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Potential of Hydroxysafflor yellow A, the main compound of Kasumba Turate (*Carthamus tinctorius*) as Anti-Inflammatory in Lung, Liver and Cardiac Tissues: A Literature Review

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ABSTRACT

Inflammation is the body's physiological response to stimuli such as infection, trauma, and chronic disease. Its exacerbation can lead to deterioration in health and damage to tissues in organs such as the lungs, liver and cardiac tissues. The drive behind the development of anti-inflammatory drugs is to improve treatment efficacy and reduce adverse effects. The primary aim of this article is to deliberate on the pharmacological properties of compound from *Carthamus tinctorius* as an anti-inflammatory agent. Through an extensive study of data we made a literature review. The authors conducted a comprehensive review of 1,250 abstracts and 70 full-text articles, of which 17 were identified as eligible for data extraction from database google scholar and Scopus database period from 2012 to 2022. C. tinctorius can alleviate inflammation by inhibiting NF-κB activation and suppressing TGF-β1 promoter binding. These processes could reduce lung injury by limiting the inflammatory response through the TLR4-dependent pathway, thereby improving the health of rats suffering from pulmonary fibrosis, a condition characterised by inflammation and vascular tissue repair. In addition, compounds in *C. tinctorius* are effective in reducing T lymphocyte (CD4) apoptosis in sepsis through their anti-apoptotic and anti-inflammatory effects. The anti-inflammatory mechanism is also demonstrated by the reduction of IL-6, in the lungs, liver, and cardiac tissues.

INTRODUCTION

The body's natural reaction to various stimuli, such as infections, injuries, and chronic illnesses, can impact the respiratory, circulatory, digestive, and excretory systems, manifesting as inflammation. In these conditions, inflammation is a major factor that exacerbates tissue damage, such as lung, liver organs. Recent anti-inflammatory developments in the pharmaceutical field aim to improve treatment effectiveness, reduce side effects and provide solutions for inflammatory conditions that are difficult to treat (Tasneem et al., 2019). A number of pharmaceutical developments have been identified which have the potential to reduce inflammation (Yeung et al., 2018). These include targeted therapy on Janus Kinase (JAK) inhibitors, immunotherapy and the development of traditional medicines (Hoffman et al., 2020). The use of traditional medicine has been a component of medical practice in China for

thousands of years, with a particularly strong tradition in Indonesia, particularly in the province of South Sulawesi. The use of medicinal plants to treat a wide range of health conditions, including inflammation, is one of the most important aspects of traditional medicine. One medicinal plant that has been shown to have potent anti-inflammatory activity and is widely used in traditional medicine is *Carthamus tinctorius* (Print et al., 2015). In China, *C. tinctorius* is referred to as 'honghua' (red flower), in India and Pakistan it is known as 'kusum' and in South Sulawesi as Kasumba turate. One of the main compounds found in the plant and which has been researched to have anti-inflammatory abilities is Hydroxysafflower Yellow A (HSYA).

Previous studies have shown that HSYA protects lung tissue from acute lung injury (ALI) by reducing inflammatory responses and increasing antioxidant enzyme activity. (Song et al., 2013**;** Liu *et al.*, 2014b**;** Yang *et al.*, 2015). Further trials are required to explore the potential of HSYA as an anti-inflammatory agent in humans. This review aims to evaluate the potential of C. tintorius as an anti-inflammatory agent in various disease conditions, in the hope of providing new insights into the development of more effective and safe anti-inflammatory therapies in humans..

