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Review Article

DETAILED STUDY ON THERAPEUTIC PROPERTIES, USES AND PHARMACOLOGICAL APPLICATIONS OF SAFFLOWER (*CARTHAMUS TINCTORIUS* L.)

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ABSTRACT

Safflower (*Carthamus tinctorius* L.) belongs to the family Asteraceae. Safflower has been grown mainly for orange-red dye (carthamin) extracted from its flower used in food coloring and flavoring. Safflower seed oil is highly rich in linoleic acid (unsaturated fatty acid) which makes it highly suitable for human consumption. The whole plant of C. tinctorius possesses many pharmacological activities like antifibrosis, antidiabetic, antitumour, anti-inflammatory, hepatoprotective, antihperlipidemic, anticoagulant, and antioxidant activities. Regardless of it numerous uses, this crop is under the category of minor and neglected crop, therefore additional research work is required for its commercialization. The present review critically deals with botanical description, distribution, classification, uses, pharmacological activities and chemical constituents present in safflower.

KEYWORDS: Botany, distribution, uses, pharmacological activities, chemical constituents.

INTRODUCTION

Safflower (*Carthamus tinctorius* L.) is an oil yielding crop which is a member of the family Compositae or Asteraceae. In India, it is most commonly known as kusum in Hindi and in China it is known ashong hua. [1] As it resembles with the saffron it is also called as false saffron, thistle saffron, dyer's saffron etc. Safflower is a multipurpose crop which has been grown for centuries in India and in other parts of worlds for various purposes. It is an extremely important plant as it provides the alternative source for oil. The research and development on safflower still have not received great interest, although it has potential to grow in varied environmental conditions with very high yield potential and also has numerous uses of different plant parts.

However, this crop has attracted the scientists mainly because of the following reasons:

1. This plant is able to grow in adverse environmental conditions like draught, salinity stress making it suitable for those countries having these kinds of problems so it could be grown effectively on dry lands.
2. The safflower seed oil is high in linoleic acid, an unsaturated fatty acid for which safflower is well known, that aids in lowering the cholesterol level in the blood. The preference of consumers for healthy oil with less amounts of saturated fats which is useful in reduction of the risk of human arteriosclerosis.
3. The therapeutic uses of safflower plant and extraction of edible dyes from flowers have become more widely known.

Botany

Morphological characters

Safflower plant is bushy, herbaceous and possesses several branches. Safflower has mainly two types of varieties- spiny and spineless. Spiny varieties have spines on the leaves and the modified leaves associated with flower heads. It is considered that varieties with reduced or absent spines have been lower in oil content than spiny varieties.Safflower can grow to height of about 3 ft (1 m) even in poor, dry soils in full sun. Safflower production in India is mostly confined to rain-fed conditions during winter.

Initially, the germination of the seed of safflower is comparatively slower process. This slow growing period is named as rosette period which can vary from 20 to 35 days, in which numerous leaves are produced at stem base. After completion of this period, elongation of stem and branches starts. Each branch produces flowering heads commonly called capitula and has a composite type of inflorescence. Each capitulum consists of several flowers, with the number ranging from 20 to 250 [Fig 1(a)]. The flowering period in safflower lasts for a month. The flowers of *Carthamus* are pale yellow to red-orange [Fig 1(b)], tubular disk florets; there are no ray florets in this thistle-like head. Flowers are enclosed by bracts in circular order. The plant produces white, shiny and smooth seeds (fruits) [Fig 1(c)] having thick pericarp, called achenes, each weighing from 0.01 to 0.1g. Safflower attains maturity in 30 to 35 days from the time when flowering ends. Safflower has a taproot system that elongates to 2 to 3 m in soils with adequate depth. The safflower has deep root system which helps to extract the water and nutrients from much deeper layers of soil, and thus make it an ideal plant for rain-fed cropping systems.

