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"CARTHAMUS TINCTORIUS (SAFFLOWER): A HOLISTIC REVIEW OF ITS THERAPEUTIC SIGNIFICANCE AND PHARMACOLOGICAL PROPERTIES

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Abstract:

Keywords:

1. Introduction:

The plant *Carthamus tinctorius* L., commonly known as Safflower or false saffron, belongs to the Compositae or Asteraceae family and is characterized by its thistle-like appearance (1). Typically thriving in arid climates, it is predominantly found in regions such as Southern Asia, China, India, Iran, and Egypt. In Iran alone, it coexists with six other species. The vernacular names for this plant in Iran include “Golrang,” “Kajireh,” and “Kafesheh,” cultivated extensively for its flower petals rich in red and orange pigments. Other aliases for safflower include “Zaffer,” “Fake Saffron,” and “Dyer’s Saffron” (2). The scavenging activities of safflower petals yield a spectrum of colors ranging from orange to white, making it valuable for culinary and textile applications. While synthetic aniline dyes have largely replaced it, safflower is still cultivated for its oilseed and birdseed, boasting high nutritional value with 70% polyunsaturated fatty acid (linoleic acid), 10% monounsaturated oleic acid, and trace amounts of stearic acid. Safflower exhibits notable purgative, analgesic, and antipyretic properties and is utilized in the treatment of poisoning (3). Clinically, it has shown efficacy in managing menstrual cramps, post-partum hemorrhage, whooping cough, chronic bronchitis, rheumatism, and sciatica. Traditionally, safflower flowers are employed in treating cardiovascular, cerebrovascular, and gynecological issues. Phytotherapeutic potential has been highlighted, particularly in cardiovascular diseases, along with anticoagulant, vasodilating, antihypertensive, antioxidative, neuroprotective, immunosuppressive, and anticancer properties. Active constituents such as flavonoids, phenylethanoid glycosides, coumarins, fatty acids, and steroids have been identified from various parts of the plant (4). Recent pharmaceutical studies have explored its antioxidative, anti-inflammatory, and anti-epileptic applications (5). While existing literature mainly focuses on plant varieties, main constituents, and pharmaceutical uses, this study aims to expand understanding of its traditional uses, clinical properties, and pharmacological potentials, particularly in the context of modern medicine and various ethnomedical systems, including traditional Iranian medicine. Medicinal activities are examined through in vitro, in vivo, and clinical evidence (6-10).

2. World Distribution

Safflower cultivation is a widespread commercial activity across several nations, including India, the U.S., Mexico, Ethiopia, Kazakhstan, Australia, Argentina, Uzbekistan, China, and the Russian Federation. Additionally, Pakistan, Spain, Turkey, Canada, Iran, and Israel contribute to safflower production to varying degrees. Historical data indicates that Mexico held the position of the world's leading safflower producer until 1980 (11). However, in subsequent years, both the area under cultivation and production of safflower in Mexico experienced a substantial decline, reducing to only 10% of their previous levels. Presently, India holds the title of the largest safflower producer globally, followed by the U.S., Mexico, and China. Within India, the states of Maharashtra and Karnataka play significant roles, collectively representing 72% and 24% of safflower cultivation area and production, respectively.

3. Botanical Description

The safflower plant exhibits a bushy, herbaceous growth habit with multiple branches. It is categorized into two main varieties: spiny and spineless (12). Spiny varieties are distinguished by the presence of spines on leaves and modified leaves surrounding flower heads. It is noted that varieties with reduced or absent spines generally exhibit lower oil content compared to spiny varieties. Safflower is capable of reaching heights of up to approximately 3 feet (1 meter) even in impoverished, arid soils under full sun exposure. In India, safflower production primarily occurs under rain-fed conditions during the winter season (13).

The germination process of safflower seeds is initially slow. This period, known as the rosette period, typically spans from 20 to 35 days, during which numerous leaves are produced at the base of the stem. Following this phase, stem and branch elongation commence. Each branch bears flowering heads, referred to as capitula, featuring a composite type of inflorescence (14). Capitula consist of several flowers, numbering from 20 to 250. The flowering stage of safflower lasts for approximately one month. Carthamus flowers range from pale yellow to red-orange, with tubular disk florets; ray florets are absent in these thistle-like heads. Flowers are enveloped by bracts arranged in a circular manner. Safflower yields white, glossy, and smooth seeds (fruits) with thick pericarps, known as achenes, each weighing between 0.01 to 0.1 grams. Safflower typically matures within 30 to 35 days after the cessation of flowering. With a taproot system that extends up to 2 to 3 meters in soils of adequate depth, safflower possesses a deep root system facilitating water and nutrient extraction from deeper soil layers, rendering it well-suited for rain-fed cropping systems (15).

4. Phytochemical composition

C. tinctorius has been the subject of extensive study, with over 200 compounds identified, including flavonoids, phenylethanoid glycosides, coumarins, fatty acids, steroids, and polysaccharides. Notable among these are linoleic acid (63%–72%), oleic acid (16%–25%), and linolenic acid (1%–6%) found in the seeds, as well as luteolin and its glucopyranosides in the leaves (8). Recent discoveries include tinctormine and safflor yellow B, along with established compounds like nicotiflorin. The petals yield five flavonoids, and quinochalcones are responsible for the characteristic pigmentation. Flavonoids, especially flavonol glycosides, are extensively researched for their antioxidant properties. Alkaloids like N-feruloylserotonin and N-feruloyltryptamine are prevalent, with serotonin derivatives exhibiting antioxidant activity. Unique compounds like safflospermidine A and B have been isolated, along with polyacetylenes and various organic acids present in safflower oil. Additional compounds like roseoside, uridine, uracil, erythro-alkane-6,8-diol, lignans, and aromatic glucosides have been identified (12). Several pure compounds, including Kinobeon A and traceloside, have demonstrated notable biological activities, such as antioxidant and antiestrogenic effects. Moreover, the bioactive triterpenoid saponin exhibits anti-inflammatory properties (16).

5. Traditional Uses

Historically, safflower seeds, garlands of florets, and safflower-based products have been ubiquitous in ancient Egypt, often found in the presence of mummies (17). Additionally, raw safflower consumption is common in various regions of Iran. Safflower dye has been employed in Italian, French, and British cuisine for both flavoring and coloring purposes. Florets have been utilized diversely as dyes, colorants, flavorings, cosmetics, and medicinal potions. Particularly, safflower dyes played a crucial role in the carpet-weaving industries of Eastern Europe, the Middle East, and the Indian subcontinent (18, 19). The significance of its application is evident in the second half of its binomial name; species bearing the term "tinctorius" or its derivatives often have a historical background in dye production. In Thailand, aqueous extracts of safflower flowers are commonly used to promote hair color. In Indian traditional medicine, safflower is employed for various ailments such as scabies, arthritis, and mastalgia (20). Chinese folklore also attributes therapeutic properties to safflower for conditions like amenorrhea, gastric tumors, and wounds. Iranian traditional medicine suggests safflower remedies for skin issues, baldness, phlegm, and colic. Persian folklore highlights the use of C. tinctorius for diabetes, phlegmatic fever, melancholia, and dropsy. Additionally, various plants from the Compositae family are traditionally associated with abortion-inducing properties (21). The aqueous extract of safflower is utilized in traditional medicine to alleviate painful menstruation, act as a laxative for constipation, and provide anti-inflammatory effects. Carthami flos, the dried floret of C. tinctorius, is highly esteemed for its therapeutic effects on coronary heart disease, angina pectoris, gynecological ailments, stroke, and hypertension (22-24).

