Potential effects of hydroxysafflor yellow A on reducing pulmonary inflammation and fibrosis due to SARS-COV2

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Abstract

Cytokine storm is a condition that is characterized by a massive production of proinflammatory cytokines. Failure in balancing the up-regulation and down-regulation causes excessive production of proinflammatory cytokines in the fight against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus infection, leading to lung damage and acute respiratory distress syndrome; in addition, high levels of IL-6 can activate the clotting pathways and vascular endothelial cells, which can inhibit blood circulation and heart muscle function and cause pulmonary, kidney, and liver fibrosis. Hydroxysafflor Yellow A (HSYA) is a compound that has been shown to reduce tissue lung damage through Toll-Like Receptor (TLR) 4, inhibits phosphorylation of the NF-κB pathway, and plays a role in balancing the up-regulation and down-regulation of inflammatory cytokines. This review of literature discusses the ability of HSYA to reduce inflammation that causes pulmonary cell and tissue damage. HSYA can inhibit the activation of the NF-κB signaling pathway and suppress the binding of the TGF-β1 promoter. This molecular mechanism can reduce lung damage by attenuating the inflammatory response by inhibiting the TLR 4-dependent pathways that can improve the condition of mice affected by pulmonary fibrosis, including inflammation that leads to vascular tissue repair. The molecular mechanism of HSYA can inhibit inflammatory mechanisms in lung injury, vascular tissue damage, and liver and kidney fibrosis. Therefore, this literature review can be used as a reference for *in vivo* research and clinical trials for further research on the ability to heal patients with cytokine storm that causes cardiovascular tissue damage and lung injury in patients infected with SARS-CoV-2.

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Introduction

Cytokine storm refers to the hyperinduction of proinflammatory cytokine production, one of which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viruses that can lead to complications and even death. Severe pneumonia caused by pathogenic SARS-CoV2 is often associated with rapid viral replication, massive inflammatory cell infiltration, and increased proinflammatory cytokine or chemokine response resulting in acute lung injury and respiratory distress syndrome.[1] Additionally, a previous study experimentally infected animals and demonstrated the critical role of virus-induced immunopathological events in causing fatal pneumonia following coronavirus infection.[2] Hydroxysafflor Yellow A (HSYA) is a compound proven to be anti-inflammatory which reduces excessive inflammatory cytokine secretion through the Toll-Like Receptor 4 (TLR4) pathway. HSYA can significantly inhibit the phosphorylation of Nuclear factor-κB (NF-κB) p-p65, extracellular signal regulated kinase (ERK) , c-Jun N-terminal kinase (JNK), and p38, which are associated with suppressed secretion of inflammatory cytokines such as Tumor Necrosis Factor-α (TNF-α), Interleukin (IL)-1β, and Nitric Oxide (NO).[3] Therefore, this article will discuss the possibility of the ability of HSYA compounds to play a potential pharmaceutical role in patients who experience cytokine storm symptoms that result in organ fibrosis.

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The electronic databases used were PubMed, Google Scholar, and Scopus. The years 2010 to 2020 were traced and the morphological features, traditional uses, and medical reports of HSYA were reviewed.

Cytokine storm in SARS-CoV2 infection

The SARS-CoV2 virus is a virus that attacks the respiratory tract. This virus enters host cells via the angiotensin-converting enzyme 2 (ACE2) in target organs such as the lungs, heart, renal system, and gastrointestinal tract. The S protein in SARS-CoV2 facilitates the entry of the coronavirus into target cells.[4] The incubation period for the SARS-CoV2 virus is 3–14 days, characterized by normal or slightly decreased leukocyte and lymphocyte levels. Then the virus spreads through the bloodstream, mainly to the angiotensin-converting enzyme 2 (ACE2)-expressing organs, and the patient begins to experience mild symptoms. Four to seven days from the initial symptoms, the condition worsens, characterized by the emergence of shortness of breath, decreased lymphocytes, and worsening lung lesions. If this phase is not resolved, Acute Respiratory Distress Syndrome (ARDS), sepsis, and other complications can occur.