(a). Whole plant **(b). Flower** **(c). Seeds**

Figure 1: *Carthamus tinctorius* (a) whole plant (b) flower and (c) seeds

World Distribution and Production

Safflower is grown commercially in India, the U.S., Mexico, Ethiopia, Kazakhstan, Australia, Argentina, Uzbekistan, China, and the Russian Federation. Pakistan, Spain, Turkey, Canada, Iran, and Israel also grow safflower upto the certain extent. According to records, Mexico was the largest producer of safflower in the world until 1980. However, the area and production of safflower in Mexico decreased significantly in later years, becoming only 10% of the area and production. [2] Presently, India is the largest producer of safflower in the world, followed by the U.S., Mexico, and China. In India, Maharashtra and Karnataka states account for 72 and 24% of safflower area and production, respectively.

Comprehensive study on historical, general and clinical uses of safflower

Oil and meal are two important products that are received from current safflower production. Oil is the primary product and has importance in both food and industries. Safflower meal which is a by-product of the oil industry contains high amount of protein which is very good substitute for animal feed if not too spiny, can be used for green fodder or silage. [3] Safflower seeds can be processed to produce edible oil.

In India, since very ancient times safflower has got multiple uses which can be divided into three parts namely, historical uses, general uses and clinical uses. These are discussed in the table (1, 2, and 3) given below:

Table 1: Detailed account on Historical uses

S. No.	Historical Uses
1.	In Egypt, dye from safflower was used to color cotton and silk as well as ceremonial ointment used in religious ceremonies and to anoint mummies prior to binding. Safflower seeds and packets and garlands of florets have been found with 4000-year-old mummies.

2	By the 18th century, safflower dye was used in Italy, France and Britain to color cheese and flavor sausage. Carthamin dye was used extensively to colour cloth until the 19th century, when cheaper aniline dyes became available. Safflower dyes were particularly important to the carpet-weaving industries of eastern Europe, the Middle East and the Indian subcontinent.
3.	Safflower has been used in the Middle East, India and Africa for purgative and alexipharmic (antidote) effects, as well as in a medicated oil, to promote sweating and cure fevers.
4.	Florets were widely used to colour and flavor soups and rice as well as cloth, potions and unguents. Safflower was used as a pot herb and as a laxative.
5.	Hebrew writings since the 2nd century AD have described the use of tablets of carthamin dye for food colouring, rouge and medicine.

Table 2: Detailed account on general Uses

S.No.	General Uses
1.	Young leaves and thinnings are eaten boiled, as a vegetable side dish with curry or rice in India, Pakistan and Burma.
2.	**Coloring food and cosmetic:** True saffron is world's most costly spice, and safflower is a common adulterant or substitute. Rice, soup, sauces, bread and pickles take on a yellow to bright orange colour from the florets. Health concerns regarding synthetic food colourings may increase demand for safflower-derived food colouring. The Japanese cosmetic named as 'beni' is made from carthamin dye and lipsticks include safflower colouring. [4]
3.	**Dyes:** The water-soluble yellow dye, carthamidin, and a water-insoluble red dye, carthamin, which is readily soluble in alkali, can be obtained from safflower florets. Dye manufacture has virtually ceased in Asia, but dye is still prepared on a small scale for traditional and religious occasions.
4.	Safflower oil is also better suited to hydrogenation for margarine production than are soy or canola oils. Safflower oil is nonallergenic, and therefore suitable in injectable medications. [4]
5.	In China, safflower is grown almost exclusively for its flowers, which are used in treatment of many illnesses as well as in tonic tea. Safflower has a bitter herbal taste, but the Institute of Botany of the Chinese Academy of Sciences in Beijing has developed non-bitter, sweet-smelling tea which contains amino acids, minerals and vitamins B1, B2, B12, C and E. Safflower preparations should be stored in light-resistant containers.
6.	Safflower oil is highly stable, and its consistency remains the same at low temperatures, thereby making it suitable for application in frozen/chilled foods.