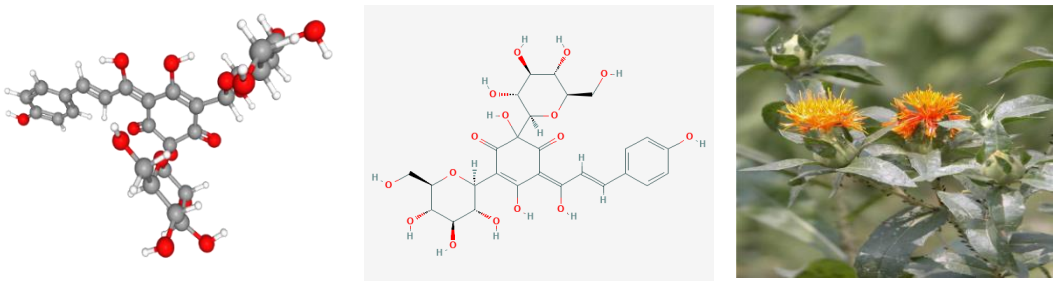
METHODS

A literature review was conducted to scientifically assess the treatment effects using a search string and Boolean operators "(("Carthamus tinctorius" OR "Kasumba Turate" OR "safflower") AND ("Hydroxysafflor Yellow A" OR "HSYA")) AND (("anti-inflammatory" OR "inflammation") AND ("lung" OR "liver" OR "cardiac tissues")) AND (("cytokines" OR "NF-κB" OR "oxidative stress") OR ("in-vitro" OR "in-vivo" OR "clinical trial"))" accessed on 30 August 2022. The electronic databases employed were Google Scholar, Scopus, and PubMed, spanning the period from 2012 to 2022, with the objective of identifying studies related to the potential of HSYA from *C. tinctorius* (Kasumba turatea) to reduce inflammation, which is known to cause a range of immunopathological cell and tissue damage. The authors reviewed 1.250 abstrak and 70 full text, seventeen articles were eligible for data abstraction. The authors conducted a comprehensive review of 1,250 abstracts and 70 full-text articles, of which 17 were identified as eligible for data extraction.

Articles were included if they focused on the pharmacological effects of *Carthamus tinctorius* or its compounds, specifically Hydroxysafflor Yellow A (HSYA), investigated anti-inflammatory mechanisms or pathways such as NF-κB, TLR4 signaling, or cytokine suppression, examined outcomes related to inflammation in lung, liver, or cardiac tissues, were published in peer-reviewed journals, written in English, and consisted of in-vitro, in-vivo, or clinical studies. Articles were excluded if they focused on other plants or unrelated compounds, did not evaluate anti-inflammatory effects, lacked sufficient experimental details or were review articles without original data, were published in languages other than English, or were inaccessible in full-text format. This rigorous process ensured the inclusion of high-quality and relevant studies to evaluate the anti-inflammatory potential of *Carthamus tinctorius*

DISCUSSION

Hydroxysafflor Yellow A (HSYA) demonstrates significant anti-inflammatory properties across various diseases, including lung, cardiac, and liver-related conditions. In lung diseases, HSYA targets key pathways such as NF-κB, TNF-α, IL-6, MAPK, TLR4, and TGF-β1, thereby alleviating lung injury, pulmonary fibrosis, and asthma by inhibiting cytokines, regulating signaling pathways, and balancing immune responses (**Table 1**). Similarly, in cardiac conditions such as ischemic stroke, sepsis, and myocardial ischemia/reperfusion (MI/R) injury, HSYA exerts its effects by inhibiting pathways like TLR4 and mTOR, reducing oxidative stress, modulating apoptosis, and providing neuroprotection, which collectively improve cardiac function, reduce infarct size, and attenuate inflammation and cell death (**Table 2**). Furthermore, in hepatocellular and liver-related diseases, HSYA inhibits ERK1/2 and NF-κB pathways in hepatocellular carcinoma, while reducing TGF-β1 expression, attenuating fibrosis, and offering antioxidant protection in chronic liver disease and liver injury. Additionally, HSYA suppresses pro-fibrotic markers, alleviates oxidative stress, and protects hepatocytes, thereby supporting liver repair and regeneration (**Table 3**). These results highlight the potential of HSYA in treating



A B C

Figure1. Structure A and B is Structure Hydroxysafflor Yellow A , it is compound can be found in the *C. tinctorius* extraction . C. The plant of *C. tinctorius*

inflammatory and degenerative diseases across organ systems.

C. tinctorius L., a member of the Asteraceae family, is a flowering plant that is characterised by bright yellow to orange flowers with flattened petals, which are grouped together in a compound flower (**Fig 1C**). HSYA is a bioactive compound from *C. tinctorius*, its have anti-inflammatory and antioxidant activity. Its structure consists of two benzene rings connected by a carbonyl and hydroxyl group, which enhances polarity and facilitates interaction with biological targets, thereby influencing solubility and bioavailability in inflammation-related diseases (**Fig 1B,C**). The flowers are traditionally used for colouring, flavouring and medicinal purposes. Major component of *C. tinctorius* flowers is hydroxysafflor yellow A, a C-glycosyl, 3,4,5-trihydroxycyclohexa-2,5-dien-1-one compound. The compound has roles as an anti-inflammatory agent, antioxidant, platelet aggregation inhibitor, antineoplastic agent, inhibitor of several molecular mechanisms sucrose alpha-glucosidase, neuroprotective agent (Zhou et al., 2014;Delshad et al., 2018;Print et al., 2015). HSYA can carry out mechanisms on several metabolic pathways and inflammatory pathways as shown in **Tables 1, 2 and 3.**