6. Pharmacological activities.

6.1 Anticancer

SPS (Safflower polysaccharide) demonstrated potent inhibitory effects on HeLa cell proliferation, showing similar suppression to the positive control (cisplatinum) at 0.32 mg/mL. At higher concentrations (0.64 mg/mL and 1.28 mg/mL), SPS significantly inhibited proliferation, with IC50 values indicating up to 91.23% inhibition after 72 hours. Flow cytometry analysis revealed dose-dependent increases in apoptosis rates, with significant upregulation of BAD expression and downregulation of Bcl-2, suggesting apoptosis induction via PI3/AKT pathway modulation (25). Similarly, SPS effectively suppressed proliferation in HN-6 cells, inducing apoptosis and G0/G1 cell cycle arrest at 0.64 mg/mL. In vivo studies showed consistent inhibition of tumor xenograft growth, accompanied by alterations in Bcl-2, COX-2, Bax, and cleaved caspase-3 expression(26). Tracheloside (TCS) from safflower inhibited colorectal cancer cell proliferation by upregulating p16 and downregulating cyclin D1 and CDK4, inducing cell cycle arrest and apoptosis via mitochondrial-mediated pathways and Bcl-2 family regulation (27). Hydroxysafflor yellow A (HSYA) and other safflower compounds exerted anticancer effects by modulating molecular pathways. HSYA suppressed proliferation, invasion, and migration of EC cells by regulating NF-κB signaling. Combination therapy of hydroxysafflor yellow B (HSYB) and Doxorubicin (DOX) decreased Bcl-2 expression and increased caspase 9, BAX, and caspase 3 levels, inducing apoptosis through ROS elevation and cytochrome c release (28, 29).

6.2. Hepatoprotective.

In rats, safflower extract administration led to decreased lipid peroxidation (MDA) and increased GSH levels, along with elevated antioxidant enzyme activity (SOD, CAT). Treatment with 200mg/kg safflower extract for 30 days restored biochemical parameters (ALT, AST, ALP, total bilirubin) towards normal levels. Histological examination showed reduced necrotizing hepatocytes and mild steatosis compared to CCl4-treated rats, indicating safflower's hepatoprotective effect via enhanced antioxidant defense mechanisms and modulation of signal transduction pathways (30). Another study demonstrated Carthamus red's efficacy in reducing serum ALT, AST, ALP, and total protein levels in a hepatitis-mouse model. Safflower's hepatoprotective properties were attributed to

its rich polyphenol and flavonoid content, including carthamin, quercetin, kaempferol, and phenolic acids such as caffeic acid (31).

6.3. Antimalaria.

The ethanolic extract of safflower displayed potent in vitro antimalarial activity, with an IC50 value of 1.06 μg/mL . However, the essential oil exhibited weaker activity against chloroquine-resistant P. falciparum strains (D6) and (W2), with an IC50 of 47,600 μg/mL (32). While the chloroform and n-butanol fractions showed no parasitemia inhibition, the ethyl acetate fraction exhibited considerable activity, surpassing 50% inhibition at 100 μg/mL and achieving a maximum of 94.48% inhibition. Notably, the ethyl acetate fraction demonstrated significant antimalarial activity, with an IC50 of 1.25 μg/mL (33).

6.4. Antidiabetic.

Safflower extract, administered at doses of 200 mg/kg and 300 mg/kg over 30 days, notably increased insulin levels compared to the diabetes control group, indicating potential hypoglycemic properties. This effect may stem from safflower's ability to enhance insulin secretion, possibly due to its anti-inflammatory effects. Notably, safflower contains carthamin, mainly comprising polyunsaturated fatty acid (78% linolenic acid), which possesses potent antioxidant properties, aiding in scavenging free radicals and mitigating oxidative stress, thus contributing to improved blood glucose levels (34).Other studies have supported safflower's antidiabetic effects. Oral administration of safflower methanol extract at concentrations of 30 mg/kg BW and 20 mg/kg BW led to significant reductions in blood glucose levels at the 5th and 7th hours. This decrease may be attributed to flavonoid compounds known for their effectiveness in managing various diabetes-related complications, such as heart disease, neuropathy, and retinopathy (35). Furthermore, Hydroxysafflor yellow A (HSYA) demonstrated antidiabetic effects through its antioxidant and anti-inflammatory mechanisms, acting via the JNK/c-jun pathway, NOX4 pathway, and macrophage differentiation, both in vitro and in vivo. In DMT2 mice, HSYA was observed to inhibit pancreatic cell apoptosis, enhance insulin sensitivity, and regulate glycolipid metabolism. Consequently, safflower utilization can be safely recommended for both the prevention and treatment of type 2 diabetes mellitus (36).