COVID-19 patients with ARDS have decreased CD4, and CD8 T cells, associated with hyperreactive immune response. ARDS results from an uncontrolled increase in proinflammatory mediators or a cytokine storm. This will result in lung damage and the formation of fibrous tissue, resulting in organ failure.[5] Laboratory findings of cytokine storm conditions include elevated C-reactive protein, which correlates with severity. There is a marked increase in serum levels of inflammatory cytokines, such as interferon (IFN)-γ (or CXCL9 and CXCL10, IFN-induced chemokines), IL-6, IL-10, and soluble IL-2 alpha receptor, a marker of T cell activation; usually, very high serum IL-6 levels can be found.[6]

In COVID-19 disease, the cytokine storm was due to a failure of the immune system to remove the virus. Previous studies have explained the mechanism of the cytokine storm. In the early stages, it was reported that patients with COVID-19 will have a temporary immunodeficiency, shown by delayed secretion of IFN.[7] Later on, overactive immune activity was shown by excessive secretion of proinflammatory cytokines. This later stage was characterized by the overproduction of IL-6 and TNF-α.[8,9] It is also explained that infection from SARS-Cov2 leads to hyperactivation of NF-κB and signal transducer and activator of transcription 3 (STAT3) , causing overactive inflammation response.[10] Hyperactivation of NF-κB and STAT3 can induce IL-6 amplifiers to produce many proinflammatory cytokines and chemokines such as IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1) and vascular endothelial growth factor (VEGF)[10]. Other proinflammatory cytokines that were released hours after the incubation of the virus were IL-31 and IL-33.[11,12] Recently, the role of IL-31 and IL-33 were reported in the literature. Overexpression of these cytokines had a crucial role in the inflammation of the lung that is mediated by the activation of Th2 cell.[13]

Structure and therapeutic effects of hydroxysafflor yellow A

HSYA is the main active ingredient extracted from safflower. It has been reported to exert a range of biological and pharmacological effects, such as pro-angiogenesis, anti-inflammatory, and antioxidant effects.[14,15] HSYA is one of the natural flavonoid compounds that reduce oxidative stress and inflammatory cytokine-mediated damage.[16] HSYA is also known as Safflomin A or 2,4-di-β-D-glucopyranosyl-3,4,5-trihydroxy-6-[(2*E*)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]-2,5-cyclohexadien-1-one.[17] It has a molecular formula of $C_{27}H_{32}O_{16}$.[18] This substance has an attractive yellow color and is usually used for dye. HSYA has an unstable bond, a C-glycoside bond, located between the 1,3-diketone on ring A. Another side of the bond is the hydroxyl group. It is located at the C-2 position in the glycoside and is conveniently condensed with the adjacent enol owing to the strain effect. The cyclization process will make the pyranose ring turn into an oxyfuran in 2 to 3 days.[19] Light, high temperature and alkaline environments are all known to degrade HSYA. Due to the lack of solid planar orientation in the chemical structure, HSYA generates weak fluorescence at 450 nm in aqueous solution.[20] Under alkaline conditions, HSYA loses its stability and is most unstable at pH 9.

There exists very extensive literature on the pharmacologic effect of HSYA on several non-communicable diseases. HSYA was reported to have low toxicity, so it was used in various studies *in vitro* and *in vivo* for treating diseases (Table 1). As shown in Table 1, HSYA has been used for the treatment of cardiovascular diseases and as an anticoagulant anti myocardial ischemia and antihypertensive agent. According to the literature, several brain diseases such as dementia,[21] cerebral ischemia,[22] Parkinson's disease,[23] and brain injury had been treated using HSYA as a potential therapy from natural sources.[24] HSYA has recently been reported to have an anti-fibrotic effect on hepatic disorders.[25] There is a broad interest and literature about the pulmonary protective effect that HSYA offers.[26,27] It has been used to treat lung fibrosis, acute lung injury, and chronic obstructive pulmonary disease.[15] An increased prevalence of COVID-19 with higher mortality was observed in Autoimmune Systemic Disease (ASD) patients.[28,29] HYSA may have beneficial effects for treating ASD with COVID-19. HSYA could bind with Xanthine Oxidase causing inhibition of lipopolysaccharide (LPS)-induced the Nod-Like Receptor (NLR) family pyrin domain-containing 3 (NLRP3) inflammasome activation, reducing the secretion of IL-1 and IL-18 (Table 1).[30]