Table 3: Detailed account on clinical uses

S.No.	Clinical Uses
1.	**Heart Disease**: Safflower dilates arteries by lowering blood cholesterol, reduces hypertension and increases blood flow and, hence, oxygenation of tissues. In 90% of patients it also inhibits thrombus formation and, over time, dissolves thrombi. In 83% of patients with coronary disease, blood cholesterol levels have been reduced after 6 weeks of treatment. [5] Hence it can be used by persons suffering from cardio vascular disorders.
2.	**Constipation**: A very popular Unani laxative medicine called Twarishe Qhurtum is prepared from safflower seeds.
3.	**Asthma**: Safflower seeds acts as an expectorant and reduces the spasms by liquefying the tenacious sputum. Safflower, along with other herbs, has been used to treat respiratory diseases including pertussis (whooping cough) and chronic bronchitis. [5]
4.	**Sexual Debility**: Safflower decoctions have been used successfully for treatment of male sterility and dead sperm excess disease. [6]
5.	**Female Disorders**: A brew made from safflower foliage is said to prevent abortion and the female sterility. Labor can be induced by a preparation of safflower, ideally along with

	rupture of membranes.
6.	**Rheumatism**: safflower was successful in treatments of sciatica [5] and thorax rheumatism. [7] Safflower wine is recommended for 62 types of rheumatism. Safflower prescriptions have been very effective treatments for rheumatoid arthritis. [8]
7.	**Chronic hepatitis (hepatitis C):** EH0202 is a traditional Japanese Kampo therapy containing safflower seed extract and is used for immunostimulation. EH0202 may decrease hepatitis C virus-RNA levels in patients with high viral titers. More studies are needed to describe safflower's effect on hepatitis C.
8.	Daily or twice daily doses of safflower with ground beetle in glutinous rice or millet wine helps muscle injuries heal within a week. [5]
9.	Safflower eye drops reduce myopia, especially in children. [9]
10.	**Diabetes mellitus type 2**: Lipid (fat) abnormalities are commonly associated with diabetes, and complications of atherosclerotic disease are frequently associated with diabetes. Safflower oil may negatively affect glucose metabolism due to the extra intake of energy or fat, but these effects may be less pronounced than in fish oil.
11.	A tea made from safflower foliage is used to prevent abortion and infertility by women in Afghanistan and India. All parts of the plant are sold by herbalists in India and Pakistan as 'pansari' to remedy various ailments and as an aphrodisiac. [10]
12.	**Hypertension** (high blood pressure): Based on preliminary evidence, safflower oil may be involved in synthesis of prostaglandins, which are responsible for vascular regulation and inflammatory responses and may affect hypertension (high blood pressure). However, clinical studies have shown that safflower oil ingestion decreases or does not affect blood pressure. Due to the conflicting evidence, additional study is needed in this area.
13.	**Total paranteral nutrition**: Parenteral nutrition requires a certain percentage of fats to provide full nutrition. Various sources of fats have been used, including safflower oil. Overall, clinical trials have shown safflower oil total parenteral nutrition (TPN) to be safe when used at the doses in the trials. However, more studies should be conducted to see if safflower oil is superior to other sources of TPN lipids.
14.	Quercetin, which is one of the flavonoids found in safflower, is a well-known antioxidant.

Varieties of *Carthamus tinctorius* (L.)

The important high yielding varieties of safflower are as given below (Table 4)

Table 4: Different varieties of *Carthamus tinctorius* in India

S.No	Name of variety	Releasing Year	Recommended State	Maturity Time (in days)	Morphological characteristics of plant	Oil content (%)	Annual Production (quintals per hectares)
1.	N-62-8	1959	Ahemdabad, Pune, Solapur and Nasik districts of Maharashtta	140	Flowers are yellow in colour, seeds are medium in size and white	30	9-12
2.	Nag-7		Maharashtra.	140	Its seeds are white, medium in size		10-13
3.	Tara	1976	Maharashtra states	120-125	Leaves have serrated margins and spines. The flowers are yellow turning to orange. Its seeds are white in colour	32.5	12-14
4.	A-I	1976	Entire country	125	Seeds are of medium size and white in color.	30-35	8 -8.50
5.	A-300		Drought prone	125	Flowers are yellow. Its	31.9	8-10

