Pharmacological properties and underlying mechanisms of aurantio-obtusin (Review)

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Abstract. Herbal medicine has been widely applied for a range of diseases in China since antiquity. *Cassia obtusifolia L. a*nd *Cassia tora L.* are plants whose seeds have high reported medicinal values and have been documented to function as a laxative, to lower lipid level and to lower blood pressure. The main active ingredient in *Cassia* seeds is aurantio-obtusin (AO), which is an anthraquinone monomer compound. Currently, AO is listed in China as a quality control index component of *Cassia* seeds. In clinical practice in China, AO is typically used to treat obesity, diabetes and its complications, non-alcoholic fatty liver disease and allergic reactions. In addition, AO has been reported to confer insecticidal activities and antimalarial effects. Previous studies have even suggested that AO is a potential therapeutic candidate for a variety of diseases with research value. Therefore, the present review summarizes and discuss the existing literature on AO to provide a review of its pharmacological activity and mechanism of action, with the aim of providing a basis for its development and utilization in a clinical setting.

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Abbreviations: AGEs, advanced glycation end products; AhR, aryl hydrocarbon receptor; AO, aurantio-obtusin; AR, aldose reductase; AVP, vasopressin; COPD, chronic obstructive pulmonary disease; eNOS, endothelial nitric oxide synthase; IgE, immunoglobulin E; IR, insulin resistance; LPS, lipopolysaccharide; NAFLD, nonalcoholic fatty liver disease; RLAR, rat lens aldose reductase; SASP, senescence-associated secretory phenotype; WAT, white adipose tissue

Key words: aurantio-obtusin, traditional Chinese medicine, pharmacological activity, mechanism of action

Contents

1. Introduction

Cassia seeds are the dried mature seeds of *Cassia obtusifolia L.* or *Cassia tora L.*, which belongs to the Leguminosae family (1). The seeds are widely used in China, Japan and Korea for improving visual acuity, and having laxative, antioxidant, neuroprotective and anti-bacterial effects, in addition to lowering the blood pressure (2-5). *Cassia* seeds contain anthraquinones, naphthopyrrolidones and fatty acids, with anthraquinone being the main active ingredient. Anthraquinones have a planar and rigid anthracene ring in the 9th and 10th positions, with two ketone groups, so that this structure allows the absorption of light at specific wavelengths (6) (Fig. 1), which also have reported anti-cancer, antitumor, antioxidant and antimalarial biological activities (7-10). The main anthraquinones in *Cassia* seeds include aurantio-obtusin (AO), chrysophanol, emodin and rhein (11).

As a lipophilic anthraquinone compound extracted from *Cassia* seeds, AO is the main bioactive component of *Cassia* seeds and is currently listed as a quality control index component of *Cassia* seeds in the Pharmacopoeia of the People's Republic of China (5). The Pharmacopoeia of the People's Republic of China stipulates that *Cassia* seeds should contain not less than 0.080% of AO on a dried basis. AO is also known as 1,3,7-trihydroxy-2,8-dimethoxy-6-methyl-9,10-anthracenedione (Fig. 2) and has a variety of documented pharmacological effects, including anti-hyperlipidemic (12,13), and anti-inflammatory effects (14,15) This renders AO to be a potential candidate for the treatment of various diseases. However, to the best of our knowledge, there are no systematic reviews on this topic at present. Therefore, the present paper reviewed and discussed the relevant literature on AO and its pharmacological activity.

2. Pharmacological activity

Treatment of obesity. Obesity is a condition in which adipose tissues accumulates excessively in the body to an extent that it exerts detrimental effects on health (16). It is characterized by weight gain, which is caused by excessive fat accumulation due to excessive daily food intake and insufficient calorific expenditure (17). Obesity increases the risk of coronary artery disease (18), hypertension (19), type 2 diabetes (20), asthma (21), cancer (17), venous thromboembolism (22), periodontal disease (23) and Coronavirus disease 2019 (Covid-19) (24,25).

