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REVIEW ARTICLE

Stigma and petals of *Crocus sativus* L.: Review and comparison of phytochemistry and pharmacology

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Crocus sativus L.;
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Abstract *Crocus sativus* L. (*C. sativus*), known as "plant gold ", has numerous functions in traditional Chinese medicine, including promoting blood circulation, removing blood stasis, cooling blood, detoxifying, relieving depression, and calming the nerves. Its stigma, the main medicinal part, performs extremely low yield and high price, thus the scarce resources, while its petals, the by-product, are usually discarded or employed as fertilizer or feed, resulting in huge waste, as the petals have been proved to contain various chemical components covering terpenoids, flavonoids, and glycosides, which exhibits pharmacological activities of analgesia, anti-inflammatory, cardiovascular protection, liver protection, and antidepressant. This paper aims to compare the material basis of the pharmacological similarities or differences between stigmas and petals, clarify their research status, and evaluate the potential application value of petals. As a by-product of a precious traditional herbal medicine, the petals of *C. sativus* have been elucidated in previous studies. This review explores the chemical constituents and pharmacological effect of stigma and petals of *C. sativus*, confirming their similar material bases, and the application prospect of petals.

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1. Introduction

Crocus sativus L. (*C. sativus*), a bulbous herb of the genus Crocus of the family Iridaceae, native to Iran, Spain, India and other countries, was introduced to China through Tibet (Basker and Negbi 2008), and first recorded in *Compendium of Materia Medica*. It has been employed as a natural traditional Chinese medicine for thousands of years. The historical records of Iranian traditional medicine take that *C. sativus* relieves headaches and toothache, and promotes diuresis, restoration, cosmetology, aphrodisiac, detoxification, antihypertensive, and blood circulation (Liu 2007, Shariatifar et al., 2014), while traditional Chinese medicine books record that *C. sativus* has the function of promot-

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ing blood circulation, removing blood stasis, cooling blood, detoxifying, relieving depression, and calming the nerves (Commission 2020). In addition, it is adopted as a high-grade dye owing to the carotenoids contained, while its unique aroma as a spice (Fabre 2003). There exist many studies on the pharmacological effect and chemical constituents of *C. sativus*, validating its role in preventing cardiovascular diseases such as ischemia reperfusion injury (Farjah et al., 2017), hyperlipidemia (Tajaddini et al., 2021), and atherosclerosis, and determining its main active components of terpenoids and flavonoids (Hatziagapiou and Lambrou 2018). Lambrianidou et al reviewed the anti-cancer effect of *C. sativus*, with crocin, crocetin, picrocrocin, and safranal serving as the main active component (Lambrianidou et al., 2020). In reality, only the stigma at the top of the 3 pistils in each *C. sativus* is rationally employed (Salehi et al., 2022). This part is completely harvested by hand, and only about 1 g of dry stigma can be obtained from about 90 flowers, which explains its extremely low yield (Serrano-Díaz et al., 2014). The petals, however, are usually used as fertilizer, fodder, or even discarded, leading to a huge waste.

The chemical constituents and pharmacological effect of the non-medicinal parts of *C. sativus* have caught the eyes of researchers, thus the growing reports on the petals of *C. sativus*. The chemical composition of petals is complex, including flavonoids and their glycosides, terpenoids and their glycosides, alkaloids, and organic acids, among which terpenoids and their glycoside are the main components (Chen and Yang 2018). Lu Zhuo et al. (Lv et al., 2021)explored the amino acids and trace elements in petals using an amino acid analyzer, inductively coupled plasma mass spectrometry (ICP-MS), Kjeldahl nitrogen analyzer, etc., revealing the 6 essential amino acids (threonine, valine, isoleucine, leucine, phenylalanine, and lysine) required by the human body, and 6 trace elements (chromium, iron, cobalt, copper, molybdenum and zinc). It also proved petals' role in antioxidation (Huang et al., 2013, Zhao and Qu 2013), cardiovascular system and nervous system protection (Khazdair et al., 2015), liver and kidney protection (Azizi et al., 2019), antifungal and cytotoxic effects, etc. (Chen and Yang, 2018).