			areas of Karnataka.		seeds are white and medium in size.		
6.	Manjira	1976	Andhra Pradesh	105-110	Flowers are yellow in color, seeds are partly white in color.	35	12-14
7.	K-l	1976	Tamil Nadu	120	seeds are medium in size	30.5	6-8
8.	JSF-l (Sweta)	1984	Rajasthan	120-125	It has white flowers	30	15
9.	K59-2-1	1976	Bihar state	155	It has yellow flowers, seeds are white and small	31	5-6
10.	Sagarmu-tbialu (APRR-3)	1985	Andhra Pradesh and Bihar states	125	Resistant to rust	33	10-12
11.	Malviya Kusum (HUS-305)	1986	Varanasi(U.P.), also salt affected areas of West Bengal	132-169	Resistant to Alternaria leaf blight	36	13
12.	CO-1	1979	Tamil Nadu	125	It is a spineless variety selected from Egyptian germplasm and tolerant to Alternaria, moderately resistant to wilt	33	7-9
13.	Bhima	1982	Maharashtra (both in moisture and drought prone areas)	130-135	It has creamy white flowers which turn to dirty whitish pink after fading.	32.5	12-14

Novel development in varieties of *Carthamus*

Disease Resistance

Safflower is vulnerable to many diseases as it is attacked by many factors like fungi, bacteria, viruses, or physiological disorders due to abiotic stresses. According to survey, in last 25 years there is a noticeable reduction in safflower in India. [11] It was reported that safflower is recorded to be infested around the world by 57 pathogens, including 40 fungi, 2 bacteria, 14 viruses, and 1 mycoplasma. [12] Of these, Alternaria leaf spot caused by *Alternaria carthami* and wilt caused by *Fusarium oxysporum* are the most devastating ones and can cause 13 to 49% losses. The safflower production is also affected by many insects. Out of over 80 species of insect, mite and nematode pests, safflower aphid (*Uroleucon compositae* Theobald) is the most destructive pest of safflower. The safflower aphid is a major pest which causes 30 to 80 per cent yield loss and approximately 37% in India. [13]

Though some cultivars showing partial or full resistance to some of the major diseases have been identified. Australian safflower cultivar Sironaria, showing resistance to Alternaria blight and moderate resistance to Phytophthora root rot, has been developed by backcrosses. Safflower cultivars resistant to Alternaria blight, viz., Sidwill, Hartman, Oker, Girard, and Finch, have been successfully developed in the U.S. Some germplasm lines exhibiting a tolerance to aphids have been identified in safflower. Two wild species *C. flavescens* and *C. lanatus*, have been reported to be carrying genes for resistance against safflower fly. [14] It is a major concern that safflower is grown by small and marginal farmers, therefore the plant do not receive any protective measures therefore breeding and integrated pest management of safflower is the most efficient and suitable method for controlling diseases in safflower.

Increased oil content

In past few years there has been an increased demand by consumers for vegetable oil with low saturated fatty acid such as olive oil, safflower oil, sunflower oil, and canola oils. Oil content and fatty synthesis is affected by many factors such as genotype, ecology, morphology, physiology and management. [15] It is considered that varieties with reduced or absent spines have been lower in oil content than spiny types. [16]

Increased oil levels in the US were achieved by the reduction of hull thickness, and by single genes, such as those associated with striped-hull, reduced-hull, and partial-hull. Safflower varieties released for commercial production in India in general possess low oil content of 28 to 32%, except HUS-305, NARI-6, and nonspiny hybrid NARI-NH-1, each of which contain 35% oil. Many studies have shown a negative association between hull content and oil content in safflower. Therefore, reduction in hull content directly increases oil content. Some scientists reported that draught can be a factor that decrease safflower oil and seed yield especially in sensitive phenological stages. [17] To decrease these adverse effects, atrazine foliage spraying in low concentration acts as an anti-transpirant. After applying atrazine, especially in flowering stage, significantly increase oil content from almost 30 to more than 35%. It also increased photosynthesis rate and seed and oil yield.