For the treatment of obesity, reducing daily intake whilst increasing daily calorific expenditure and increasing the metabolic rate in the body can confer a significant effects. In a previous study on the effects of AO on obesity, hepatic lipid metabolism and insulin sensitivity using high-fat diet-induced obese mice, AO was found to significantly reduce body weight and inhibit lipid accumulation in the liver and the white adipose tissue (WAT) (26). The mechanism of action was found to be mainly due to AO increasing peroxisome proliferator-activated receptor (PPAR)-α mRNA expression and decreasing PPAR-γ mRNA expression in the liver. PPAR-α expression can inhibit triglyceride synthesis and promote fatty acid oxidation (27) in another study, while decreasing PPAR-γ expression can reduce the differentiation of preadipocytes into adipocytes to decrease fatty acid storage (28). This suggests to a certain extent the inhibitory effects AO can exert against obesity.

Treatment of diabetic complications. Diabetes is a condition in which the combination of genetic and environmental factors contributes to either absolute or relative insulin deficiency and reduced insulin sensitivity in target tissue cells (29). This results in metabolic disorders in the body, which are characterized by hyperglycemia (29). Diabetic complications caused by the prolonged exposure to hyperglycemic conditions are the main causes of organ dysfunction and even mortality in patients with diabetes (30). Diabetic complications can affect almost all organs of the body, including the nervous system, heart, kidney, eyes and blood vessels (29), which can be classified as macroangiopathy and microangiopathy. Macroangiopathy includes cardiovascular and heart disease, whereas microangiopathy includes diabetic nephropathy, cataract and retinopathy (31,32). Diabetes has also been reported to predispose patients to the more severe forms of Covid-19, which increases the risk of poorer prognosis (33). Advanced glycation end products (AGEs) and aldose reductase (AR) are two important contributing components to the complications of diabetes (34). Therefore, AR inhibitors have been proposed to be a viable option for the treatment of diabetes mellitus. In the AGE formation and rat lens aldose reductase (RLAR) inhibition assay (35), AO showed no inhibitory activity on AGE formation, but showed significant inhibitory activity against RLAR with an IC_{50} value of 13.6 μM, suggesting that AO can exert inhibitory effects against AR. In addition, it was found in another study that AO can activate the insulin signaling pathway to increase sensitivity to insulin whilst also improving obesity (26). Therefore, AO is a potential candidate for the treatment of diabetic complications and associated diseases.

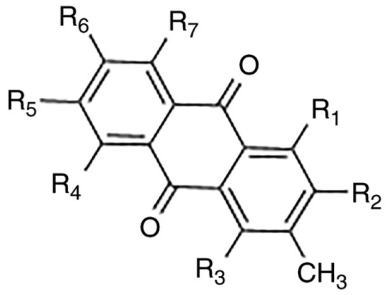

Figure 1. Chemical structure of anthraquinone.

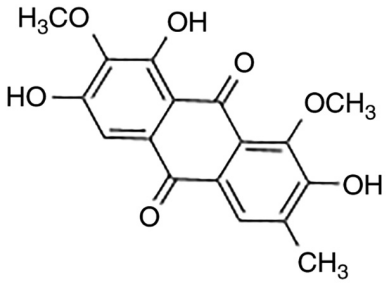

Figure 2. Chemical structure of aurantio-obtusin.

Reduction of non-alcoholic fatty liver disease (NAFLD). NAFLD is defined as a disease caused by excessive hepatic adipose accumulation associated with insulin resistance (IR) (36). It is a general term used for a range of diseases with histological hepatic alterations, including simple hepatic steatosis, non-alcoholic hepatitis characterized by hepatocellular damage with inflammation and varying degrees of fibrosis, cirrhosis and hepatocellular carcinoma (37,38). IR is therefore a key factor in the pathogenesis of NAFLD. It can, on the one hand, lead to lipolysis in adipose tissue, thus providing free fatty acids to the liver, and on the other hand, it can promote *de novo* synthesis, leading to further accumulation of fatty acids in the liver (39). However, the specific mechanism driving the pathogenesis of NAFLD remains unclear, where the main strategy of treatment is to target the IR and intrahepatic lipid accumulation (40). Under conditions of high ester and high glucose conditions, AO has been found to improve IR by downregulating the mRNA expression of genes associated with lipid metabolism such as PPAR-γ and FAS, whilst suppressing the mRNA expression of inflammatory cytokines such as IL-6, IL-1β, MCP-1 and TNF-α in WAT (26). In addition, in a mouse model of NAFLD induced by high-sugar and high-fat conditions and in oleic and palmitic acid-treated mouse primary hepatocytes, AO was found to significantly promote autophagic flow and activate the transcription factor EB (41). This inhibited *ab initio* lipid synthesis and suppressed lipid accumulation to improve hepatic steatosis (41). Altogether, this provides a pharmacological treatment avenue for NAFLD and related complications.