Studies concerning *C. sativus* mostly focus on stigmas, with very few on petals. The review discusses the chemical constituents and pharmacological activities of petals with previous literature as reference, in the hope of providing theoretical support for better utilization, and giving an insight into the development and rational application of *C. sativus*.

2. Botany

C. sativus is native to southern Europe and was introduced to China through Tibet, where it is commonly cultivated throughout China, including Beijing, Shandong, Zhejiang, and Sichuan provinces. The plant is a perennial herb, and the 3 cm in diameter, the oblate-spherical build is covered in a membranous layer that is yellowish brown in cover. It contains 9–15 basal leaves that are banded, grayish-green, 15–20 cm long, and 2–3 mm wide, and have inverted margins, 4–5 membranous sheath-like leaves are enclosed within the base of the plexus. The flower's stalk is quite short and does not stick out above the surface. The ovary is narrowly spindle-shaped, and the stigma is orange-red, somewhat flattened, wedge-shaped at the apex, and shallowly serrated. Flowers begin to bloom in late October and open during the day before closing at night.

3. Chemistry and bioactivity of stigma and petals compounds

C. sativus is a mixture of various chemical constituents, including primary metabolites (like polysaccharides, proteins, fats, and vitamins), compounds of different classes of secondary metabolites (like carotenoids, monoterpenoids, flavonoids, and anthocyanins) (Masi et al., 2016), fat-soluble pigments represented by zeaxanthin, phytoene, phytoene, β-carotene, etc., volatile components represented by *C. sativus* aldehyde and isophorone, and flavonoids represented by kaempferol and its glycosides (Mykhailenko et al., 2019, Abu-Izneid et al., 2022). Metabolites with pharmacological activity are classified into four categories. The first refers to water-soluble crocus acid; the second crocin, the glycoside of crocetin, which is the colored component of *C. sativus* and its main component, as well as an uncommon water-soluble carotenoid (dicarboxylic acid polyene monosaccharide ester); the third picrocrocin, which is largely responsible for the bitterness of *C. sativus*; while the fourth safranal, which is a volatile oil that largely explains the characteristic odor and aroma of *C. sativus*. (Wang et al., 2015).