6.5. Antibacterial.

Safflower essential oil displayed significant antimicrobial efficacy against Cryptococcus neoformans ATCC 90113, with an IC50 value of 8 μg/mL. Additionally, safflower extract at 0.5% concentration inhibited the growth of Salmonella pullorum and Escherichia coli, yielding inhibition zones ranging from 11 to 19 mm. The bioactive constituents of safflower extract, including flavonoid derivatives, glycosides, sterols, and serotonin, employ various mechanisms to impede bacterial growth, such as inhibiting protein synthesis and cell membranes, interfering with enzyme binding (like ATPase), suppressing bacterial oxygen utilization, and denaturing bacterial cell proteins while damaging the cytoplasmic membrane. Furthermore, hydrophobic components in safflower essential oil effectively combat both gram-positive and gram-negative bacteria (37). Interestingly, safflower formulated into emulsion-type eye drops demonstrated bactericidal activity against Staphylococcus aureus ATCC 6538-P, with a growth suppression zone measuring 9.0 ± 0.0 mm (2).

6.6. Antiacne and antifungal.

In the antiacne assessment, the positive control and solvent control (each 20 mm in diameter) showed inhibition zones of 11 mm and 20 mm, respectively, indicating no inhibition. This highlights safflower's significant antimicrobial efficacy against acne-causing bacteria. In the antidandruff evaluation, safflower extract produced a microbial inhibition zone of 9 mm, while fluconazole (the antifungal agent) exhibited a 3 mm zone, with no inhibition observed for the solvent control. This underscores safflower's capability, attributed to saponins and stigmasterols, to

regulate microbial growth. Notably, saponins can form soap, aiding in disrupting microbial cell walls and inducing leakage of proteins and enzymes from these cells (38).

6.7 Antiadipogenic.

Icariside H and (2S)-4',5,6,7-tetrahydroxyflavavone 6-O-β-D-glucopyranoside compounds efficiently inhibit de novo adipocyte formation and lipid accumulation, with a significant reduction observed in mRNA expression of adipocyte marker genes Adipsin and Fabp4 (39). Similarly, (2E,4E)-Dihydrophaseic Acid Methyl Ester-3-O-β-D-Glucopyranoside, extracted from safflower, inhibits de novo adipogenesis and lipid accumulation in 3T3-L1 preadipocytes, along with reducing the expression of adipogenic genes, including Fabp4 and Adipsin (40).Moreover, Polyacetylene Glycosides from safflower display inhibitory activity against adipogenesis in 3T3-L1 preadipocytes. They promote adipogenesis while preventing lipid accumulation by suppressing lipogenic gene expression and increasing the expression of lipolytic genes. Additionally, these glycosides activate AMPK, facilitating lipid metabolism (41).

6.8 Antiobesity.

Safflower oil exhibits an antiobesity effect by reducing belly fat volume, serum triglycerides, and leptin levels, while increasing adiponectin levels. This effect is attributed to compounds like Hydroxysafflor yellow A and safflower-yellow compounds, which reduce fat mass index and improve liver function and glucose metabolism. These compounds also enhance the expression of antioxidant enzymes in adipose tissue and the liver. Oral intake of hydroxysafflor yellow A counteracts high-fat diet-induced obesity by mitigating fat gain, enhancing insulin sensitivity, restoring glucose homeostasis, reducing inflammation, improving gut integrity, and boosting short-chain fatty acid production. Additionally, safflower yellow A lowers serum glucose levels and fat mass index, restores insulin sensitivity in obesity, and increases mRNA gene levels related to the insulin-signaling pathway in subcutaneous adipose tissue (42).

6.9. Antifibrosis.

Oxidative stress-induced liver fibrosis, mediated by hepatic stellate cells (HSC) activation and PPARγ suppression, is a crucial mechanism. Hydroxysafflor yellow A (HSYA) effectively addresses this by enhancing antioxidant enzyme activity, modulating PPARγ and MMP-2 expression, and reducing TGF-β1, TIMP-1, and α-SMA levels . Additionally, HSYA counters carbon tetrachloride (CCl4)-induced liver fibrosis by downregulating α-SMA, type 1 collagen-α, MMP-9, and TIMP-1 expression, while suppressing TGF-β1 and Smad4 phosphorylation (13).Similarly, Safflower yellow (SY) shows promise as a pulmonary fibrosis inhibitor induced by bleomycin (BLM), with higher doses yielding more significant effects. SY inhibits the increase in α-SMA-positive cells and TGF-β1 expression and also suppresses α-SMA expression during lung fibroblast differentiation into myofibroblasts stimulated by TGF-β1 (13).

6.10. Cardiovascular effect.

Safflower yellow (SY) administration at doses of 1 to 2 g/kg/day reduced blood pressure in spontaneously hypertensive rats (SHR) by approximately 1.86-3.86 kPa. This decrease was associated with reduced plasma renin activity and angiotensin II levels, indicating a modulation of the renin-angiotensin system. Additionally, hydroxysafflor yellow A (HSYA) demonstrated a vasodilatory effect on pulmonary arteries (PA) by activating CV channels in pulmonary vascular smooth muscle cells (PVSMCs). Intravenous administration of HSYA led to reductions in mean arterial pressure (MAP), heart rate (HR), left ventricular systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP), maximum rate of increase in left ventricular pressure (+dp/dt(max)), and heart rate in both normotensive and SHR rats (43). Carthamin yellow (CY) demonstrates significant effects on blood viscosity, plasma viscosity, and erythrocyte aggregation index in the blood stasis model. It also reduces hematocrit and platelet aggregation, while higher

doses result in delayed prothrombin time. Safflower Yellow inhibits platelet aggregation induced by PAF, reduces 5-HT release by platelets, and increases free calcium levels in platelets (43, 44).
Similarly, Safflower yellow A (SYA) exhibited protective effects against anoxia/reoxygenation (A/R) in cultured rat cardiomyocytes, while safflower yellow B (SYB) showed potential against angiotensin-II-induced vascular endothelial cell (VEC) injury (43). The cardioprotective effects of Carthamus tinctorius (CT) extract were investigated both in vivo and in vitro, demonstrating promising results. In an animal model of myocardial ischemic injury induced by left anterior descending coronary artery occlusion, CT treatment reduced infarct size and improved cardiac function. In vitro studies suggested that CT attenuates oxidative stress damage and apoptosis. Injection of C. tinctorius also showed cardioprotective effects against acute myocardial infarction (AMI) in mice, potentially through suppressing TNF-α and IL-6-mediated inflammation and modulating Bax/Bcl-2 ratio .Moreover, safflower was found to modulate the expression of Bax, Bcl-2, and SIRT1/FoxO1 proteins, suggesting its potential in treating coronary heart disease (CHD) by exerting anti-apoptotic effects through various pathways (45).Daily administration of safflower extract at 250 mg/kg BW to both normal and hyperlipidemic rats, induced by a 2% (w/w) cholesterol diet, resulted in weight loss in rats fed with the diet supplemented with dichloromethane fraction for a week. After 14 and 30 days of treatment, there was a significant reduction in total cholesterol and HDL cholesterol levels, alongside a notable increase in HDL cholesterol levels in hypercholesterolemic rats. Safflower was also found to have a reparative effect on ox-LDL-induced apoptosis and mitochondrial membrane potential in vitro (45).

6.11. Antihemolitic.

The antihemolytic effect of safflower extract against PbANKA infection in rats showed a dose-dependent response, with significant effects observed compared to the untreated control group ($P < 0.05$ and < 0.01). There was a notable decrease in % Hct compared to the normal group ($P < 0.01$). When compared to green tea extract, safflower extract exhibited lower antihemolytic activity but higher activity than mulberry extract. Interestingly, no effect on %Hct was observed in normal ICR mice treated with the extract at a maximum dose of 3000 mg/kg. The presence of polyphenols and flavonoids in the extract may play a crucial role in protecting red blood cells against oxidative stress and inflammation induced by malaria infection. Moreover, the extract was noted for its ability to maintain blood pH and shield red blood cells from acidosis triggered by malaria infection (46).

6.12. Anticoagulant and antitrombotic.

The decoction and ethanol extract of Safflower demonstrated significant inhibition of ADP-induced platelet aggregation both in vitro and in vivo in rats and rabbits. Safflower yellow (SY), extracted from the water extract, extended plasma prothrombin time (PT), thrombin time (TT), and activated partial thromboplastin time (APTT). SY notably reduced plasma fibrinogen levels in mice, primarily hindering ADP-induced platelet aggregation. Additionally, SY suppressed rabbit platelet adhesion, 5-HT release, and intraplatelet Ca^{2+} levels induced by PAF. Carthamins yellow (CY), another compound extracted from Safflower, reduced the model's relative index, hematocrit, and platelet aggregation in a dose-dependent manner, delaying prothrombin time. This suggests potential benefits for patients with hemorheological disorders. Furthermore, Hydroxysafflor yellow A (HSYA) demonstrated the ability to inhibit PAF receptor binding and suppress PAF-induced rabbit platelet adhesion. HSYA's mechanism involves inhibiting thrombosis formation and platelet aggregation, along with regulating prostacyclin/thromboxane (PGI2/TXA2) levels, ultimately reducing blood viscosity, plasma viscosity, and erythrocyte aggregation index, thus alleviating blood stasis (13).

6.13 Osteoporosis

Safflower seed offers protective effects against estrogen deficiency-induced bone loss, primarily due to its polyphenolic compounds stimulating osteoblast proliferation. Its high linoleic acid content in the seed oil exhibits anti-inflammatory properties, moderating prostanoid formation and

ameliorating bone loss post-ovariectomy, while enhancing intestinal calcium absorption. In rat models, minerals present in safflower seed oil, such as calcium, magnesium, and potassium, helps prevent ovariectomy-induced osteoporosis. Oral administration of safflower seed oil to ovariectomized rats for 30 days resulted in favorable changes compared to controls. Moreover, Safflower flower extract counteracts reactive oxygen species (ROS)-induced dysfunction and oxidative damage in osteoblastic cells. Additionally, HSYA compounds influence bone metabolism by enhancing femoral load threshold, augmenting tibial cartilage and bone, increasing osteoblast count, and decreasing osteoclast count, along with reducing the expression levels of CA2 and proteins linked to osteoclast differentiation (47).

6.14. Effect on cerebrovascular function

Studies have explored the functional regulation of monoamine transporters by Safflower and its derivatives. The nonpolar fraction of Kasumba turate demonstrated notable inhibition of serotonin uptake in cells expressing the serotonin transporter. Hydroxysafflor yellow A (HSYA) compounds exhibited reductions in IL-1β and TNF-α levels in ischemic brain tissue, along with protective effects against hypoxic injury in cerebral cortical neurons and suppressing inflammation after ischemia/reperfusion (I/R) in mice (48).

In an acute I/R stroke mouse model, HSYA treatment showed significant protective effects, reducing infarct volume and improving neurological function. Mechanistic studies suggested that HSYA activated Akt-mediated autophagy in penumbral tissue, particularly in neurons. Additionally, safflower extract increased antioxidant enzyme activity and reduced oxidative stress in rats with acute cerebral ischemic injury. HSYA compounds attenuated cerebral ischemia/reperfusion injury in mice by reducing oxidative stress markers and enhancing antioxidant enzyme activity (49).

6.15. Neuroprotector

Safflower demonstrated significant neuroprotective effects, reducing neuronal cell death and oxidative stress markers in the hippocampus. It also mitigated memory impairment induced by muscarinic antagonists, potentially through modulation of cholinergic transmission. Hydroxysafflor yellow A (HSYA), a key active compound in Safflower, showed neuroprotective effects against cerebral ischemia and protected cultured rat fetal cortical neurons. Additionally, safflower calyx extract inhibited glial cell death induced by glutamate and reduced oxidative damage markers in rat brain tissue (50).

6.16. Antioxidant.

The lyophilized compound from Safflower seed extract showed antioxidant activity with an IC50 value of 263.02 μg/mL, while another study reported a lower IC50 value of 1.7 μg/mL for Safflower seed extract. In vitro antioxidant assays revealed that the extract from C. tinctorius L. honey effectively scavenged free radicals DPPH and ABTS+. Various flavonoids and quinochalcones in Safflower possess antioxidant properties by neutralizing free radicals. Safflower calyx water extract neutralized superoxide (O2), hydroxyl (-OH), 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals, and singlet oxygen, with carthamin content correlating with DPPH radical scavenging activity (12). Furthermore, its flower extract protected osteoblastic MC3T3-E1 cells against H2O2-induced oxidative damage, reducing alkaline phosphatase, collagen, and calcium deposition while increasing nuclear factor-kB ligand-receptor activator (RANKL) production, potentially shielding osteoblasts from oxidative stress toxicity. Hydroxysafflor yellow A (HSYA), known for inhibiting mitochondrial permeability transition pores (mtPTP) opening in rat brains, exhibited free radical scavenging action. Additionally, inoculation significantly boosted safflower plant antioxidant defense mechanisms under Cd stress by increasing antioxidant compound levels and enhancing antioxidant enzyme activities (51).

