

# PHARMACOLOGICAL MODULATION OF NRF2

*Prof. Luciano Saso*

*Faculty of Pharmacy and Medicine, Sapienza University of Rome, Rome, Italy*

[luciano.saso@uniroma1.it](mailto:luciano.saso@uniroma1.it)

<https://www.researchgate.net/profile/Luciano-Saso>

Oxidative stress (OS) plays an important role in many diseases but very often it is not clear if it is among the causes or the consequences of the pathological conditions. In the last two decades, it has become clear that the main *in vivo* mechanism of action of antioxidants is not related to the direct scavenging of free radicals (reactive oxygen, nitrogen or sulphur species) but to the activation of the nuclear factor erythroid 2-related factor 2 (NRF2), the master regulator of endogenous antioxidant enzymes.

Recently, it has been clarified that NRF2 plays a very significant role not only in the antioxidant response and xenobiotic detoxification but also in the regulation of genes involved in proteosomal and autophagic function, iron, lipid and carbohydrate metabolism and DNA repair.

From the pharmacological point of view, the picture is particularly complex because in diabetes and other diseases NRF2 can play a protective or pathogenic role depending on the timing and duration of its activation.

Despite the presence of several contradictory publications, in type 2 diabetes, the most common form of diabetes, the activation of NRF2 before the development of diabetic outcomes seems to be beneficial. However direct electrophilic activators of NRF2 can have several off-target effects and better drugs capable of disrupting the NRF2-KEAP1 binding should be developed.

## **Selected references**

Dodson M, Shakya A, Anandhan A, Chen J, Garcia JGN, Zhang DD. NRF2 and Diabetes: The Good, the Bad, and the Complex. *Diabetes*. 2022 Dec 1;71(12):2463-2476.

Firuzi O, Miri R, Tavakkoli M, Saso L. Antioxidant therapy: current status and future prospects. *Curr Med Chem*. 2011;18(25):3871-88. doi: 10.2174/092986711803414368. PMID: 21824100.

Ghareghomi S, Rahban M, Moosavi-Movahedi Z, Habibi-Rezaei M, Saso L, Moosavi-Movahedi AA. The Potential Role of Curcumin in Modulating the Master Antioxidant Pathway in Diabetic Hypoxia-Induced Complications. *Molecules*. 2021 Dec 17;26(24):7658

Hussain Y, Khan H, Alotaibi G, Khan F, Alam W, Aschner M, Jeandet P, Saso L. How Curcumin Targets Inflammatory Mediators in Diabetes: Therapeutic Insights and Possible Solutions. *Molecules*. 2022 Jun 24;27(13):4058.

Singh A, Kukreti R, Saso L, Kukreti S. Mechanistic Insight into Oxidative Stress-Triggered Signaling Pathways and Type 2 Diabetes. *Molecules*. 2022 Jan 30;27(3):950.