Table 1. The anti-inflammatory mechanism of the HSYA in the lungs

No	The anti-inflammatory mechanism	Related to the disease	Reference
1.	HSYA has been shown to reduce the early inflammatory response. HSYA may provide valuable insight into its anti-inflammatory properties by inhibiting key inflammatory mediators such as NF-κB, TNF-α, and IL-6 in lung tissue.	Lung injury	(Jin et al., 2018)(Wu et al., 2012)(Jin et al., 2016)
2.	HSYA attenuates the inflammatory response in mice affected by acute lung injury through inhibition of TLR 4 signaling pathway.	Acute Lung injury	(Liu et al., 2014), (Zhang et al., 2017)
3.	HSYA attenuates lipopolysaccharide-induced pulmonary inflammation in mice, with protective effects associated with MAPK and NF-κBp65 inhibition.	Acute Lung injury	(Wang et al., 2014)
4.	TβRII responsible for the inhibitory effect of HSYA on pathological changes induced by TGF-β1 in pulmonary fibrosis.	Pulmonary fibrosis	(Pan et al., 2017)
5.	HSYA treatment leads to a significant reduction in the expression of pro-inflammatory cytokines, such as TNF-α and IL-6, in human fetal lung fibroblasts. Furthermore, the downstream targets of NF-κB and MAPK signaling appeared to be attenuated following HSYA treatment, supporting the notion of its anti-inflammatory effects.	Pulmonary fibrosis	(Liu et al., 2019)
6.	The evidence presented in these studies strongly supports the notion that HSYA exerts a protective effect against OVA-induced asthma through its multifaceted actions by balance process on Th1 and Th2 cells and the subsequent activation of the MAPK signalling pathway.	Asthma	(Zheng et al., 2019)

Table 2. The anti-inflammatory mechanism of the HSYA related Cardiac Inflammation

No	The anti-inflammatory mechanism	Related to the disease	Reference
1.	In relation to ischaemic stroke, HSYA have anti-inflammatory and neurotrophic functions. This effect is achieved by inhibiting signalling responses mediated by the TLR4 pathway.	Ischemic stroke	(Lv et al., 2015),
2.	The diverse mechanisms of action of HSYA include anti-apoptotic, anti-inflammatory, antioxidant pathways, indicating its potential as a promising therapeutic agent for neuroprotection by modulating the TLR4 pathway-mediated signalling, HSYA may confer neuroprotection against apoptotic stimuli and maintain neuronal integrity.	Ischemic stroke	(Lv et al., 2016),
3.	The efficacy of HSYA in alleviating sepsis-induced CD4(+) T lymphocyte apoptosis has been demonstrated in preclinical studies.	Sepsis	(Wang et al., 2017)
4.	HSYA exerts its effects through multiple signaling pathways, including the inhibiting the mTOR pathways, as well as by modulating the expression of various genes involved in apoptosis and oxidative stress. HSYA can attenuate oxidative stress, reduce inflammation, and inhibit cell death pathways, ultimately leading to improved cardiac function and reduced infarct size.	Myocardial ischemia/reperfusion (MI/R) injury	(Ye et al., 2020)

HSYA suppresses PKA, a signalling pathway involved in the maintenance effects of lung injury (Zhang et al., 2017**;** Wang *et al.*, 2013**;** Wang et al., 2014). HSYA has been shown to reduce ALI via the TLR 4 pathway (Bai et al., 2018). HSYA protects by preventing MAPK activation and NF-κB p65, as well as altering inflammatory cytokine expression, which is linked to inflammation and increase the activity of antioxidant enzymes (Sun et al., 2010; Wang et al., 2013)**.**

HSYA also inhibited the phosphorylation of interferon regulatory factor 3 (IRF 3) and the translocation of NF-kB p65 by inhibiting inhibitory kappa B-α. In addition, HSYA suppressed the mRNA expression of TNF-α and ICAM-1 in rat lung while balancing plasma IL-6 and IL-1β levels. It significantly suppressed the secretion of inflammatory cytokines such as TNF-alpha, interleukin 1-beta and nitric oxide. (Liu et al., 2014; Lv et al., 2015; Wang et al., 2010). It's been shown that arabinogalactan can boost the immune system by encouraging the production iNOS and cytokines (TNF-α and IL-1β) in lymphocytes and macrophages (Yao et al., 2018). HSYA primarily suppresses pulmonary fibrosis by reducing the inflammatory response through the inhibition of TLR4-dependent pathways, thereby alleviating acute lung injury in experimental animal models (Liu et al., 2014b).

