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PHYTOCONSTITUENTS, PHARMACOLOGICAL AND TRADITIONAL USES OF *CROCUSSATIVUS* Linn.: AN UPDATED REVIEW

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Abstract

Crocus sativus Linn., (family- Iridaceae) commonly known as saffron (Kesar), is grown widely in tropical and subtropical regions and is used both in the home and for medicine. Various chemical constituents present in the stigma of *Crocus sativus*, including crocetin (**14**), crocin (**15**), safranal (**16**) and picrocrocin (**17**) which are very important volatile and aromatic compounds. The presence of these constituents makes the herb very costly and imparts different medicinal properties to it. Since prehistoric times, saffron is used as a traditional/ herbal medicine in Asian countries. It is reported that *Crocus sativus* L. has antioxidant, aphrodisiac, antigenotoxic, antiproliferative, anxiolytic, anticonvulsant, antidepressant, antinociceptive, hypotensive, anti-inflammatory and relaxant effects. In this review, a comprehensive detail of the salient features, chemical constituents, and therapeutic uses of *C. sativus* L. has been highlighted.

Keywords: Saffron, Crocetin, *Crocus sativus* L., Crocin, Safranal

1. Introduction

One of the foremost costly herbs in the world, Crocus sativus from the family Iridaceae and is mostly called Saffron. From the French term 'Saffran', the word saffron has been derived, which was acquired from 'safranum', which is a Latin word, and from the Arabic word 'asfar' (meaning 'yellow').[1] It is widely distributed in Iran and Spain, but is also cultivated on a large scale in Africa, Greece, India, and China. Crocus sativus prefers well-drained soils to grow and is an autumn flowering herb. This herb usually flowers in October month and mostly in leaf form from October to May.1 It has hermaphrodite, light purple flowers. The best feature of the light purple saffron flowers are the three threadlike reddish-colored stigmas (25-30 mm long), drooping over the petals towards the end of the carpels.[2] This stigma part of the Crocus sativus flower is the most important and has been used as a spice and as a natural pigment.[3,4] The flower also has three yellow stamens, which are not collected as it has no active components. Crocus sativus blooms once a year and within a short period of time it has to be collected. The flowers can be hand-picked from October to November in 3 to 4 weeks. The high price of saffron

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is related to its method of cultivation.[5] The corms, or bulb, which is the underground part of the plant, is used to produce new plants, and each bulb produces one to seven flowers. It requires18 °C for germination and it requires nearly 1-6 months and nearly 3 years is required to flower.[6,7] The chemicals picrocrocin and safranal are responsible for the peculiar hay-like fragrance and the bitter taste of saffron.[8] Crocin, Picrocrocin, and safranal present in saffron are responsible for the highest value of saffron stigmas.[9,10]

Traditional Usage

In folk medicine and in ayurveda, Crocus sativus L. (Saffron) stigmas were used for various activities like aphrodisiac, antispasmodic, expectorant, antidepressant, and stomachic agent.[11-13] It was also used in several folk remedies to treat scarlet fever, smallpox, colds, asthma, and eye and heart ailments.[14-16] It was used in many opioid formulations to relieve pain from the 16th to 19th centuries.[17]

2. Chemistry and Phytoconstituents

Crocus sativusL. (saffron) contains primary metabolites such as carbohydrates, minerals, fats, vitamins, and many volatile and non-volatile components [10] as sown in Figure-1**.** Its phytochemistry has been extensively studied, revealing the presence of various secondary metabolites such as apcarotenoids, flavonoids, anthocyanins and phenolic compounds. The apocarotenoids are mainly crocins, crocetin, picrocrocin, and safranal which is present in saffron.Crocins are responsible for the characteristic color of saffron and have antioxidant and anti-inflammatory properties Figure 2. These componentsinclude different α- and β-carotenesflavonoids,carotenoids (zeaxanthin) and lycopene.[18]However, the four main bioactive compounds of saffron are crocetin (8,8'-diapocarotene-8,8'-dioic acid 10), crocin (8,8'-diapocarotene-8,8'-dioic acid-bis -(6 -O - β-D-glucopyranosyl-D-glucopyranosyl ester), picrocrocin (4-beta-d-glucopyranosyloxy-2,6,6-trimethylcyclohex-1-ene-1- carboxaldehyde), safranal(2,6,6-trimethylcyclohexa-1,3-diene-1-carboxaldehyde).[19]Broken carotenoid compounds crocin and crocetin give *Crocus sativus*L. golden yellow-orange color. Safranal, an oxidation product of carotenoids, gives saffron its flavor, while picrocrocin, a glucoside, gives it its bitter taste.[18]