Molecular mechanisms of hydroxysafflor yellow A

Inflammation

According to the literature, many studies have been carried out to investigate the molecular mechanisms of HSYA as an anti-inflammatory agent. HSYA can execute molecular mechanisms through up and down-regulation of multiple inflammatory pathways. HSYA could compete with TNF-α to bind with Tumor necrosis factor

Table 1. Pharmacologic effects of HSYA

Effects on organ	References
Cardiovascular effect	31-33
Hepatoprotective effect	34,35
Anti-tumor effect	36,37
Neuroprotective effect	38,39
Pulmonary protective effect	40-42
Metabolic regulation effect	43,44

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receptor 1 (TNFR1) and hamper the binding of TNFR1 to the Transforming growth factor-β (TGF-β)-activated kinase 1 (TAK1)-binding protein 2 (TAB2) complex. In addition, HSYA could also inhibit the activation of the NF-κB signaling pathway and suppresses the binding of the Transforming growth factor beta 1 (TGF-β1) promoter with Activator protein 1 (AP-1).[41] HSYA exerts anti-inflammatory effects by reprogramming the Toll like receptor 9 (TLR9) signaling pathway.[22] The anti-inflammatory effect of HSYA is by inhibiting the translocation of the NF-κB pathway and expression of TLR4 receptors .[45,46] NF-κB is a form of protein in the cytoplasm of cells that is bound in an inactive form that functions to regulate inflammation, immune responses, wound healing, and cell death.[47] NF-κB regulates the expression of genes that produce proinflammatory cytokines and chemokines. As a result of NF-kB activation, many genes whose products mediate inflammatory and immune responses experience a coordinated increase in expression. For example, the recruitment and activation of neutrophils are facilitated by the coordinated stimulation of the genes for E-selectin, IL-8, and TNF-α. IL-1b and TNF-α, two proinflammatory cytokines, both activate and are activated by NF-kB.[48]

Lung fibrosis

Lung or pulmonary fibrosis is a chronic lung disease marked by Excessive Extracellular Matrix (ECM) accumulation and remodeling of the lung architecture, as well as observable clinical, physiological, and radiological findings.[49] A previous study reported that in pulmonary fibrosis, there was overstimulation of cytokines including IL-13, TGF-β, and TNF-α. These mediators will enhance the proliferation, migration, and ECM production in fibroblast cells.[50] Various studies show the ability of HSYA in maintaining pulmonary fibrosis that occurs due to various factors, including against LPS which is an antigen on bacteria.[51] It has also been proved that these compounds could suppress the stimulation of TNF-α on the proliferation and inflammatory response of human fetal lung fibroblasts.[41] Furthermore, the binding between TNFR1 and TAK1-TAB2 complex can be inhibited by HSYA, due to its ability to compete with TNF-α for binding to TNFR1. This suggests that HSYA affects the TNF-induced proliferation and inflammatory response of human fetal lung fibroblast cells via the NF-κB/AP-1 signaling pathway, which could provide a theoretical basis for treating pulmonary fibrosis.[42] The underlying molecular mechanism of HSYA in reducing lung damage is attenuating the inflammatory response through inhibition of TLR 4-dependent signaling pathways that can improve the condition of mice affected by pulmonary fibrosis.[45] Lung fibrosis is also caused by TGF-β mediated signaling pathway. This mediator is most commonly involved in the mechanism of lung fibrosis.[52] There has been previous research on this using HYSA for treating lung fibrosis. Previous research with mice reported that HYSA reduces expression of TGF-β, α-smooth muscle actin, and collagen I mRNA levels.[53]

The underlying molecular mechanism of HSYA in reducing lung damage is attenuating the inflammatory response through inhibition of TLR 4-dependent and TGF-β mediated signaling pathways that can improve the condition of mice affected by pulmonary fibrosis.[1,53]