There are several studies showing the ability of *C. tinctorius* to reduce pulmonary fibrosis caused by various factors. The results of the study by Liu et al. showed that the compound can suppress TNF-α stimulation on inflammatory and proliferation reaction in MRC-5 cells (Liu et al., 2019). HSYA significantly attenuated the TNF-α-induced inflammatory response in MRC-5 cells, as evidenced by a reduction in pro-inflammatory cytokine production and inhibition of apoptosis. This suggests that HSYA may have therapeutic potential in mitigating TNF-α-mediated damage to lung tissue, providing insights for the discovery of novel interventions for inflammatory lung diseases. (Liu et al., 2019; Pan et al., 2016).

In addition, "HSYA demonstrates its capability not only in acute lung injury but also in pulmonary fibrosis and ashma. HSYA have potential therapeutic use in conditions linked to TGF-β1 pathway dysregulation. Furthermore, elucidating the inhibitory effects of HSYA on the

Table 3. The anti-inflammatory mechanism of HSYA on various hepatocellular and liver cells

No	The anti-inflammatory mechanism	Related to the disease	Reference
1.	HSYA has been shown to inhibit ERK1/2 phosphorylation and regulate NF-κB activation, and to downregulate the mRNA expression of genes that promote cell proliferation (cyclinD1, c-myc, c-Fos) compared to the negative control group	Hepatocellular carcinoma	(Yang et al., 2015)
2.	HSYA may act through several mechanisms, including reduced expression of (TGF)-β1, antioxidant activities, and modulation of signalling pathways involved in fibrosis.	Chronic liver disease	(Zhang et al., 2011)
3.	HSYA exerts its protective effects from long-term alcohol damage through antioxidant and anti-inflammatory mechanisms, as well as by modulating key TGF-β1 expression pathways involved in liver injury and regeneration	*Liver injury*	(He et al., 2015)
4.	The results showed that HSYA treatment significantly reduced liver fibrosis by suppressing the regulation of pro-fibrotic biomarkers such as α-SMA and collagen I. In addition, HSYA intervention was found to alleviate inflammation and oxidative stress in the liver, thereby protecting hepatocytes from damage.	Liver fibrosis	(Liu et al., 2014)

TGF-β1 pathway may lead to the identification of novel HSYA-based therapeutic interventions. (Pan et al., 2017).

HSYA has been shown to regulates the levels of inflammatory cytokines such as immunoglobulin E, platelet-activating factor, IL-1β, interleukin-6, and interleukin-4 while increasing the levels of TNF-α and IFN-gamma. The activation of p38 MAPK has been associated with a number of processes in asthma, including eosinophil differentiation, mast cell migration, IgE synthesis, the exacerbation of Th2 responses and airway remodelling. This research show the potential of HSYA as a treatment strategy for asthma by balancing Th1/Th2 cells and inhibiting the MAPK pathway (Zheng et al., 2019).

C. tinctorius is employed as a constituent in preparations designed to enhance blood circulation. Modern pharmacological research indicates that *C. tinctorius* exhibits a range of bioactivities, including the dilation of coronary arteries, modulation of the immunity and improvement of myocardial ischemia (Han et al., 2013). This study found several compounds that have anti-aggregation, anticoagulant (Kurniawan et al., 2023). antioxidant and anti-proliferative effects (Zhang & Niu, 2022). In addition, this study also revealed the potential pharmacological mechanism of safflower in inhibiting NF-kB (Kim et al., 2023; Wu et al., 2011).

HSYA could reduce the size of myocardial infarction and alleviate cardiac impairment in mice following I/R. Furthermore, HSYA was found to inhibit myocardial apoptosis, reduce the levels of interleukins in mouse serum, reduce the production of inflammatory NLRP3 and induce autophagy (Ye et al., 2020).