Crocin [20]**(15)** is one of the key components and is responsible for the color of saffron. Crocin can be a monoglycosyl or can be a diglycosyl polyene ester of crocetin and follows the class of hydrophilic carotenoids. Crocetin **(14)** is 8,8′-diapo-8,8′-carotenoic acid, which is a hydrophobic diterpenic dicarboxylic acid [21] Picrocrocin **(17)** is a bitter glucoside present in Saffron which is composed of a carbohydrate and an aldehyde submolecule Safranal **(16)**. Picrocrocin is the glycoside of the terpene aldehyde Safranal and is produced by oxidative cleavage of Carotenoid zeaxanthin **(19)**.[22]Safranal, the volatile oil that is responsible for the distinctive aroma of saffron and is less bitter than Picrocrocin [23,24]and consists of a majority volatile quantity in some fractions the dry saffron.[22] The second molecule responsible for the aroma of saffron is Lanierone (2-hydroxy-4,4,6-trimethyl-2,5-cyclohexadien-1-one) **(25)**, a pheromone and a volatile component, which imparts saffron a dried hay-like aroma. Although it is present in small quantities compared to Safranal, which gives the characteristic fragrance of saffron.[22]Dry saffron has to be stored in air-tight and light-resistant containers, as it is heat resistant and very pH sensitive and can be sensitive to light and oxidizing agents**.**

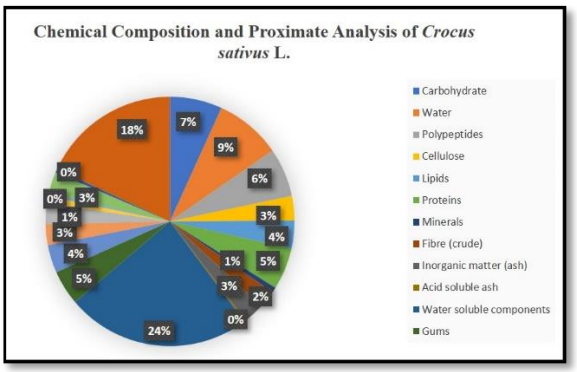


Fig 1. Chemical Composition and Proximate Analysis of *Crocus sativus* L. (Saffron)

Numerous studies have proved the presence of vitamins such as riboflavin and thiamine, anthocyanins, amino acids, proteins, starches, minerals, gums, flavonoids, and bioflavonoids in

Crocus sativus species.[26,27] Crocetin which is present in Saffron has been found to be mainly responsible for its therapeutic and pharmacological activities.[28]

3. Therapeutic Applications

Studies have reported that *Crocus sativus*L has various pharmacological and therapeutic activities.[29,30]The therapeutic activities of saffron is mainly due the presence of apocarotenoids such as crocin, crocetin, picrocrocin and safranal. Other bioactive compounds like anthocyanins, flavonoids and phenolics are also responsible for its therapeutic activities. This valuable herb can be put to medicinal use as

Anticancer and antigenototoxic agent. Among the main plant components of *Crocus sativus* (crocetin, picrocrocin, crocin and safranal), crocin and safranal are the only components that show excellent therapeutic activity against cancer and can prevent tumor cell proliferation. Many studies have reported that *Crocus sativus* crocetin exhibits significant antiproliferative activity. It also demonstrated inhibition in cellular RNA and DNA synthesis. *Crocus sativus* is found to reduce the viability of HeLa cells in a dose-dependent manner. Crocetin shows a dose-dependent reduction in breast cancer cell proliferation. Crocin from *Crocus sativus* also can significantly inhibit cell proliferation in colorectal cancer cells. These studies proposed that isolated carotenoid components and saffron itself might be used as potential chemo preventive agents against cancer.[30,31]

Antihypertensive agent. Many investigations showed the effect of *Crocus sativus*L. flower extract on blood pressure when tested in rats. Various extracts of *Crocus sativus* petals showed a dose-dependent reduction in basal blood pressure.[32] The flavonoids and polyphenols present in*Crocus sativus* can help with cardiovascular regulations. Crocin isolated from *Crocus sativus* showed a significant reduction in hypertension when tested in rats.[32,33]