Spineless Safflower

Safflower production has been largely limited mainly because of its spiny nature, especially in non-traditional areas and in areas where mechanized cultivation has not yet been introduced. In India, too, safflower production is dominated by the spiny cultivars.

Although spineless cultivars CO-1 and JSI-7 were available, but because of their poor yielding ability as compared to spiny cultivars, they could not command a significant safflower area. JSI-7, the first spineless cultivar in India, was released in 1990. After few years later, in 2000, the spineless NARI-6 was released by NARI, as the florets can easily be collected. The yield capacity of the two cultivars is same as compared to spiny cultivars and they are reported to have better tolerance to foliar and wilt diseases than to spiny ones.

Chemical constituents present in *Carthamus tinctorius* (L.)

More than 200 compounds have been isolated from *C. tinctorius* and the commonly known ones are flavonoids, phenylethanoid glycosides, coumarins, fatty acids, steroids and polysaccharides. [18] Important chemical compounds present in safflower are shown in Figure 3. Oil content of the seeds is similar to that of olive and includes linoleic acid (63%–72%), oleic acid (16%–25%) and linolenic acid (1%–6%). [19] Luteolin and its glucopyranosides have been also found in the leaves. [20] A new quinoc-halcone C-glycosides, tinctormine, was isolated from the plant together with safflor yellow B. Nicotiflorin is a natural flavonoid extracted from coronal of *C. tinctorius*. [21] From the dried petals of *C. tinctorius*, five flavonoids, 6-hydroxykaempferol, 6- hydroxykaempferol 3-glucoside, 6-hydroxykaempferol 3,6-diglucoside, 6-hydroxykaempferol 3,6,7-triglucoside and 6-hydroxykaempferol 3-rutinoside-6-glucoside, were isolated along with 13 known compounds (Fig.2). Various compounds isolated from different parts of safflower are shown in Table 5.

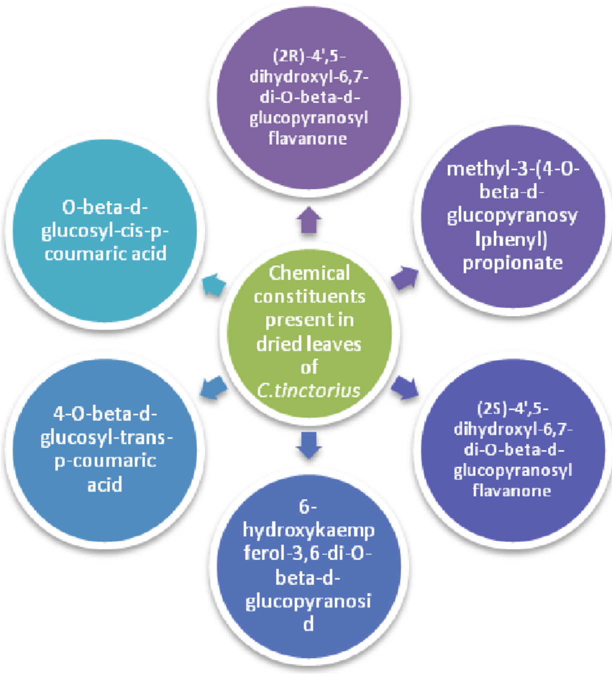

Figure 3: The figure represents the different chemical constituents present in dried leaves of *C.tinctorius.*