HSYA can also reduce vascular adventitial proliferation and cell hyperplasia during the remodelling process (Yuan et al., 2014) In addition to its impact on MAPK and signaling pathways, HSYA has shown promise in modulating inflammatory responses. It has been reported to inhibit the mRNA expression of tumor necrosis factor-α and ICAM-1 in rat lung (Yang et al., 2015). In animal models of ventricular hypertension, HSYA also inhibits cell apoptosis and suppresses metalloproteinase expression (Wang et al., 2014). Therefore, from the description, it is known that *C. tinctorius* has the ability to promote blood circulation and protect the heart. Research shows that the

compound HSYA can reduce the size of myocardial infarction, inhibit myocardial apoptosis, and reduce inflammation and cell proliferation. A has the ability to inhibit the development of liver fibrosis (Wang et al., 2013). The compound works by inhibiting macrophage activation. In a previous study, rats were administered urther studies have revealed its ability to reduce serum transaminase levels and mitigate inflammation and liver necrosis. Moreover, HSYA has been shown to diminish the expression of inflammatory cytokines, underscoring its potential as a therapeutic agent in combating inflammatory diseases and liver disorders**.** In addition to experimental animals, the ability of HSYA compounds has also been tested in vitro on RAW264.7 macrophage cells, showing a decrease in migration response and inflammatory cytokine production. Furthermore, pre-treatment with HSYA resulted in a reduced in matrix metalloproteinase-9 expression and the inhibition of NF-κB recruitment and P38 phosphorylation in RAW264.7 cells. Consequently, HSYA may be an effective means of reducing inflammation associated with acute liver injury(Jiang et al., 2014)**.**

Research by Yang et al. (2015) showed that ERK1/2 molecularly activates NF-κB and regulates its activity by decreasing p65 gene expression, regulating p65 levels and inhibiting IκB-α degradation. HSYA decreased the expression levels of genes that induce cell proliferation (cyclinD1, c-myc, c-Fos) and increased the spleen index, demonstrating the compound's ability to protect the immune system. These results indicate the potential of HSYA in the management of hepatocellular carcinoma (Yang et al., 2015).

The anti-inflammatory capacity of the liver was also demonstrated by Hu et al. The findings were extremely promising, indicating that HSYA significantly block transforming growth factor β1 (TGF-β1) and reduce the level of malondialdehyde (MDA) and reactive oxygen species (ROS) in liver tissue. This implies that HSYA protects the rat liver effectively from inflammation resulting from alcohol-induced long-term liver injury (He et al., 2015).

CONCLUSIONS

C. tinctorius has been studied for its potential anti-inflammatory effects in various research studies. Several studies have shown that the active compounds have the ability to reduce inflammation in lung injury, vascular tissue damage, as well as cardiac tissues inflammation. These findings suggest that C. tinctorius may hold promise as a natural anti-inflammatory agent, presenting opportunities for further exploration and development in the field of pharmaceutical research and drug discovery.

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BIBLIOGRAPHY

Bai, J., Zhao, J., Cui, D., Wang, F., Song, Y., Cheng, L., Gao, K., Wang, J., Li, L., Li, S., Jia, Y., & Wen, A. (2018). Protective effect of hydroxysafflor yellow A against acute kidney injury via the TLR4/NF-κB signaling pathway. *Scientific Reports*, *8*(1), 1–11. https://doi.org/10.1038/s41598-018-27217-3

Han, S.-Y., Li, H.-X., Ma, X., Zhang, K., Ma, Z.-Z., Jiang, Y., & Tu, P.-F. (2013). Evaluation of the anti-myocardial ischemia effect of individual and combined extracts of *Panax notoginseng* and *Carthamus tinctorius* in rats. *Journal of Ethnopharmacology*, *145*(3), 722–727. https://doi.org/10.1016/j.jep.2012.11.036

He, Y., Liu, Q., Li, Y., Yang, X., Wang, W., Li, T., Zhang, W., Cui, Y., Wang, C., & Lin, R. (2015). Protective effects of hydroxysafflor yellow A (HSYA) on alcohol-induced liver injury in rats. *Journal of Physiology and Biochemistry*, *71*(1), 69–78. https://doi.org/10.1007/s13105-015-0382-3

Hoffman, R. D., Li, C. Y., He, K., Wu, X., He, B. C., He, T. C., & Gao, J. L. (2020). Chinese Herbal Medicine and Its Regulatory Effects on Tumor Related T Cells. *Frontiers in Pharmacology*, *11*(April), 1–14. https://doi.org/10.3389/fphar.2020.00492

Hu, N., Duan, J., Li, H., Wang, Y., Wang, F., Chu, J., Sun, J., Liu, M., Wang, C., Lu, C., & Wen, A. (2016). Hydroxysafflor Yellow A Ameliorates Renal Fibrosis by Suppressing TGF-β1-Induced Epithelial-to-Mesenchymal Transition. *PloS One*, *11*(4), e0153409. https://doi.org/10.1371/journal.pone.0153409

Jiang, S., Shi, Z., Li, C., Ma, C., Bai, X., & Wang, C. (2014). Hydroxysafflor yellow A attenuates ischemia/reperfusion-induced liver injury by suppressing macrophage activation. *International Journal of Clinical and Experimental Pathology*, *7*(5), 2595–2608.

