Myricetin, inhibits Trifloxystrobin-induced apoptosis and the OMA1-DELE1-HRI ISR mitochondrial pathway

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H. Chaabani[I,II], I. AYED[III], D. Arnoult[IV], S. Abid[V]

[I]Higher institute of biotechnology of Monastir, Monastir, Tunisia, [II]Laboratory for Research on Biologically Compatible Compounds, Faculty of Dental Medicine, Monastir, Tunisia, [III]Faculty of Science of Gafsa, Gafsa, Tunisia, [IV]INSERM U 1197, Hopital Paul Brousse, VILLEJUIF CEDEX, France, [V]Laboratory for Research on Biologically Compatible Compounds, Faculty of Dental Medicine, University of Monastir, Monastir, Tunisie, Tunisia

Human exposure to pesticides is mostly linked to occupational exposure in agricultural production or residues in food. Trifloxystrobin (TFX) has a lipophilic nature, which allows it to accumulate in the brain. Therefore, it is critical to investigate effective methods for preventing or treating brain damage caused by TFX. One interesting approach is the use of natural chemicals that are frequently present in our food. According to their various structural and sterical characteristics, flavonoids are a significant subgroup of chemicals with potent antioxidant activity. We decide to assess the potential protective benefits of Myricetin, a flavonoid with a broad range of pharmacological actions, against toxicities brought on by TFX. Cell viability, cell cycle arrest and ISR activation via the OMA1-DELE1-HRI ISR pathway were all used to assess the cytotoxicity caused by this fungicide. Apoptosis was evaluated by measuring the externalization of phosphatidylserine, release of cytochrome C, Bax and caspase 3 activation, DNA fragmentation, cytoskeleton disruption, and mitochondrial transmembrane potential ($\Delta\Psi m$). Myricetin pretreatment of SH-SY5Y cells two hours prior to Trifloxystrobin exposure was found to significantly increase cell survival and restore S phase DNA synthesis. Furthermore, cells pretreated with Myricetin two hours prior to exposure to TFX did not exhibit ISR activation, as seen by the lack of peIF2α phosphorylation, downstream of activating transcription factor 4 (ATF4) and pro-apoptotic transcription factor C-EBP homology protein (CHOP). Myricetin also reduced chromatin condensation, phosphatidylserine externalization, DNA fragmentation, cytoskeleton disruption, loss of mitochondrial membrane potential, cytochrome C release, Bax and caspase 3 activation. All of these results point to myricetin as a potent natural substance that may shield cells from the cytotoxicity, ISR induction and apoptosis caused by Trifloxystrobin.