Transcrocetin Inhibits Endometriosis Growth by Regulating Autophagy and Perturbing Redox Balance

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Endometriosis is a benign gynecological disease characterized by the abnormal growth of endometrial-like tissues and fragments outside the uterus. Due to lack of alternative non-hormonal therapeutic targets for endometriosis, our focus has been on investigating autophagy regulation and role of mitochondria in progression of endometriosis. Natural compounds have emerged as promising candidates in recent years for targeting mitochondrial dysfunction and autophagy. Among them, transcrocetin is a carotenoid and retinoic acid known for its potent antioxidant properties and antiproliferative effects in various diseases. In the present study, we examined therapeutic mechanisms of transcrocetin in endometriosis using the End1/E6E7 and VK2/E6E7 cell lines. Our findings reveal that transcrocetin effectively suppresses the viability and proliferation of these cell lines while sparing normal uterine stromal cells. We observed an increase in p21 Waf1/Cip1, a cell cycle regulator and target of p53, upon transcrocetin treatment, leading to G1 phase of cell cycle arrest through inhibition of cyclin-dependent kinase activity and subsequent cell death. Additionally, we identified endoplasmic reticulum stress by activating GRP78, IRE1A, and phosphorylation of eIF2α and dysregulation of calcium ions in the cytosol and mitochondrial matrix, resulting in disruption of mitochondrial membrane potential by transcrocetin. Also, it was found to suppress mitochondrial bioenergetics and downregulate the expression of oxidative phosphorylation-related genes. Moreover, transcrocetin-induced oxidative stress was implicated in regulating the proliferation of End1/E6E7 and VK2/E6E7 cells. Furthermore, we observed impaired autophagic flux in both endometriotic cells using pre-treatment of chloroquine. These findings collectively suggest that transcrocetin holds promise as a potent therapeutic alternative for endometriosis.