Genipin protects against H_2O_2-induced oxidative damage in retinal pigment epithelial cells by promoting Nrf2 signaling

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Abstract. Oxidative stress serves a vital function in the pathogenesis of age-related macular degeneration (AMD); genipin (GP) possesses antioxidative properties. The present study aimed to investigate the effects of GP on retinal pigment epithelial (RPE) cells induced by H_2O_2 and the underlying mechanism. ARPE-19 cells were subjected to H_2O_2 treatment to induce oxidative damage. Cell viability was determined via an MTT assay. Reactive oxygen species (ROS) levels and cell apoptosis were detected by flow cytometry. Nuclear factor-erythroid 2-related factor-2 (Nrf2) signaling-associated and the expression of apoptosis-associated factors were measured using reverse transcription-quantitative polymerase chain reaction assay and western blotting. The results revealed that 200 μM H_2O_2 and 30 μM GP were determined to be the optimal concentrations for subsequent experimentation. GP reversed the inhibitory effects of H_2O_2 by promoting cell viability, attenuating ROS accumulation and cell apoptosis, and increased the expression of Nrf2, heme oxygenase-1 (HO-1) and NAD(P)H: Quinine oxidoreductase 1 (NQO1); Nrf2 silencing inhibited HO-1 and NQO1 expression. In addition, Nrf2 silencing enhanced the effects of H_2O_2 by promoting ROS production and cell apoptosis. Compared with H_2O_2, Nrf2 silencing further decreased the expression levels of B-cell lymphoma-2 (Bcl-2), but increased that of Bcl-2-associated X protein and cleaved-caspase-3. The results of the present study revealed that Nrf2 silencing attenuated the protective effects of GP on H_2O_2-induced injury in ARPE-19 cells by promoting apoptosis and oxidation. Collectively, GP attenuated oxidative damage induced by H_2O_2 in ARPE-19 cells. Furthermore, the molecular mechanism may be associated with the Nrf2 signaling pathway. The findings of the present study nay provide insight into a potential therapeutic agent for the treatment of AMD.

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Introduction

Age-related macular degeneration (AMD) is an age-associated macular disease, and the most common disease of blindness in people >60 years old (1). Its main feature is the retinopathy of the retina and choroid, which causes decreased visual function and reduced central vision in particular (2). Oxidative stress serves a vital role in the pathogenesis of AMD (3). Retinal pigment epithelial (RPE) cells, as the most metabolically active type of cellin eye tissue, can engulf the outer disc of the retina photoreceptor cells and produce a large number of lipid peroxides and H_2O_2 (4). Furthermore, the photo-oxidation effect occurs when RPE is illuminated over long durations (5). Therefore, RPE has a higher susceptibility to oxidative stress. In addition, due to aging, the resistance of the antioxidant system of RRE declines (6,7). Oxidative stress and decreased antioxidant capacity may lead to functional disorders and structural abnormalities of the RPE, which have been identified as important pathological alterations associated with AMD (3,6,7).

Genipin (GP), is a glycosidic ligand derived from iridoid glycosides and is widely distributed in plants, including Mast and *Eucommia ulmoides*. GP is the main metabolite of geniposide in humans or animals, and is also the main active form with pharmacokinetic function (8). Studies have demonstrated that GP has certain properties, including anti-infection, anti-inflammation, antioxidation and antitumor (9-12). In addition, GP has been widely regarded as a specific inhibitor of uncoupling protein 2 (UCP2) (13). UCP2 is a functional protein in the mitochondrial inner membrane, which regulates the proton pump of mitochondria (14). Specifically, UCP2 is involved in modulating the opening of the ion channels on the mitochondrial membrane, inhibiting the production of reactive oxygen species (ROS), there by suppressing the apoptosis of cells and damage to mitochondria (15). However, the role of GP on RPE cell injury induced by oxidative stress is unknown.

Nuclear factor-erythroid 2-related factor-2 (Nrf2), as a transcription factor, serves a vital function in opposing cell damage due to endogenous and exogenous stresses (16).