Antiallergic effect. Allergy is an acquisitive hypersensitivity by the immune system to harmless environment substances (42). This spectrum includes allergic rhinitis, allergic asthma, food allergies and atopic dermatitis (also known as eczema) (43,44).

Immunoglobulin E (IgE) is one of the key drivers of allergic responses (45). Although it is the least abundant antibody in the human serum, it can induce an effective inflammatory immune response in various tissues and organs, whilst also serving as a Th_2 biomarker involved in the regulation of Th_2 inflammatory responses (46,47). Previous studies on the effects of AO on IgE-mediated allergic responses and lipopolysaccharide (LPS)-induced RAW264.7 cells have found that AO can inhibit the expression of TNF-α and IL-4 mRNA whilst also suppressing the expression of prostaglandin E2 and cyclooxygenase-2 (48,49).

Aryl hydrocarbon receptors (AhRs) is a ligand-activated transcription factor and is present in important signaling pathways in the mammalian immune system (50). In addition, they can regulate the differentiation of monocytes into dendritic cells and that of T cells into regulatory T cells and Th_{17} cells (51). AhRs also serves an important role in anticancer effects, energy metabolism, immunity and drug metabolism (50,52,53), such that it has been shown that activation of AhRs decreases the immune response; AO exhibits significant AhRs activity and it may be a significant natural AhR agonist (54). It has also been found that the natural plant extract mixture AF-343, obtained from *Cassia tora L., Ulmus pumila L.* and *Taraxacum officinale*, is potentially a natural candidate for the prevention and treatment of mast cell-induced allergic diseases, such as allergic inflammation (55,56). Since the natural active compounds of AF-343 also include AO, this suggests the possible benefits of using AO for the treatment of allergy-related disorders.

Treatment of asthma and chronic obstructive pulmonary disease. In 2019, chronic obstructive pulmonary disease (COPD) and asthma were respiratory diseases with high morbidity and mortality rates in China, the United States and other regions (57,58). Airway smooth muscle contraction is one of the causes of both of the aforementioned diseases, rendering bronchodilators to be an effective drug for their treatment (59). In a previous study on the effects of *Cassia* seeds on airway smooth muscle contraction (60), the ethanolic extract of *Cassia* seeds have been found to inhibit the contraction of airway smooth muscle by inhibiting voltage-dependent L-type-mediated Ca^{2+} influx. Further studies have demonstrated that the main component of the ethanol extract of *Cassia* seeds that can induce the relaxation of airway smooth muscle is AO. Therefore, AO may serve as a viable therapeutic agent for the treatment of asthma and COPD.

Other effects. Mosquitoes are vectors of a number of diseases, such as malaria, dengue fever, dengue shock syndrome and yellow fever (61,62). Therefore, controlling their population can control these aforementioned infectious diseases (63). Generally, control is done at their larval stages because they are more accessible compared with adults, where they are more concentrated and less likely to change their habitat (64). AO has been shown to be effective for controlling the larvae of *Anopheles gambiae*, with a median lethal dose of 1 mg/ml (65,66). In addition, besides killing this species of mosquitoes, AO can also protect against cowpea weevil beetle infestation, which can be applied as a protective agent for stored cowpea seeds and other crops (67). Furthermore, a previous review of plant-based insecticides from 2000 to 2018 showed that AO can be used as a potential larvicide (68).

