Synthesis and Pharmacological Evaluation of New anti-Parkinson Drug Candidates Designed by Molecular Hybridization of Curcumin and Resveratrol

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Abstract

Parkinson's disease (PD) is the second most common multifactorial neurodegenerative disease worldwide, leaving behind only Alzheimer's disease. PD is mainly a result of dopamine deficiency caused by death of dopaminergic neurons. Recent studies point to the importance of oxidative stress in the onset and development of PD, which is caused by an imbalance between the antioxidant capacity and the production of reactive oxygen species (ROS) by autoxidation and monoamine oxidase (MAO)-mediated metabolism of dopamine. The pharmacotherapy of PD is based on the use of different substances in order to increase the amount of dopamine and to control the oxidative stress at dopaminergic neuron level, focusing on the restore of mitochondrial activity, induction of endogenous antioxidants including glutathione (GSH) and inhibition of α-synuclein toxicity. Some natural products (NP), such as curcumin (**1**) and resveratrol (**2**), have been reported to increase GSH as well as to inhibit the toxicity mediated by neurotoxin 6-hydroxydopamine (6-OHDA), MAO-B and α-synuclein. The use of NP as inspiration for the design of new biologically active compounds is a well-known way to obtain innovative drug candidate prototypes. In this study we used molecular hybridization (figure 1) in the design of a novel series of curcumin-resveratrol-like hybrid compounds, leading to 28 new compounds that were evaluated for antioxidant and neuroprotective activity. Among these compounds, a lead compound showed the highest antioxidant activity against DPPH radical (EC_{50}, 0.93 μM) and ROS formation evoked by t-BOOH (EC_{50}, 0.62 μM) in dopaminergic cells. The lead compound also recorded the ability to increase the intracellular GSH level and the resistance of dopaminergic cells against 6-OHDA. Further studies are ongoing to characterize the potential multi-target profile of this compound such as its ability to inhibit the α-synuclein aggregation and MAO activity.

Image

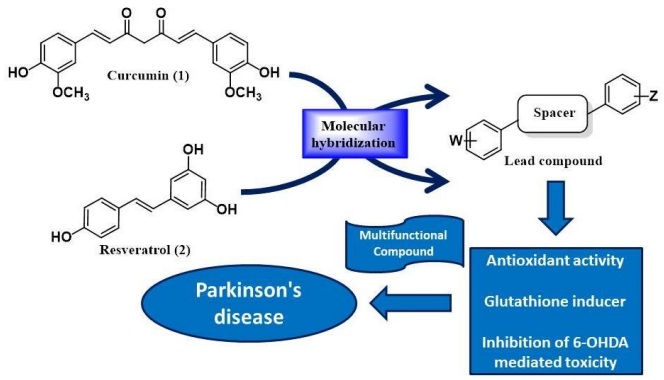


Figure 1. Illustrative scheme of the design of the new series of curcumin-resveratrol hybrid compounds

Recent Publications

1. Hosseinzadeh, A.; Khalili, M.; Sedighi, B.; Iranpour, S.; Haghdoost, A. A. (2018) Parkinson's Disease and Risk of Hip Fracture: Systematic Review and Meta-Analysis. Acta Neurologica Belgica 118: 201–210.
2. Kujawska, M.; Jodynis-Liebert, J. (2018) Polyphenols in Parkinson's Disease: A Systematic Review of In Vivo Studies. Nutrients 10: 642–677.
3. Kuo, Y.-C.; Rajesh, R. (2018) Current Development of Nanocarrier Delivery Systems for Parkinson's Disease Pharmacotherapy. J. Taiwan Inst. Chem. Eng. 87: 15–25.
4. Ji, H.-F.; Shen, L. (2014) The Multiple Pharmaceutical Potential of Curcumin in Parkinson's Disease. CNS Neurol. Disord. - Drug Targets 13: 369–373.
5. Jin, F.; Wu, Q.; Lu, Y. F.; Gong, Q. H.; Shi, J. S. (2008) Neuroprotective Effect of Resveratrol on 6-OHDA-Induced Parkinson's Disease in Rats. Eur. J. Pharmacol. 600: 78–82.



Biography

Matheus F Silva has experience in design, synthesis and biological evaluation of new compounds planned by molecular hybridization. These compounds were designed as multifunctional ligands capable to act as neuroprotective, antioxidant, anti-inflammatory, acetylcholinesterase inhibitors and anticancer. He is graduated in Pharmacy, Master in Pharmaceutical Sciences and is attending the third year of PhD in Medicinal Chemistry at the Federal University of Alfenas (UNIFAL-MG), Brazil. Currently he leaves in Italy, where he is developing his sandwich PhD at the University of Bologna (UNIBO), focusing the pharmacological evaluation of the previously synthesized molecules.

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Notes/Comments: