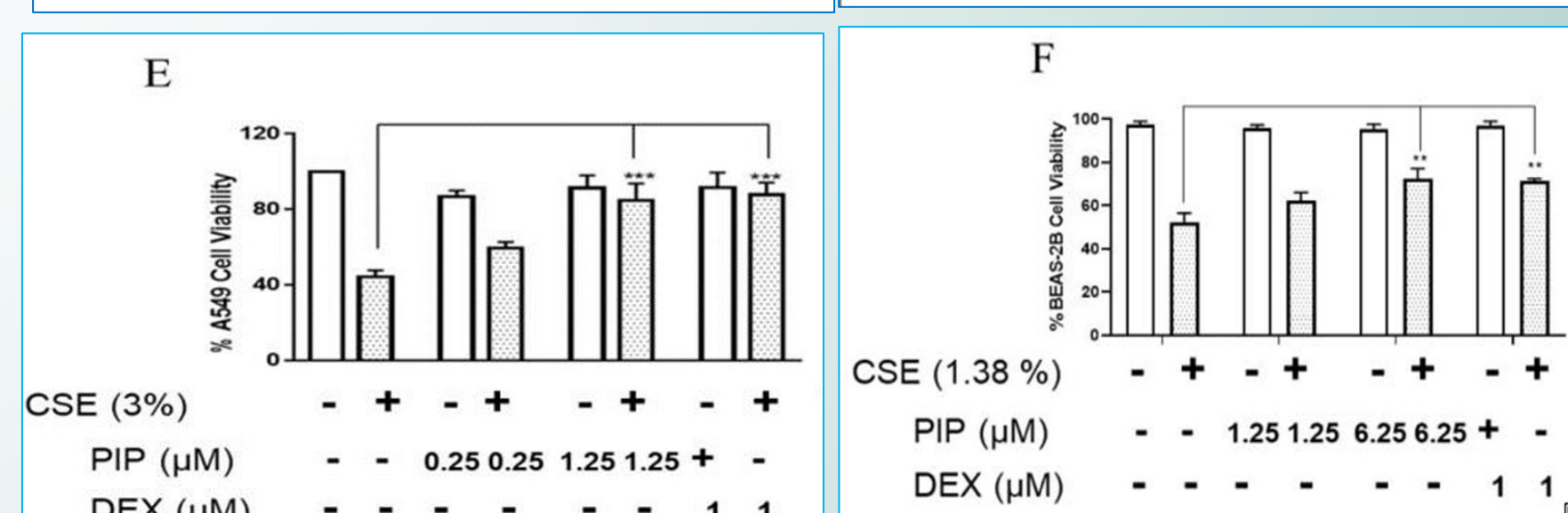
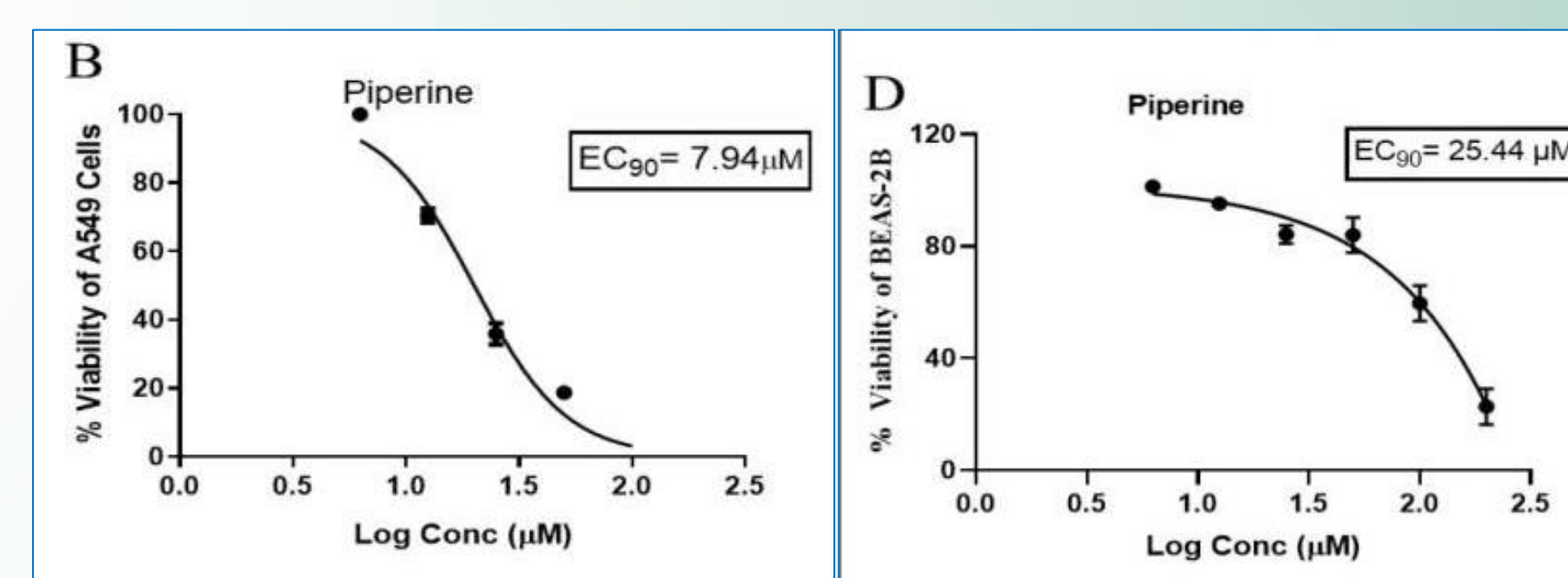
A novel piperine derivative, HJ105, obtained through structure-based design and optimization was revealed in 2021, as a potent small molecule for treatment of Alzheimer disease. This structure promoted effective suppression of Keap1-NRF2 complex formation, and additional neuroprotective mechanisms of 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, and the ways it modulate NRF2 pathways should be studied further.

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### References:

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Cytotoxicity assessment by Saha et al., 2022 of cigarette smoke and piperine by using MTT assay:  
(B) Represents % viability of A549 cell line exposed to different concentrations of PIP (0, 1.56, 3.12, 6.25, 12.5, 25, 50, and 100  $\mu$ M).  
(D) Represents % viability of BEAS-2B cell line exposed to different concentrations of piperine (0–200  $\mu$ M).