Anticonvulsant agent. Many studies report that the ethanolic extract of *Crocus sativus* can possess an anticonvulsant effect when tested in mice. In many countries, *Crocus sativus* had been used traditionally as an anticonvulsant agent. It was shown that *Crocus sativus* extracts decreased motor activity in mice and exhibited extended sleeping time. This activity shown by the extracts may be due to secondary metabolites such as crocin, crocetn, and safranal present in *Crocus sativus*. Studies have shown that safranal can delay the onset of tonic convulsions, shorten the duration of seizures, and protect mice from death in a dose-dependent manner. Crocin did not show anticonvulsant activities with dose of 22 mg / kg, ip .[34]

Antitussive agent. The *Crocus sativus* exhibited antitussive activity when tested in Guinea pigs. The ethanolic extracts of *Crocus sativus* proved to reduce the number of coughs in a dose-dependent manner when tested. There was no antitussive activity with the secondary metabolite crocine when tested.[35]

Anxiolytic agent. The anxiolytic properties of isolated crocin and safranal were assessed by the elevated plus maze test, and locomotor activity was assessed by the open field test and motor coordination with the rotarod test. There was a dose-dependent reduction in locomotor activity by the aqueous extract. No anxiolytic, hypnotic, or myorelaxation effects were demonstrated with crocin. Safranal did not demonstrate any effects on motor coordination. But there were significant axiolytic and hypnotic effects shown by the aqueous extract and the Safranal.[36]

Antidepressant agent. Ethanolic extracts of*Crocus sativus petals* were evaluated for antidepressant activity using a forced swim test against the standard drug fluoxetine HCL. These extracts improved mobility time in mice compared to the control group. The study proved that *Crocus sativus* petals are effective in treating mild to moderate depression.[37,38]*Crocus sativus* petals have been shown to have good antidepressant activity in comparison to its stigma.[39]

Relaxant agent. Ethanolic and water extracts of *Crocus sativus* showed a significant relaxant effect in a dose-dependent manner when compared with theophylline. Safranal also proved to possess relaxant activity, but compared with the extract it showed less activity. The extracts also showed a relaxant effect on the smooth muscles of the trachea. Crocetin also has vaso relaxation in endothelial vessels.[40]

Anti-Alzheimer's Agent. Saffron contains a carotenoid called transcrocin-4, which is an ester of crocetin and can inhibit β- fibrillogenesis which is produced by the oxidation of fibrils of amyloid β -peptide fibrils in Alzheimer's disease. Studies

proved that the extracts of *C. sativus* stigma can inhibit this in a dose-dependent manner.[41]

Hypolipidemic agent. It is proved that the *Crocus sativus* extracts exhibit lipid lowering effects. It can be due to the effect of the secondary metabolite crocin by obstructing pancreatic lipase, thus inhibiting fat and cholesterol absorption. Studies shows the extracts of saffron can reduce the elevated concentrations of lipid in the serum.[42]

Antinociceptive effect: This effect of the various extracts of *Crocus sativus* stigma and petals were evaluated using writhing test and hot plate method. Both stigma and petal extracts produced significant antinociceptive effect.The presence of safranal in saffron is what gives it its strong antinociceptive properties.[28]

Anti-inflammatory agent. It has been reported that the anti-inflammatory effects of stigmas and saffron petals were assessed using xylene-induced ear edema in mice and formalin-induced edema in rat paws. This study supports the traditional use of saffron in anti-edema drugs. [28]

Antioxidant agent. The radical scavenging activity of Saffron is evaluated in the alcoholic extract and for its metabolites Safranal and Crocin. The results showed significant radical scavenging activity; henceforth, it may be used in cosmetics as anti-aging and also as a food supplement.[43]The secondary metabolite of saffron, Crocin, possessed a greater radical scavenging activity compared to alpha tocopherol in some studies.[44]

Antipruritic and emollient agent. Numerous studies have shown that topical preparations of *Crocus sativus* are effective in atopic dermatitis, ichthyosis vulgaris, and other less severe dry skin conditions.[45]

Cardioprotective agent. Saffron and its secondary metabolite crocetin, shows cardio protective effects by decreasing lactate dehydrogenase which is a cardiac marker, and increasing the mitochondrial potential of norepinephrine-treated cardiomyocytes.[29,46] The calcium-antagonizing effects of saffron have also been reported. It can inhibit the extracellular Ca^{2+} entry via the receptor-mediated Ca^{2+} channels and voltage-gated Ca^{2+} channels.[47] Crocetin has been shown to have good antioxidant activity and, therefore, can prevent norepinephrine-induced cardiac hypertrophy. Increased levels of antioxidant enzymes also significantly improved norepinephrine-induced myocardial changes.[47]