Table 5: Chemical compounds isolated from *Carthamus tinctorius*

Chemical compounds isolated from *Carthamus tinctorius*					
Antioxidative serotonin derivatives from safflower oil [22]	**Triterpene alcohol constituents from Flower of safflower [23]**	**Compound from petals[24]**	**Compound from flower[25]**	**Compound from *C. tinctorius* flowers essential oil [26]**	**Flavanoids [20]**
N-[2-(5-hydroxy-1H-indol-3-yl)ethyl]ferulamide	Heliaol	Carthamin, safflower yellows A and B	flavone luteolin and its glucopyra-noside luteolin 7-O-beta-D-glucopyranoside	Caryophyll-ene	quercetin-7-O-(6-O-acetyl)-β-D-glucopyranosi-de
N-[2-(5-ydroxy-1H-indol-3-yl)ethyl]-p coumaramide	α-amyrin	safflomin A and C	luteolin-7-O-(6''-O-acetyl)-beta-D glucopyranoside	p-allyltoluene, 1-acetoxytetralin	luteolin
N-, N-[2,2'-(5,5-dihydroxy-4,4'-bi 1H-indol-3,3'-yl) diethyl]- di-pcomaramide	β-amyrin	Isocartha-min	lauric acid	heneicosane	quercetin
N-[[3'[2-(p-comaramido) ethyl]-5, 5'-dihydroxy-4,4'-bi-1H-indol-3-yl]ethyl] ferulamide	lupeol	Isocartha-midin	myristic acid		luteolin-7-O-β-D-glucopyranosi-de
N,N'-[2,2'-(5,5'-dihydroxy-4,4'-1H-indol-3,3'yl) diferulamide	cycloartenol	Hydroxysa-fflor yellow A	palmitic acid		luteolin-7-O-(6-O-acetyl)-β-D-glucopyranosi-de
N-[2[5-(beta-D glucosyloxy)-1Hindol- 3-ylethyl]-p- comatamide	24-methylenecyclo artanol	tinctormine	linoleic acid		quercetin7-O-(6-O-acetyl)-β-D-glucopyranosi-de
N-[2-[5-(beta- D-glucosyloxy)-1H-indol-3-yl]-ethyl] ferumaramide	tirucalla-7		arachiidic acid		acacetin-7-O-β-D-glucuronide
	24-dienol		oleic acid		apigenin-6-C-β-D-glucopyrano-syl 8-C-β-D-glucopyranosi-de

MEDICINAL ACTIVITIES PRESENT IN *CARTHAMUS TINCTORIUS*

Antifibrosis activity

Oxidative stress caused hepatic fibrosis by activating hepatic stellate cells (HSCs), which were implemented by depressing PPARγ activation. Hydroxysafflor yellow A (HSYA) as a nature active ingredient with antioxidant capacity was able to effectively attenuate oxidative stress mediated injury. So it will be very interesting to study effect of HSYA on HSCs activation and liver fibrosis, and reveal the role of PPARγ·CCl_4 and H_2O_2 were used to mimic oxidative stress mediated hepatic injury in vitro and in vivo respectively. Results showed that HSYA was able to effectively inhibit oxidative stress mediated hepatic injury by increasing the activities of antioxidant enzymes, up regulating the expression of PPARγ and MMP-2, and down regulating the expression of TGF-β1 and TIMP-1, and reducing α-SMA level. Taken together, these results demonstrate that HSYA is able to significantly protect the liver from oxidative stress, which requires for HSYA to stimulate PPARγ activity, reduce cell proliferation and suppress ECM synthesis. [27]

Antidiabetic activity

Safflower is useful for treatment of diabetes and its complications. The flower aqueous extract can reverse the metabolic disorders occurring in alloxan induced diabetes. *C. tinctorius* flowers regenerates and restorates of Langerhan islets, thus the insulin level would be elevated. Safflower enhances the secretion of insulin from the beta cells of the islets of Langerhans. Further, it has an ability to restore the protein breakdown and enhance the glycogenesis process in the liver of diabetic rats. Serotonin derivatives such as N-p-coumaroyl serotonin and N-feruloyl serotonin isolated from *C. tinctorius* seeds were active as α-glucosidase inhibitors. These compounds showed a potent inhibitory activity.