Jin, M., Wang, L., Wu, Y., Zang, B. xia, & Tan, L. (2018). Protective effect of hydroxysafflor yellow A on bleomycin- induced pulmonary inflammation and fibrosis in rats. *Chinese Journal of Integrative Medicine*, *24*(1), 32–39. https://doi.org/10.1007/s11655-017-2094-z

Jin, M., Wu, Y., Wang, L., Zang, B., & Tan, L. (2016). Hydroxysafflor Yellow A Attenuates Bleomycin-induced Pulmonary Fibrosis in Mice. *Phytotherapy Research*, *30*(4), 577–587. https://doi.org/10.1002/ptr.5560

Kim, S.-Y., Hong, M., Deepa, P., Sowndhararajan, K., Park, S. J., Park, S., & Kim, S. (2023). Carthamus tinctorius Suppresses LPS-Induced Anti-Inflammatory Responses by Inhibiting the MAPKs/NF-κB Signaling Pathway in HaCaT Cells. *Scientia Pharmaceutica*, *91*(1), 14. https://doi.org/10.3390/scipharm91010014

Kurniawan, Y. I., Louisa, M., Dewi, B. E., Hansur, L., Zaini, J., & Estuningtyas, A. (2023). The Effect of *Carthamus tinctorius* in Combination with Dexamethasone on Coagulation Markers in Mice Induced by SARS-CoV2 Spike Protein. *Research Journal of Pharmacognosy*, *10*(4), 31–41. https://doi.org/10.22127/RJP.2023.400248.2129

Liu, Q., Wang, C. Y., Liu, Z., Ma, X. S., He, Y. H., Chen, S. S., & Bai, X. Y. (2014). Hydroxysafflor yellow A suppresses liver fibrosis induced by carbon tetrachloride with high-fat diet by regulating PPAR-γ/p38 MAPK signaling. *Pharmaceutical Biology*, *52*(9), 1085–1093. https://doi.org/10.3109/13880209.2013.877491

Liu, S., Wang, Y., Wen, H., Sun, X., & Wang, Y. (2019). Hydroxysafflor Yellow A Inhibits TNF-α-Induced Inflammation of Human Fetal Lung Fibroblasts via NF-κB Signaling Pathway. *Evidence-Based Complementary and Alternative Medicine : ECAM*, *2019*, 4050327. https://doi.org/10.1155/2019/4050327

Liu, Y.-L., Liu, Y.-J., Liu, Y., Li, X.-S., Liu, S.-H., Pan, Y.-G., Zhang, J., Liu, Q., & Hao, Y.-Y. (2014). Hydroxysafflor yellow A ameliorates lipopolysaccharide-induced acute lung injury in mice via modulating toll-like receptor 4 signaling pathways. *International Immunopharmacology*, *23*(2), 649–657. https://doi.org/10.1016/j.intimp.2014.10.018

Lv, Y., Qian, Y., Fu, L., Chen, X., Zhong, H., & Wei, X. (2015). Hydroxysafflor yellow A exerts neuroprotective effects in cerebral ischemia reperfusion-injured mice by suppressing the innate immune TLR4-inducing pathway. *European Journal of Pharmacology*, *769*, 324–332. https://doi.org/10.1016/j.ejphar.2015.11.036

Lv, Y., Qian, Y., Ou-Yang, A., & Fu, L. (2016). Hydroxysafflor Yellow A Attenuates Neuron Damage by Suppressing the Lipopolysaccharide-Induced TLR4 Pathway in Activated Microglial Cells. *Cellular and Molecular Neurobiology*, *36*(8), 1241–1256. https://doi.org/10.1007/s10571-015-0322-3

Pan, R., Zhang, Y., Zang, B., Tan, L., & Jin, M. (2016). Hydroxysafflor yellow A inhibits TGF-β1-induced activation of human fetal lung fibroblasts in vitro. *The Journal of Pharmacy and Pharmacology*, *68*(10), 1320–1330. https://doi.org/10.1111/jphp.12596

