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Genipin relieves diabetic retinopathy by down-regulation of advanced glycation end products via the mitochondrial metabolism related signaling pathway

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Background: Glycation is an important step in aging and oxidative stress, which can lead to endothelial dysfunction and cause severe damage to the eyes or kidneys of diabetics. Inhibition of the formation of advanced glycation end products (AGEs) and their cell toxicity can be a useful therapeutic strategy in the prevention of diabetic retinopathy (DR). Gardenia jasminoides Ellis (GJE) fruit is a selective inhibitor of AGEs. Genipin is an active compound of GJE fruit, which can be employed to treat diabetes.

Aim: To confirm the effect of genipin, a vital component of GJE fruit, in preventing human retinal microvascular endothelial cells (hRMECs) from AGEs damage in DR, to investigate the effect of genipin in the down-regulation of AGEs expression, and to explore the role of the CHGA/UCP2/glucose transporter 1 (GLUT1) signal pathway in this process.

Methods: *In vitro*, cell viability was tested to determine the effects of different doses of glucose and genipin in hRMECs. Cell Counting Kit-8 (CCK-8), colony formation assay, flow cytometry, immunofluorescence, wound healing assay, transwell assay, and tube-forming assay were used to detect the effect of genipin on hRMECs cultured in high glucose conditions. *In vivo*, streptozotocin (STZ) induced mice were used, and genipin was administered by intraocular injection (IOI). To explore the effect and mechanism of genipin in diabetic-induced retinal dysfunction, reactive oxygen species (ROS), mitochondrial membrane potential (MMP), and 2-[N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl) amino]-2-deoxy-d-glucose (2-NBDG) assays were performed to explore energy metabolism and oxidative stress damage in high glucose-induced hRMECs and STZ mouse retinas. Immunofluorescence and Western blot were used to investigate the expression of inflammatory cytokines [vascular endothelial growth factor (VEGF), SCG3, tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-18, and nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing 3 (NLRP3)]. The protein expression of the receptor of AGEs (RAGE) and the mitochondria-related signal molecules CHGA, GLUT1, and UCP2 in high glucose-induced hRMECs and STZ mouse retinas were measured and compared with the genipin-treated group.

Results: The results of CCK-8 and colony formation assay showed that genipin promoted cell viability in high glucose (30 mmol/L D-Glucose)-induced hRMECs, especially at a 0.4 μmol/L dose for 7 d. Flow cytometry results showed that high glucose can increase apoptosis rate by 30%, and genipin alleviated cell apoptosis in AGEs-induced hRMECs. A high glucose environment promoted ATP, ROS, MMP, and 2-NBDG levels, while genipin inhibited these phenotypic abnormalities in AGEs-induced hRMECs. Furthermore, genipin remarkably reduced the levels of the pro-inflammatory cytokines TNF-α, IL-1β, IL-18, and NLRP3 and impeded the

expression of VEGF and SCG3 in AGEs-damaged hRMECs. These results showed that genipin can reverse high glucose induced damage with regard to cell proliferation and apoptosis *in vitro*, while reducing energy metabolism, oxidative stress, and inflammatory injury caused by high glucose. In addition, ROS levels and glucose uptake levels were higher in the retina from the untreated eye than in the genipin-treated eye of STZ mice. The expression of inflammatory cytokines and pathway protein in the untreated eye compared with the genipin-treated eye was significantly increased, as measured by Western blot. These results showed that IOI of genipin reduced the expression of CHGA, UCP2, and GLUT1, maintained the retinal structure, and decreased ROS, glucose uptake, and inflammation levels *in vivo*. In addition, we found that SCG3 expression might have a higher sensitivity in DR than VEGF as a diagnostic marker at the protein level.

Conclusion: Our study suggested that genipin ameliorates AGEs-induced hRMECs proliferation, apoptosis, energy metabolism, oxidative stress, and inflammatory injury, partially via the CHGA/UCP2/GLUT1 pathway. Control of advanced glycation by IOI of genipin may represent a strategy to prevent severe retinopathy and vision loss.

Key Words: Genipin; Human retinal microvascular endothelial cells; Angiogenesis; Vascularization; Secretogranin III; Diabetic retinopathy.

Biography

Sun Kexin is PhD candidate in ophthalmology at Chongqing Medical University. Her advisor is Dr. Ke Hu, is the Deputy Director of the department of ophthalmology in the first affiliated hospital of Chongqing Medical University. Her studied Geni pin Ameliorates Diabetic Retinopathy via the HIF-1 α and AGEs -RAGE Pathways. She applied western blot, qPCR, cell transfection, immunofluorescent staining, cell proliferation assay, scratch wound assay, STZ-mice model, and bioinformatics analysis for research. She worked in the Oncology Lab of the First Affiliated Hospital of Chongqing Medical University. By using CoIP, ChIP, Xenograft to explore NTF4 plays a dual role in breast cancer in mammary tumorigenesis and metastatic progression and ZNF662 inhibits tumor progression via transcriptional control of NEDD9/ PI3K/ AKT axis in colorectal cancer.

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