Circulation

Myocardial ischemia or injury is a pathological condition characterized by an inflammatory response due to cardiomyocyte apoptosis during the acute phase. The NLRP3 inflammasome is activated by reperfusion, and IL-1, IL-18, and active caspase-1 are produced, which are all involved in the ischemic or injury process.[54] Previous research in experimental animal models indicated that inhibiting or deleting the NLRP3 inflammasome reduced the extent of myocardial infarction and improved cardiac function.[55] In the literature, there is a broad range of results from experiments that support the role of HSYA in repairing blood vessels and circulation. The study results in mice showed that HSYA decreased the size of myocardial infarction and attenuated cardiac dysfunction. HSYA also inhibits myocardial apoptosis, decreases inflammatory cytokine levels, reduces the inflammatory expression of NLRP3, and induces autophagy.[55] It can decrease vascular adventitia proliferation and hyperplasia during remodeling.[56] HSYA can suppress tumor growth by inhibiting the secretion of the angiogenesis factor and vascular endothelial growth factor receptor.[57] HSYA has an inhibitory effect on cell apoptosis and suppresses metalloproteinase expression in an animal model of ventricular hypertension.[58]

Liver and kidney fibrosis

Direct cellular damage from the ischemia-reperfusion injury could lead to the activation of inflammatory pathways, which is part of the pathophysiology of liver fibrosis.[59] Many investigations have revealed that ischemia or liver fibrosis results from a series of inflammatory processes, including the formation of reactive oxygen and nitrogen stress in the liver and the activation of the inflammatory response.[59] Evidence from other studies suggests that HSYA can inhibit the development of liver fibrosis. HSYA-treated mice had reduced serum transaminase levels, attenuated inflammation and necrosis, reduced inflammatory cytokine expression, and reduced macrophages after segmental hepatic ischemia.[14] HSYA also appears to decrease reactive oxygen species and malondialdehyde in liver tissues. Alcohol-stimulated activation of TGF-β1 in rat liver tissue was significantly blocked by HSYA. Collectively, these data suggest that HSYA can effectively protect rat liver from long-term alcohol injury, which is associated with increased antioxidant capacity of liver tissue and inhibition of TGF-β1 expression.[25]

Renal or kidney fibrosis is a condition characterized by activated tubulointerstitial myofibroblast cells and the production of excessive ECM. The activated myofibroblasts are considered to be a major contribution to the mechanisms of renal fibrosis.[60] As mentioned in the previous section, TGF-β1 is a major protein that has a key role in the pathogenesis of fibrosis. In severe renal fibrosis, TGF-β1 was reported to be substantially elevated.[61] HSYA slows the progression of renal fibrosis both *in vivo* and *in vitro*. In unilateral ureteral obstructed mice, the renal function indices showed that HSYA treatment decreased serum creatinine and blood urea nitrogen levels. Decreased levels of Smooth muscle alpha-actin (αSMA), collagen-I, and fibronectin gene expression were observed in unilateral ureteral obstructed mice treated with HSYA. Furthermore, HSYA reduced the apoptotic rate of HK-2 cells stimulated by TGF-β1.[62]

The levels of IL-1, IL-6, IL-8, TNF-α, and IFNs in a patient with COVID-19 who experienced a cytokine storm are reported to show substantial changes. This has been extensively discussed in previous research. TGF-β1 is major in causing cytokine storm in virus SARS-CoV2 infection.[63] HSYA may potentially improve cytokine storm in SARS-CoV2 condition by its ability to inhibit the activation of the NF-κB signaling pathway, also by attenuating the inflammatory response through inhibition of TLR 4-dependent and TGF-β mediated signaling pathways. Thus, this condition will lead to a reduction of inflammation due to less production of IL-6 and other proinflammatory cytokines, chemokines, and adhesion molecules. HSYA, as described in the previous section, can block the activation of TGF-β1 and thus reduce the growth of fibroblasts and improve the clinical manifestation in patients infected by the virus SARS-CoV2.

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Conclusions

HSYA can inhibit the inflammatory mechanisms in lung injury, vascular tissue damage, and liver and kidney fibrosis. Therefore, this literature review can be used as a reference for *in vivo* research and clinical trials for further research on the ability to heal patients with cytokine storm that causes cardiovascular tissue damage and lung injury in patients infected with SARS-CoV-2.

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