In addition, AO showed >15% inhibition on the senescence-associated secretory phenotype (SASP) (69). SASP is a bioactive secretion produced during senescence of cells which can mediate non-cell-autonomous effects of senescence (70,71). Therefore, inhibition of SASP formation may have a role in slowing down cellular senescence. It has also been shown that AO can significantly reduce total serum cholesterol levels, triglyceride and low-density lipoprotein levels in hyperlipidemic rats (12). In Xuezhiling tablets, a Chinese patented medicine used for the treatment of hyperlipidemia, tests have identified AO to be one of the active ingredients, which is associated with the anti-hyperlipidemic effect of Xuezhiling (13). This suggests AO to be a potential drug for the treatment of hyperlipidemia. Bate-site amyloid precursor protein cleaving enzyme-1 (BACE1) inhibitors can significantly reduce the concentration of cerebrospinal fluid amyloid plaques of β-protein and are promising drugs for the treatment of Alzheimer's disease (72). It has been found that AO has a strong inhibitory effect on BACE1 with IC_{50} values of 50.9-190 μg/ml (73), which suggests that AO has some application in the development of drugs for the prevention and treatment of Alzheimer's disease.

3. Mechanism of action

Actions on vasopressin receptors. Vasopressin (AVP), a nonapeptide, is mainly synthesized in the hypothalamic supraoptic nucleus, paraventricular nucleus and the supraoptic nucleus (74). It can also be produced in other areas of the brain and organs, such as the medial amygdala, the nucleus of the terminal bed and adrenal chromophores (74,75). AVP can only be found in mammals and is involved in the regulation of blood pressure, water and salt balance, social behavior (such as learning and cognition) and regulation of emotion (such as anxiety, fear and depression) (76,77). AVP acts through three different vasopressin receptors (78): V_{1a}, V_{1b} and V_2 receptors, all of which belong to different isoforms of G protein-coupled receptors (79). A previous study has demonstrated that V_{1a} is the most abundant and widely distributed vasopressin receptor (80). V_{1a}-knockout mice show a significant reduction in anxious behavior but also severely impaired social cognition performance (81,82). V_{1a} is mainly distributed in the brain and is involved in regulation of emotional and adaptive behaviors, pain, circadian rhythm cortisol synthesis and secretion (82).

In a study that evaluated the functional effects of anthraquinones from *Cassia* seeds on various G protein-coupled receptors (83), it was previously found that only AO exhibits specific V_{1a} receptor antagonism, with an IC_{50} value of 67.70±2.41 μM. In further experiments in a C57Bl/6 mouse model of transient cerebral ischemia/reperfusion injury, therapy with AO (10 mg/kg, p.o.) significantly decreased the severity of injury in the cortex regions, medial cornu ammonis 1 and dorsal medial cornu ammonis 1, which indicated a neuroprotective effect of AO. These results emphasize the possible antagonistic effect of AO on the V_{1a} receptor. At present, there have been reports proposing the use of V_{1a} receptor antagonists for the treatment of Raynaud's syndrome, dysmenorrhea, preterm labor, reduction of cell proliferation

