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The Retinoprotective Effects and Mechanisms of Fungal Ingredient 3,4-Dihydroxybenzalacetone through Inhibition of Retinal Müller and Microglial Activation

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Abstract : Retina glial activation and neuroinflammation have been confirmed to cause devastating responses in retinodegenerative diseases. The expression and activation of matrix metalloproteinase (MMP)-9 and inducible nitric oxide synthase (iNOS) could be exerted as the crucial pathological factors in glaucoma- and blue light-induced retinal injuries. The present study aimed to investigate the retinoprotective effects and mechanisms of fungal ingredient 3,4-dihydroxybenzalacetone (DBL) isolated from Phellinus linteus in the retinal glial activation and retinodegenerative animal models. According to the cellular studies, DBL significantly and concentration-dependently abrogated MMP-9 activation and expression in TNFα-stimulated retinal Müller (rMC-1) cells. We found the inhibitory activities of DBL were strongly through the STAT- and ERK-dependent pathways. Furthermore, DBL dramatically attenuated MMP-9 activation in the stimulated Müller cells exposed to conditioned media from LPS-stimulated microglia BV-2 cells. On the other hand, DBL strongly suppressed LPS-induced production of NO and ROS and expression of iNOS in microglia BV-2 cells. Consistently, the phosphorylation of STAT was substantially blocked by DBL in LPS-stimulated microglia BV-2 cells. In the evaluation of retinoprotective functions, the high IOP-induced scotopic electroretinographic (ERG) deficit and blue light-induced abnormal pupillary light response (PLR) were assessed. The deficit scotopic ERG responses markedly recovered by DBL in a rat model of glaucoma-like ischemia/reperfusion (I/R)-injury. DBL also reduced the aqueous gelatinolytic activity and retinal MMP-9 expression in high IOP-injured conditions. Additionally, DBL could restore the abnormal PLR and reduce retinal MMP-9 activation. In summary, DBL could ameliorate retinal neuroinflammation and MMP-9 activation by predominantly inhibiting STAT3 activation in the retinal Müller cells and microglia, which exhibits therapeutic potential for glaucoma and other retinal degenerative diseases.

Keywords : glaucoma, blue light, DBL, retinal Müller cell, MMP-9, STAT, Microglia, iNOS, ERG, PLR
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