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Short Review

A Short Review Based on the Article Entitled "Isoliquiritigenin inhibits virus replication and virus-mediated inflammation via NRF2 signaling"

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Introduction

This study demonstrates that isoliquiritigenin, the 4,2',4'-trihydroxychalcone isolated from the roots and rhizomes of Glycyrrhiza spp, exhibits antiviral and anti-inflammatory effects against viral infection, which are related to its ability to activate NRF2 signaling, thus indicating that isoliquiritigenin has the potential to serve as an NRF2 agonist in the treatment of viral diseases.

Overview of Research Purpose and Background

Viral diseases pose a significant global public health challenge, causing millions of deaths each year [1]. However, due to delays in the development of vaccines against specific viruses, there is still an urgent need to identify potential antiviral therapeutic targets and antiviral drugs. Viral infections can trigger direct cytopathogenic effects and excessive inflammatory responses, such as SARS-CoV-2-induced overproduction of inflammatory cytokines, known as the "cytokine storm", which further results in fatal acute lung injury, multi-organ dysfunction and even death [2]. For these reasons, pharmacological-intervention combining antiviral and anti-inflammatory therapy not only offers a unique advantage but also is a widely used route for antiviral treatment in the clinic. Nuclear factor erythroid 2-related factor 2 (NFE2L2, also known as NRF2) is a transcription factor, which coordinates the expression of a vast array of cytoprotective and metabolic genes in response to various stress inputs to restore cellular homeostasis. Transient activation of NRF2 in cells has been recognized as a cellular defense mechanism, which is critical to maintaining intracellular redox homeostasis and suppressing excessive inflammation. Under oxidative stress or inflammation, NRF2 induces numerous antioxidant genes, including heme oxygenase-1, NAD(P)H quinone oxidoreductase 1, to eliminate reactive oxygen species [3]. Excitingly, recent studies have discovered new roles of NRF2 in regulating antiviral responses to herpes simplex virus type 1, influenza A virus, hepatitis C virus, and others [4]. Moreover, the agonists of NRF2 including 4-octyl-itaconate and the clinically approved dimethyl fumarate were reported to induce a cellular antiviral process that potently inhibits replication of SARS-CoV-2 in different cell lines [5]. These findings highlight the potential of NRF2 as an important factor in antiviral immunity and a therapeutic target for viral infectious diseases. Isoliquiritigenin, the 4,2',4'-trihydroxychalcone isolated from the roots and rhizomes of Glycyrrhiza spp., is a natural NRF2 agonist that exhibits a wide range of pharmacological activities, including anti-tumor, anti-inflammatory, cardioprotective, and neuroprotective activities [6]. Although the antiviral effects of isoliquiritigenin against hepatitis C virus and influenza A virus have been reported [7,8], the spectrum of antiviral activity and associated mechanism of isoliquiritigenin against other viruses are not well defined. Therefore, this study aimed to explore the antiviral and anti-inflammatory activity of isoliquiritigenin in viral infections based on NRF2.

Research Summary and Outlook

This study demonstrates that isoliquiritigenin inhibits the replication of vesicular stomatitis virus, influenza A virus and encephalomyocarditis virus, herpes simplex virus type 1 *in vitro* and further RNA sequencing and bioinformatic analysis indicates the NRF2 pathway is regulated by isoliquiritigenin. NRF2 knockout cells were constructed to evaluate the role of NRF2 in the pharmacological activity of isoliquiritigenin and we found the antiviral effect of isoliquiritigenin could be partially impaired by NRF2-deficiency instead of IFNAR1-deficiency. The anti-apoptosis and anti-inflammatory activities of isoliquiritigenin were demonstrated by counting cell death ratio and assessing proinflammatory cytokines expression in virus-infected cells. In addition, we evaluated the antiviral effect of isoliquiritigenin *in vivo* by measuring the survival rate, body weights, histological analysis, viral load, and cytokine expression in vesicular stomatitis virus-infected mouse model. In conclusion, isoliquiritigenin inhibits viral replication and suppresses excessive inflammation in viral infection, suggesting that isoliquiritigenin has the potential to serve as an NRF2 agonist in the treatment of viral diseases.

Mechanistically, isoliquiritigenin activates NRF2 by inducing Michael addition to the cysteine residue at KEAP1 through its α, β-unsaturated carbonyl moiety [9]. This reaction allows NRF2 to dissociate from KEAP1 and translocate into the nucleus, which is a universal mechanism of action by which chalcones regulate the NRF2 pathway [10]. Interestingly, isoliquiritigenin is not the only chalcone identified as being antiviral, chalcones have been reported to have broad antiviral activity against Middle East respiratory syndrome coronavirus, severe acute respiratory syndrome coronavirus, human immunodeficiency, influenza, human rhinovirus, herpes

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simplex and other viruses [11]. Therefore, we believe that chalcones may be a valuable source for locating potent antiviral drugs with antiviral and anti-inflammatory activity. However, the connection between the NRF2-regulatory activity and antiviral effect of chalcones requires further investigations to support.

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