In one experimental study, it was observed that safflower can reverse the metabolic disorders occurring in alloxan induced diabetic rats. Results indicate that FBS, triglyceride, cholesterol, LDL-C and VLDL-C had a significant decline in diabetic rats treated with *C. tinctorius* and diabetic rats treated with glibenclamide as compared with diabetic rats. Insulin level increased significantly in diabetic groups received treatment (glibenclamide or *C. tinctorius* L) in comparison with diabetic group with no treatment. The desirable effect of the safflower extract on the liver is also considerable. [28]These results are helpful for the proper use of safflower seed as a traditional medicine for the treatment of diabetes; moreover, it could serve to develop medicinal preparations as supplements and functional foods for diabetes. [29]

Antitumour activity

C. tinctorius, is efficient for treating breast cancer. [30] The oil extracted from the seed of *C. tinctorius* is reported to contain alkane-6, 8-diols, which have the activity to inhibit 12-*O*tetradecanoylphorbol- 13-acetate-induced tumor promotion in two-stage carcinogenesis in mouse skin. [31] To investigate the effects of *C. tinctorius* on the dendritic cell (DC)-based vaccine in cancer treatment, cytokine secretion of mouse splenic T lymphocytes and the maturation of DCs in response to *C. tinctorius* were analyzed. To analyse the antitumor activity of *C. tinctorius* extract on mouse $CD117^+$ (c-kit)-derived DCs pulsed with JC mammal tumor antigens, the JC tumor was challenged by the *C. tinctorius* treated DC vaccine *in vivo*. *C. tinctorius* stimulated IFN-γ and IL-10 secretion of splenic T lymphocytes and enhanced the maturation of DCs by enhancing immunological molecule expression. When DC vaccine was pulsed with tumor antigens along with *C. tinctorius* extract, the levels of TNF-α and IL-1β were dramatically increased with a dose-dependent response and more immunologic and co-stimulatory molecules were expressed on the DC surface. In addition, *C. tinctorius* -treated tumor lysate-pulsed DC vaccine reduced the tumor weight in tumor-bearing mice by 15.3% more than tumor lysate-pulsed DC vaccine without *C. tinctorius* treatment. *C. tinctorius* polarized cytokine secretion toward the Th1 pathway and also increased the population of cytotoxic T lymphocytes *ex vivo*. In conclusion, *C. tinctorius* activates DCs might promote the recognition of antigens and facilitate antigen presentation to Th1 immune responses.

Anti-inflammatory and Analgesic Properties

Due to the side-effects of chemical drugs, researchers are focusing to natural products to develop new anti-inflammatory drugs. [32] Many cells and mediators are involved in proceeding inflammation. For example, macrophages are representative inflammatory cells involved in acute or chronic inflammatory responses by over-production of pro-inflammatory cytokines [for example, tumor necrosis factor (TNF)-α, interleukin (IL)-1b and granulocyte/macrophage colony stimulating factor (GMCSF)] and inflammatory mediators. The intraperitoneal injection of safflower yellow A at doses of 50–100 mg/kg in mice showed sustained analgesic action. This compound also inhibited formaldehyde-induced foot swelling, histamine stimulated capillary permeability, and formation of cotton ball granuloma in rats. The central inhibition induced by barbital of chloralin mice was markedly enhanced by safflor yellow A. The coramine-induced convulsions and death were markedly reduced. Anti-inflammatory action of methanol extract of *C. tinctorius* (MEC) involves in heme oxygenase-1 (HO-1) induction. The results show that MEC induces HO-1 expression via Nrf2 translocation and inhibits nuclear factor kappa B (NF-κB) activity, which may be responsible for anti-inflammatory action. [33]

The flavone luteolin and its glucopyranoside such as luteolin 7-O-beta-D-glucopyranoside and luteolin-7-O-(6''-O acetyl)-beta-D-glucopyranoside have been reported to exert anti-inflammatory effects in vitro and in vivo and several works have shown that these compounds which are rich in *C. tinctorius* flowers inhibited NF-κB activity at concentrations in the low micromolar range. Flowers of *C. tinctorius* possess central analgesic activity (500 mg/kg) and potentially may lead to the development of morphine-like substances devoid of the side effects of morphine and related drugs. [34]