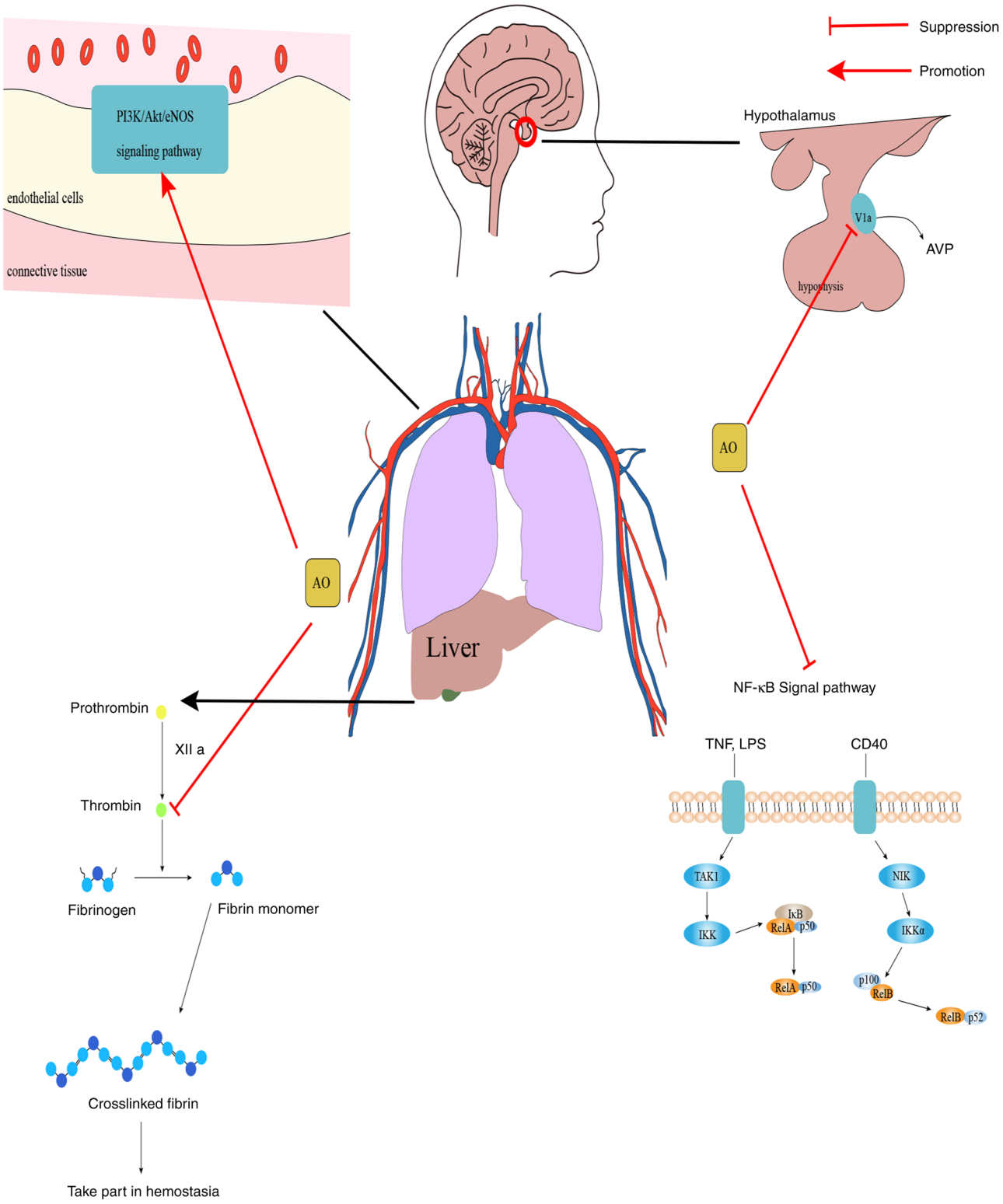

Figure 3. Mechanism diagram of AO. PI3K/Akt/eNOS is a signaling pathway that mainly operates in endothelial cells and serves an important regulatory role in dilating blood vessels and protecting endothelial cells. NF-κB signaling serves a key role in regulating the immune response to infection. AO can activate PI3K/Akt/eNOS and plays an important role in vasodilation. AO can also inhibit NF-κB, thrombin and inhibit V_{1a}, which prevent inflammation, are involved in brain emotion regulation and glycogen decomposition, this can be exploited as a potential therapeutic intervention for the prevention and treatment of thrombotic diseases and neurological diseases. AO, aurantio-obtusin; eNOS, endothelial nitric oxide synthase; V_{1a}, vasopressin receptor; NIK, NF-κB-inducing kinase; TAK1, transforming growth factor-β-activated kinase 1; AVP, vasopressin; LPS, lipopolysaccharide.

and bone metastasis growth in desmoplastic refractory prostate cancer *in vivo* (84-86), which could be used as a potential therapeutic in multiple disease types.

Action on the PI3K/Akt/endothelial nitric oxide synthase (eNOS) signaling pathway in endothelial cells. PI3K/Akt/eNOS is an important regulatory signaling pathway

in endothelial cells, and previous studies have also found that activation of the PI3K/Akt/eNOS signaling pathway can not only promote angiogenesis (87,88), improve renal microcirculation (89) and protect endothelial cells from injury (90), but can also suppress diabetes-induced atrial remodeling and atrial fibrillation (91), and can improve cardiac function in rats with myocardial infarction (92). Thus, these data suggest that the PI3K/Akt/eNOS signaling pathway plays an important role in regulating vascular activity. In a study investigating the effects of AO on isolated mesenteric arteries and its mechanism of action, AO was previously found to have an important role in activating the PI3K/Akt/eNOS signaling pathway by phosphorylating Ser^{473} to activate Akt. This enhanced eNOS activation by phosphorylating Ser^{1177} and Thr^{495} to stimulate nitric oxide (NO) production in endothelial cells (93). Therefore, these observations suggest that AO can serve as a potential vasodilator.