Anti-diabetic agent. Anti-diabetic activity is evaluated in Crocetin, which is the main secondary metabolite of Saffron.[48] The extract of *Crocus sativus* has been studied for its antidiabetic activity in rats. The extract was found to be effective in lowering fasting blood sugar levels in mild and severely diabetic rats. It has also been shown to lower HbA1C levels.[49]

Learning and Memory Potentiating Agent. The *Crocus sativus* extracts and crocin were evaluated for learning and memory potentiating skills. Crocin has been found to improve spatial learning and memory disturbance. It also possess neuro protective effects against oxidative stress. Some studies have shown that crocin can be used to inhibit amnesia in rats. It has also been shown to attenuate cognitive deficits in rats. Crocin improved the learning and memory abilities measured by MWM of deleterious effects in rats. Therefore, *Crocus sativus* and its constituents, mainly crocin, can improve memory and learning skills.[50,51]

Anti-Parkinson agent. It is suggested that Crocetin, the main constituent of *Crocus sativus,* can be used in the treatment of focal ischemia. This study was carried out in rats in a central cerebral artery occlusion model and demonstrated that decreased enzyme activity such as superoxide dismutase, Na + K + -ATPase, and catalase could be overcome by pre-treating animals with crocetin.[52] Many studies have shown that *Crocus sativus* and crocetin possess defensive activity on the development of Parkinson's disease.[53]

Respiratory ailments. *Crocus sativus* has shown a respiratory relaxing effect in guinea pigs by tracheal chain trial. The aqueous and ethanol extract and the constituent Safranal produced a good relaxing effect compared to theophylline and saline was used as negative control. It is suggested that Saffron can be used for various respiratory diseases such as asthma.[54,55]

Effects on uterus in menstrual disorders. *Crocus sativus* is traditionally used to regulate menstrual periods and soothe the lumber pains that occur along with menstrual periods. It is suggested that leucorrhoea and hysteria, which are concerns of women, can also be reduced using saffron. Saffron

pessaries could be used for painful conditions of the uterus.[56]

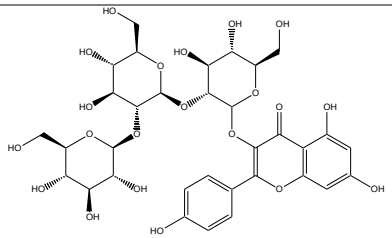
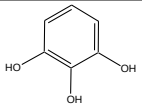
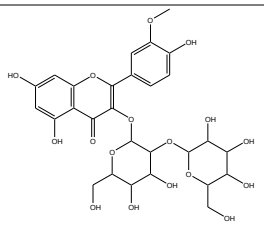
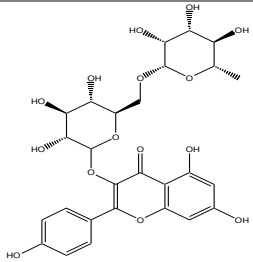
Effects on the Eye: Crocin, one of the main components of *Crocus sativus*, causes vasodilation, increases blood flow to the retina and choroid, and improves retinal function. May be used for ischemic retinopathy and age-related macular degeneration leading to blindness.[57]