Anticoagulant activity

The brain is susceptible to ischemia-induced damage followed by thrombotic block. Generally, cerebral ischemia is characterized by the state of hypercoagulability and hyperviscosity in circulation, which is prone to form thrombosis. [35] Studies have demonstrated that Hydroxysafflor yellow A (HSYA) contained in *C. tinctorius* flowers markedly extended coagulation time in mice, which raises the possibility that it might exert therapeutic actives on cerebral ischemia induced by thrombosis. Followed researches have shown that HSYA dose dependently improved the neurological deficit scores and reduced the cerebral infarct area and it bore a similarity in potency of the therapeutic effects on focal cerebral ischemia to nimodipine as the standard drug. Inhibitory activities of HSYA were observed on adenosine diphosphate (ADP)-induced platelets aggregation in a dose-dependent manner, and the maximum inhibitory aggregation rate of HSYA was 41.8%. Blood rheological parameters were markedly improved by HSYA, such as whole blood viscosity, plasma viscosity, deformability and aggregation of erythrocyte, but no significant effect of HSYA on hematocrit was found.

The underlying mechanisms exerted by HSYA might be involved in its inhibitory effects on thrombosis formation and platelet aggregation as well as its beneficial action on regulation of prostacyclin/thromboxane (PGI2/TXA2) and blood rheological changes in rats. [35] *C. tinctorius* is commonly used in Chinese medicine to promote blood circulation and remove blood stasis. Results have demonstrated that this compound significantly decreased the whole blood viscosity, plasma viscosity and erythrocyte aggregation index which were increased in blood stasis. Hematocrit and platelet aggregation were reduced while the prothrombin time was delayed. So this natural food coloring agent could be a great value in the prevention of hemorheological disorders-associated diseases in at risk patients. [36]

Antioxidant Activity

Antioxidative capacity of *C. tinctorius* were evaluated by determining its effect on 2,2-diphenyl-1- picrylhydrazyl (DPPH) radical scavenging and ferric reduction. [37] In both assays, aqueous extract of the flowers exhibited high antioxidant activity. DPPH scavenging effect was 96.65%. Total phenolic content from the flowers was determined as 2.12 and 1.32 g/100 g for methanolic and aqueous extracts respectively. [38] As the flowers contained high phenolic compounds including it confirmed that they have an important role in antioxidant activities. Ethanol extract of safflower seeds inhibited low density lipoprotein (LDL) oxidation induced in vitro by an azo-containing free-radical initiator V70 or copper ions. Two serotonin derivatives, N-(p-coumaroyl) serotonin, and N-feruloylserotonin and their glucoside derivatives were identified as the major phenolic and active constituents of the extract. It was demonstrate that these serotonin derivatives were absorbed into circulation and attenuate atherosclerotic lesion development possibly because of the inhibition of oxidized LDL formation through their strong antioxidative activity. [39]

Hepatoprotective Activity

The hepatoprotective study was done in-vivo using CCl_4 which is a known hepatotoxic. Carbon tetrachloride (CCl_4) is reported to produce trichloromethyl radical (CCl_3), which commences the oxidation of macromolecules and lipids leading to oxidative stress. In this experiment, result showed that pre-treatment with extract of safflower at dose 200mg/kg restored the biochemical parameters near the normal level compared with CCl_4 treated group. While the level of inflammatory mediator TNF-α and IL-6 was significantly decreased in animals pretreated with extract of safflower compared with CCl_4 treated rats. Histopathological finding in this study agrees with earlier reports which improved that CCl_4 causes necrosis, mononuclear cell infiltration, steatosis, foamy degeneration of hepatocytes. [40] Liver tissue of rats treated with extract of safflower at dose 200mg/kg for 30 successive days prior to CCl_4 administration showed an apparently normal organ with few necrotized hepatocytes and mild steatosis. [41] It is concluded that the hepatoprotective effect of *C. tinctorius* occur as plant contains polyphenols and flavonoids includes carthamin, quercetin, kaempferol and phenolic acids includes caffeic acid [42-43] and these compounds are responsible for antioxidant, and anti-inflammatory effects.

CONCLUSION

Despite the numerous uses and pharmacological activities of safflower it remained as ignored crop. Therefore we are more cautious and try to find out metal stress responded safflower verities and there further uses for commercial purpose. The objective of this review has been to illustrate the pharmacological and industrial importance of safflower with the exploration of *C. tinctorius* various properties to be employed in more new therapeutic drugs.

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