Pan, R., Zhang, Y., Zheng, M., Zang, B., & Jin, M. (2017). Hydroxysafflor Yellow A Suppresses MRC-5 Cell Activation Induced by TGF-β1 by Blocking TGF-β1 Binding to TβRII. *Frontiers in Pharmacology*, *8*, 264. https://doi.org/10.3389/fphar.2017.00264

Print, I., Online, I., Dehariya, R., & Dixit, A. K. (2015). A Review on Potential Pharmacological Uses of *Carthamus tinctorius* L . *World Journal of Pharmaceutical Sciences*, *July 2015*.

Song, L., Zhu, Y., Jin, M., & Zang, B. (2013). Hydroxysafflor yellow a inhibits lipopolysaccharide-induced inflammatory signal transduction in human alveolar epithelial A549 cells. *Fitoterapia*, *84*, 107–114. https://doi.org/10.1016/j.fitote.2012.11.004

Sun, C.-Y., Pei, C.-Q., Zang, B.-X., Wang, L., & Jin, M. (2010). The ability of hydroxysafflor yellow a to attenuate lipopolysaccharide-induced pulmonary inflammatory injury in mice. *Phytotherapy Research : PTR*, *24*(12), 1788–1795. https://doi.org/10.1002/ptr.3166

Tasneem, S., Liu, B., Li, B., Choudhary, M. I., & Wang, W. (2019). Molecular pharmacology of inflammation: Medicinal plants as anti-inflammatory agents. *Pharmacological Research*, *139*(October 2018), 126–140. https://doi.org/10.1016/j.phrs.2018.11.001

Wang, C., Huang, Q., Wang, C., Zhu, X., Duan, Y., Yuan, S., & Bai, X. (2013). Hydroxysafflor yellow A suppresses oleic acid-induced acute lung injury via protein kinase A. *Toxicology and Applied Pharmacology*, *272*(3), 895–904. https://doi.org/10.1016/j.taap.2013.07.021

Wang, C., Wang, C., Ma, C., Huang, Q., Sun, H., Zhang, X., & Bai, X. (2014). Hydroxysafflor yellow A of Carthamus tinctorius attenuates lung injury of aged rats exposed to gasoline engine exhaust by down-regulating platelet activation. *Phytomedicine : International Journal of Phytotherapy and Phytopharmacology*, *21*(3), 199–206. https://doi.org/10.1016/j.phymed.2013.09.018

Wang, C. Y., Liu, Q., Huang, Q. X., Liu, J. T., He, Y. H., Lu, J. J., & Bai, X. Y. (2013). Activation of PPARγ is required for hydroxysafflor yellow A of Carthamus tinctorius to attenuate hepatic fibrosis induced by oxidative stress. *Phytomedicine : International Journal of Phytotherapy and Phytopharmacology*, *20*(7), 592–599. https://doi.org/10.1016/j.phymed.2013.02.001

Wang, J., Wang, P., Gui, S., Li, Y., Chen, R., Zeng, R., Zhao, P., Wu, H., Huang, Z., & Wu, J. (2017). Hydroxysafflor Yellow A Attenuates the Apoptosis of Peripheral Blood CD4(+) T Lymphocytes in a Murine Model of Sepsis. *Frontiers in Pharmacology*, *8*, 613. https://doi.org/10.3389/fphar.2017.00613

Wang, J., Zhang, Q., Mei, X., & Zhang, X. (2014). Hydroxysafflor yellow A attenuates left ventricular remodeling after pressure overload-induced cardiac hypertrophy in rats. *Pharmaceutical Biology*, *52*(1), 31–35. https://doi.org/10.3109/13880209.2013.805791

Wang, X., Jin, M., Tong, J., Wu, W., Li, J., & Zang, B. (2010). [Protective effect of hydroxysafflor yellow A against acute lung injury induced by oleic acid and lipopolysaccharide in rats]. *Yao xue xue bao = Acta pharmaceutica Sinica*, *45*(7), 940–944.