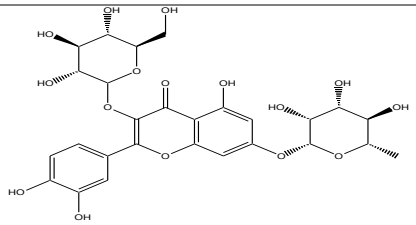
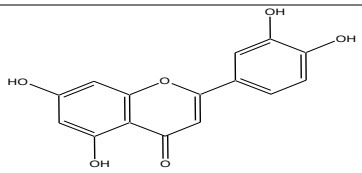
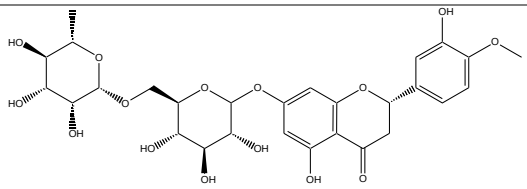
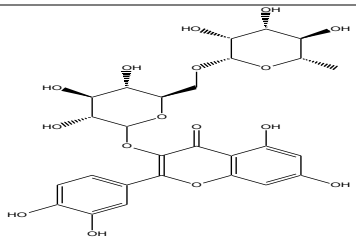
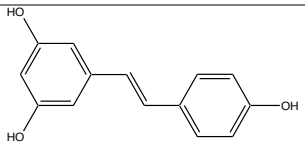
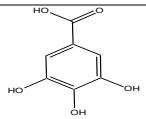
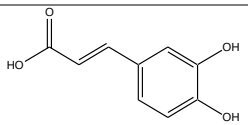
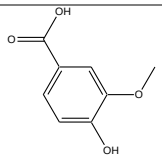
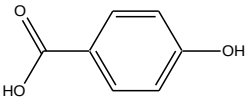
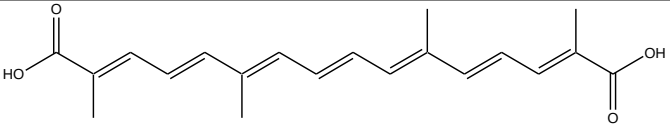
Effect on sexual dysfunction. The aphrodisiac activity of the extracts of Crocin, Safranal, and *Crocus sativus* was studied in male rats.The extracts of *Crocus sativus* and crocin exhibited a significant effect on sexual function in patients with erectile dysfunction with increased number and duration. Some studies have shown that *Crocus sativus* extracts can elevate testosterone levels. It can improve sexual function in both men and women with major depression.[58]

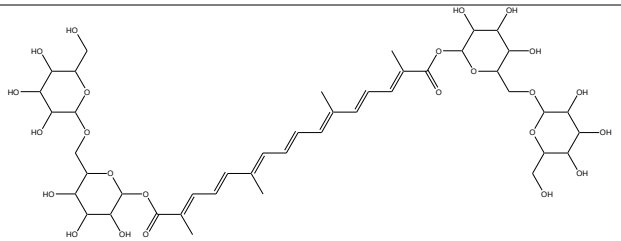
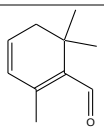
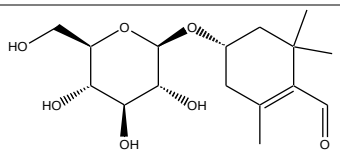
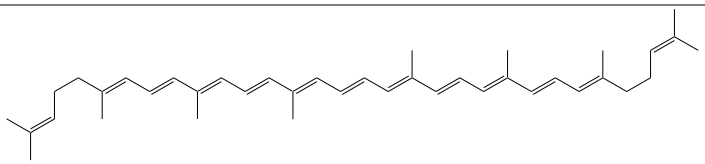
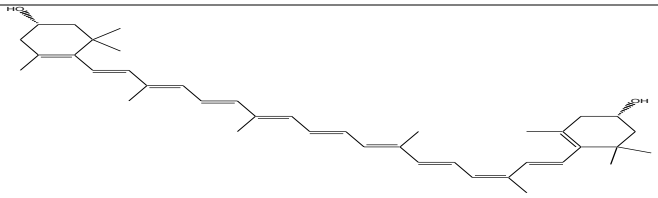
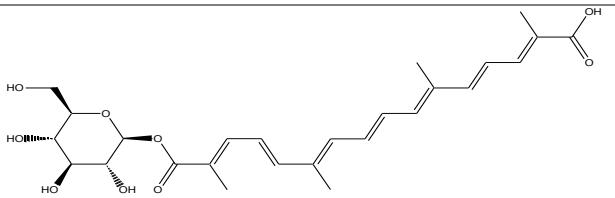
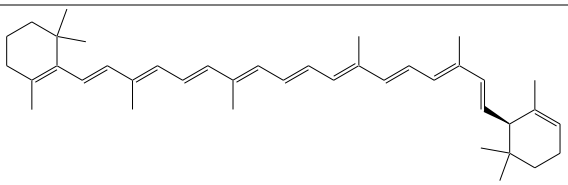
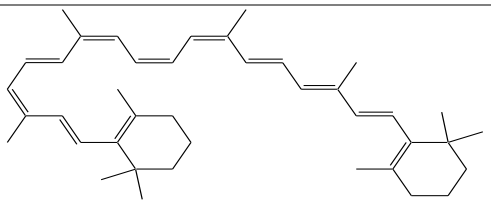
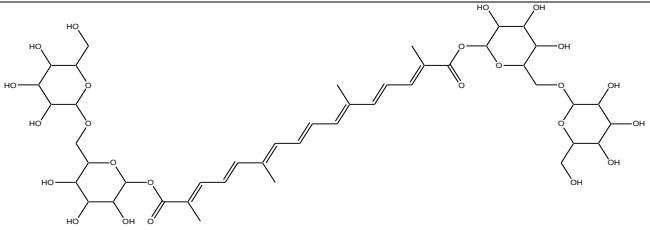
Schizophrenia: Several studies have examined the effects of *Crocus sativus* extracts on schizophrenia. Crocin has been found to attenuate ketamine-induced ataxia and hypermotility. The counteraction of crocin on ketamine-induced social isolation in social interaction is also studied. And it has been shown that there is no side effect in schizophrenic patients treated with crocin.[59]