Thrombin inhibition. AO is a potent thrombin inhibitor (94) that can readily inhibit this enzyme, with a K_i value of 10.30 μM, which was shown by previous kinetic studies. Docking simulations showed that AO can bind both the catalytic cavity and two anion-binding exosites (ABE) 1 and ABE2. Specifically, the hydroxyl group at the C-7 site and the methoxy group at the C-8 site were found to produce a critical interaction with human thrombin by forming hydrogen bonds (94). Furthermore, it has been previously shown that anthraquinones isolated from *Cassia* seeds have a thrombin-inhibiting function against thrombin-mediated Z-GGRAMC acetic acid (a thrombin-specific fluorescent substrate for the detection of thrombin production in PRP and platelet-deficient plasma) hydrolysis (95), where further docking experiments revealed that AO has an improved inhibitory effect (94,96). Therefore, AO could potentially be the lead compound for the exploration of novel thrombin inhibitors. They can be used to inhibit thrombus formation and/or vascular embolism, which can reduce the incidence of myocardial infarction, acute ischemic stroke, venous thromboembolism and pulmonary embolism (97-99). AO can be a potential therapeutic alternative for the treatment and prevention of thrombotic diseases.

Actions on the NF-κB signaling pathway. NF-κB has an instrumental role in immune homeostasis and chronic inflammation (100-102). AO has been previously found to exert anti-inflammatory effects by interrupting the activation of MAPK and NF-κB signaling, in addition to suppressing IL-6 generation in the IL-1β-treated lung epithelial A549 cells (14). In the mouse airway inflammation model of LPS-induced acute lung injury, AO exerted an inhibitory effect on the inflammatory response (14). Additionally, AO treatment was able to ameliorate acute lung injury by inactivating the MAPK and NF-κB signaling pathways (15). By studying the effect of AO on the LPS-induced inflammatory response in the mouse macrophage RAW264.7 model, it was also demonstrated that AO can prevent inflammation through inhibition of NF-κB activation (49).

In summary, AO can exert varying degrees of inhibitory effects on vasopressin and thrombin signaling, whilst also conferring agonistic effects on the PI3K/Akt/eNOS and NF-κB signaling pathways (Fig. 3). These can potentially be exploited for the development of therapeutic agents for the corresponding diseases.

4. Biosafety

Anthraquinones generally have some hepatic and renal toxicity, where AO is of no exception (103,104). Whilst examining the effects of oral administration of different doses of AO on hepatotoxicity in rats, it was previously found that medium (40 mg/kg) and high doses (200 mg/kg) of AO can cause liver damage (5). Furthermore, in a study in which *Cassia* seed aqueous extract was administered orally to rats at doses of 4.37, 15.75 and 47.30 g/kg for 28 days, histopathological changes in the livers of male rats (47.30 g/kg group) and female rats (15.75 and 47.30 g/kg groups) were found; it was demonstrated that the aqueous extract can induce hepatotoxicity in rats, where AO was one of the components that caused the hepatotoxicity (105). AO induces hepatotoxicity by activating the nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain-containing 3 inflammatory vesicle signaling pathway (106), which also causes nephrotoxicity and colorectal melanosis (107). In addition to this, AO may increase the toxicity of certain drugs. AO has been observed to significantly increase the toxicity of irinotecan compared with glucoaurantio-obtusin (108). Therefore, the biosafety of AO should be considered when developing it for the treatment of various diseases in the body.

5. Conclusions

In summary, as one of the main active components of *Cassia* seeds, AO has certain pharmacological activities and medicinal values that can be explored as a potential drug for various human diseases. However, when considering AO for potential drug development, it cannot be ignored that AO can exert certain hepatic and renal toxicity.

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Availability of data and materials

Not applicable.

Authors' contributions

ZW and YL conceived the study. YL and XS designed the study, drafted, reviewed and edited the manuscript, and produced all the figures. XH, YX and TL wrote the manuscript. YL, XS

and TL analyzed the relevant literature. All authors read and approved the final manuscript. Data sharing is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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