Wang, Y., Xue, C., Dong, F., Peng, Y., Zhang, Y., Jin, M., Zang, B., & Tan, L. (2014). Hydroxysafflor yellow a attenuates small airway remodeling in a rat model of chronic obstructive pulmonary disease. *Biological & Pharmaceutical Bulletin*, *37*(10), 1591–1598. https://doi.org/10.1248/bpb.b14-00198

Wu, W., Jin, M., Tong, J., Wang, X., & Zang, B. (2011). [Inhibitory effect of hydroxysafflor yellow A against PMN activation induced by LPS]. *Yao xue xue bao = Acta pharmaceutica Sinica*, *46*(2), 153–157.

Wu, Y., Wang, L., Jin, M., & Zang, B. X. (2012). Hydroxysafflor yellow A alleviates early inflammatory response of bleomycin-induced mice lung injury. *Biological and Pharmaceutical Bulletin*, *35*(4), 515–522. https://doi.org/10.1248/bpb.35.515

Yang, F., Li, J., Zhu, J., Wang, D., Chen, S., & Bai, X. (2015). Hydroxysafflor yellow A inhibits angiogenesis of hepatocellular carcinoma via blocking ERK/MAPK and NF-κB signaling pathway in H22

tumor-bearing mice. *European Journal of Pharmacology*, *754*, 105–114. https://doi.org/10.1016/j.ejphar.2015.02.015

Yang, G., Zhou, X., Chen, T., Deng, Y., Yu, D., Pan, S., & Song, Y. (2015). Hydroxysafflor yellow A inhibits lipopolysaccharide-induced proliferation and migration of vascular smooth muscle cells via Toll-like receptor-4 pathway. *International Journal of Clinical and Experimental Medicine*, *8*(4), 5295–5302.

Yao, Y., Yao, J., Du, Z., Wang, P., & Ding, K. (2018). Structural elucidation and immune-enhancing activity of an arabinogalactan from flowers of Carthamus tinctorius L. *Carbohydrate Polymers*, *202*, 134–142. https://doi.org/10.1016/j.carbpol.2018.08.098

Ye, J., Lu, S., Wang, M., Ge, W., Liu, H., Qi, Y., Fu, J., Zhang, Q., Zhang, B., Sun, G., & Sun, X. (2020). Hydroxysafflor Yellow A Protects Against Myocardial Ischemia/Reperfusion Injury via Suppressing NLRP3 Inflammasome and Activating Autophagy. *Frontiers in Pharmacology*, *11*, 1170. https://doi.org/10.3389/fphar.2020.01170

Yeung, Y. T., Aziz, F., Guerrero-Castilla, A., & Arguelles, S. (2018). Signaling Pathways in Inflammation and Anti-inflammatory Therapies. *Current Pharmaceutical Design*, *24*(14), 1449–1484. https://doi.org/10.2174/1381612824666180327165604

Yuan, W., Yang, D., Sun, X., Liu, W., Wang, L., Li, X., Man, X., & Fu, Q. (2014). Effects of hydroxysafflor yellow A on proliferation and collagen synthesis of rat vascular adventitial fibroblasts induced by angiotensin II. *International Journal of Clinical and Experimental Pathology*, *7*(9), 5772–5781.

Zhang, L., & Niu, Z. (2022). Hydroalcoholic Carthamus tinctorius L. Extract Attenuates TNBS-induced Ulcerative Colitis in Mice Via Downregulation of Inflammation and Oxidative Stress. *Indian Journal of Pharmaceutical Education and Research*, *56*(3), 780–788. https://doi.org/10.5530/ijper.56.3.128

Zhang, Y., Guo, J., Dong, H., Zhao, X., Zhou, L., Li, X., Liu, J., & Niu, Y. (2011). Hydroxysafflor yellow A protects against chronic carbon tetrachloride-induced liver fibrosis. *European Journal of Pharmacology*, *660*(2–3), 438–444. https://doi.org/10.1016/j.ejphar.2011.04.015

Zhang, Y., Song, L., Pan, R., Gao, J., Zang, B.-X., & Jin, M. (2017). Hydroxysafflor Yellow A Alleviates Lipopolysaccharide-Induced Acute Respiratory Distress Syndrome in Mice. *Biological & Pharmaceutical Bulletin*, *40*(2), 135–144. https://doi.org/10.1248/bpb.b16-00329

Zheng, M., Guo, X., Pan, R., Gao, J., Zang, B., & Jin, M. (2019). Hydroxysafflor Yellow A Alleviates Ovalbumin-Induced Asthma in a Guinea Pig Model by Attenuateing the Expression of Inflammatory Cytokines and Signal Transduction. *Frontiers in Pharmacology*, *10*, 328. https://doi.org/10.3389/fphar.2019.00328