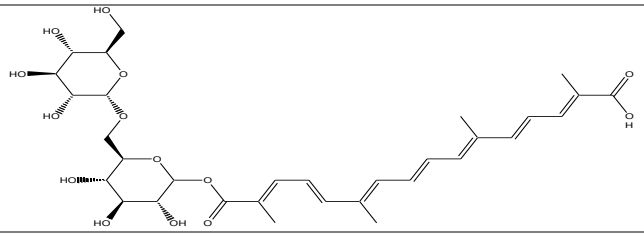
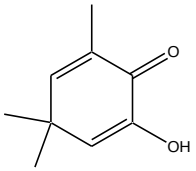
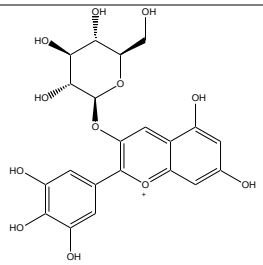
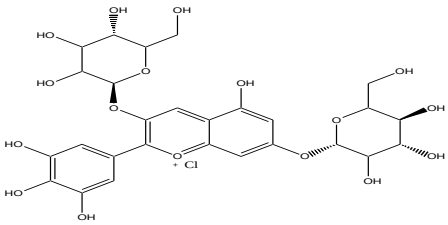
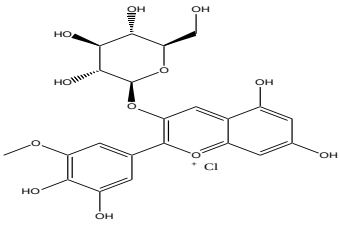
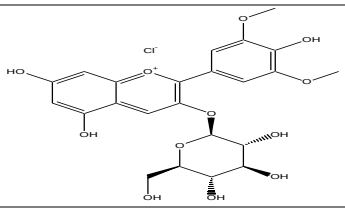
Effects on the spinal cord: 4 Spinal cord injury (SCI) is an injury caused by trauma rather than a disease that damages the spinal cord or nerve roots. The effects of crocin on chronic pain were investigated in an animal model (female Wistar rats). The treatment of chronic pain resulting from spinal cord injury has been shown to be preventable by crocin, which reduces calcitonin gene-related peptide (CGRP), a key mediator of pain and inflammation.[60]

Figure 2. Chemical constituents present in Crocus sativus L

SI No	Chemical constituents		References
I		**Flavonoids**	
1	Kaempferol 3-O-sophoroside		
2	Pyrogallol		
3	Isorhamnetin 3-O-sophoroside		(25)
4	Kaempferol 3-O-rutinoside		

5	Quercetin 3-O-glucoside 7-O-rhamnoside		
6	Luteolin		
7	Hesperidin		(22,25)
8	Rutin		
II	**Phenolic compounds**		
9	Resveratrol		
10	Gallic acid		
11	Caffeic acid		(26,27)
12	Vanillic acid		
13	4-hydroxybenzoic acid		
III	**Carotenoids/Apo carotenoids**		
14	Crocetin		(18,22,25)

15	Crocin		
16	Safranal		
17	Picrocrocin		
18	Lycopene		
19	Zeaxanthin		
20	Crocetin beta-D-glucosyl ester		
21	α-Carotene		(26,27)
22	β-Carotene		
23	Crocetin digentiobiosyl ester		

24	Beta-D-Gentiobiosyl Crocetin		
IV	**Volatile component**		
25	Lanierone		(22)
V	**Anthocyanins**		
26	Delphinidin 3-O-glucoside		
27	Delphinidin 3,7-diglucoside		(22,25)
28	Petunidin 3-O-glucoside		
29	Malvidin 3-Glucoside		

4. Conflicts of interest

The authors disclose no conflicts of interest.

5. Formatting of funding sources

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