6.17. Anti-inflammatory

Carthamus Yellow (CY), containing safflomin A and safflomin B, has shown protective effects against lipopolysaccharide-induced inflammation (LPS) in RAW264.7 macrophages. It inhibits the release of nitric oxide (NO), prostaglandin E2 (PGE2), and LPS-stimulated interleukin 1β (IL-1β) by attenuating the inducible expression of nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) proteins.Safflower methanol extract (MEC) enhances the expression of HO-1 protein in macrophages in a concentration- and time-dependent manner. Treatment with MEC inhibits iNOS and COX-2 upregulation in LPS-activated macrophages, leading to reduced NO and PGE2 production. The inhibition of iNOS and COX-2 expression by MEC is reversed by siHO-1 RNA transfection. Moreover, MEC facilitates the translocation of NF-E2-associated factor (Nrf2) from the cytosol to the nucleus and reduces NF-κB binding and activity. Additionally, MEC significantly inhibits tumor necrosis factor (TNF)-mediated VCAM-1 expression in endothelial cells (10). Moschamine, derived from C. tinctorius Linn., exhibits anti-inflammatory effects by reducing lipopolysaccharide-induced prostaglandin E2 and nitric oxide production. It decreases protein and mRNA levels of cyclooxygenase-2 and microsomal prostaglandin E2 synthase-1 while inducing nitric oxide synthase, interleukin-6, and interleukin-1β.Safflower Yellow (SY) exerts anti-inflammatory effects by inhibiting IκBα phosphorylation, thereby suppressing the NF-κB signaling pathway and nuclear translocation of p53. Additionally, SY can restrain the release of pro-inflammatory factors (52).

6.18. Immunomodulator.

Previous studies have shown that polysaccharide fractions extracted from safflower petals activate the NF-κB signaling pathway via TLR4, stimulating cytokine production by peritoneal macrophages. Additionally, combining safflower ethanol extract with black cumin extract enhances the immunostimulatory effects, boosting the activity and phagocytic capacity of macrophages in male mice (53).

6.19. Analgesic

In rats, intraperitoneal injection of Safflower Yellow A at doses ranging from 50 to 100 mg/kg showed sustained analgesic effects. Safflower has exhibited central analgesic activity at a dosage of 500 mg/kg, potentially resembling morphine-like effects without the associated side effects. Analgesic effects have also been noted with safflower oil doses at 100 and 300 mg/kg, indicating its potential application in opioid-free anesthesia. Moreover, Helenalin has been recognized for its analgesic properties, suggesting its potential as an anticancer or anti-inflammatory agent (8, 42).

7. Conclusion

This study aims to offer a comprehensive examination of safflower's morphological traits and its therapeutic and non-therapeutic potentials, particularly focusing on its traditional and folk uses worldwide, with an emphasis on Iran. This plant species exhibits beneficial effects on various medical conditions related to the cardiovascular, musculoskeletal, and digestive systems, among others. Numerous animal and clinical studies have explored these potentials, discussed herein, suggesting promising alternatives or adjuncts for specific medical conditions. Nevertheless, there remains a critical need for further phytochemical analyses and clinical trials concerning its essential oil or various extracts. For instance, the antimicrobial and antioxidant properties of safflower could be harnessed not only as food preservatives but also for potentially mitigating diseases like vitiligo, psoriasis, and mouth ulcers. Additionally, certain safflower concentrations have shown promising results in addressing myocardial ischemia, coagulation issues, and thrombosis. Despite recent evidence highlighting potential adverse effects of safflower on reproductive organs, Persian traditional medicine suggests it may improve semen quality, necessitating further exploration.

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