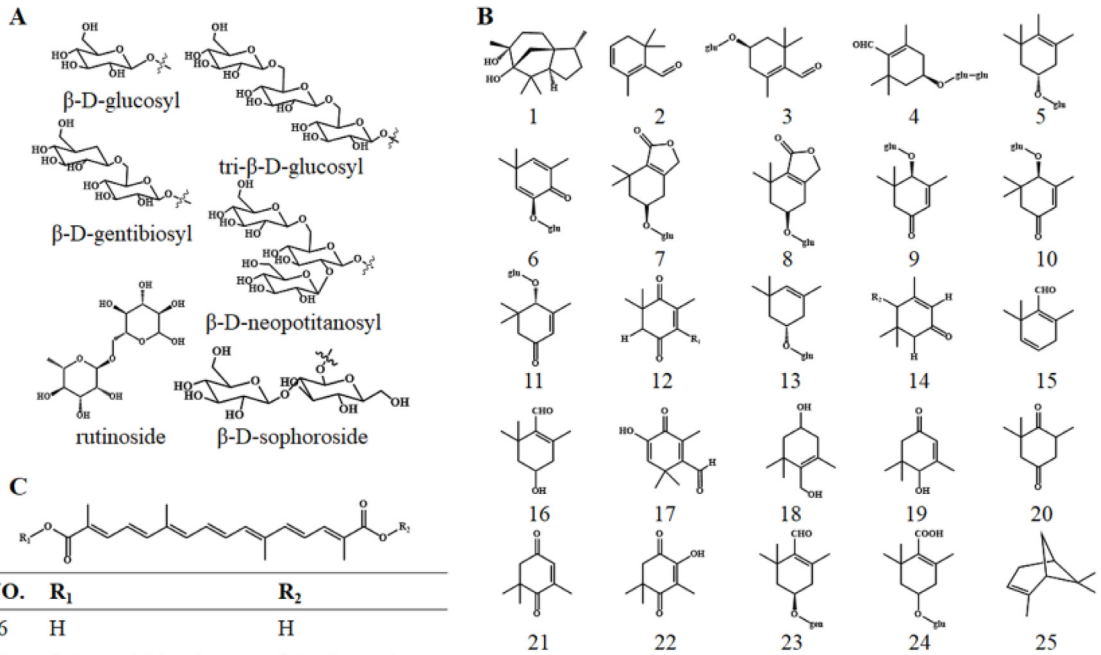
Despite the differences in the chemical components of petals and stigma, they share plentiful chemical components. The stigma contains more terpenoids, and among the 50 kinds of terpenoids collected, 36 observed in stigma cannot be found in petals, including 7 kinds of tetraterpenoids. Besides, crocin, a common component, is the only component in petals that has been reported (Wang et al., 2019). On the other hand, petals contain more flavonoids, which belong to chemical components with a higher proportion of common components in stigma and petals. Among the 43 flavonoids collected, 22 are chemical constituents isolated from petals, while 13 are common constituents of stigma and petals. The paper confirmed the chemical constituents of stigmas and petals, including 50 terpenoids, 43 flavonoids, 7 alkaloids, 5 phenylpropanoids, as well as 16 amino acids, 11 organic acids, and 2 steroids, most of which are conjugated with one or more glycosyl moieties to form glycoside esters, and the conjugated glycosyl structure is shown in Fig. 1A.

3.1. Terpenoids

Terpenoids act as the most characteristic and important phytochemicals of *C. sativus*, and the highest concentrations reported in the stigma of *C. sativus* are water-soluble crocetin and its glycoside esters conjugated with one or more glycosyls (crocin, crocetin-β-D-glucosyl ester, Dimethylcrocetin, etc.). Table 1 lists the 50 terpenoids and their glycosides in the stigma and petals of *C. sativus*, including 1 sesquiterpene, 24 monoterpenoids, 18 diterpenoids, and 7 tetraterpenoids.

3.1.1. Sesquiterpenoids and monoterpenoids

One sesquiterpene (**1**) and 24 monoterpenoids (**2**–**25**) were identified from the stigma and petals (Fig. 1 B) represented by safranal (**2**) and picrocrocin (**3**), which explain the aroma and bitterness of *C. sativus*, respectively, while picrocrocin is the precursor of safranal (Li and Wu 2002, Li et al., 2004, Mounira et al., 2015). Cedrol (**1**), as sesquiterpene alcohol isolated from petal species, is the only sesquiterpene compound that exists only in petals. Among the 24 monoterpenoids, 23 can be found in stigma, and picrocrocin (**3**) is the only common component of stigma and petals (Table 1).

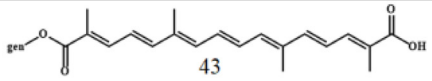


C

NO.	R_1	R_2
26	H	H
27	β-D-gentiobiosyl	β-D-glucosyl
28	β-D-glucosyl	β-D-glucosyl
29	β-D-glucosyl	H
31	β-D-gentiobiosyl	H
32	β-D-triglucoside	β-D-gentibiosyl
33	H	CH_3
34	β-D-gentabiosyl	β-D-gentabiosyl
35	β-D-gentiobiosil	β-D-gentiobiosil
37	β-D-glucopyranoylmethyl	H
38	CH_3	CH_3
39	β-D-neopolitanosyl	β-D-gentiobiosyl
41	β-D-gentiobiosil	H

D

NO.	R_1	R_2
30	β-D-glucosyl	H
36	β-D-gentiobiosil	β-D-gentiobiosil
40	β-D-gentiobiosyl	β-D-gentiobiosyl
42	β-D-gentiobiosil	H



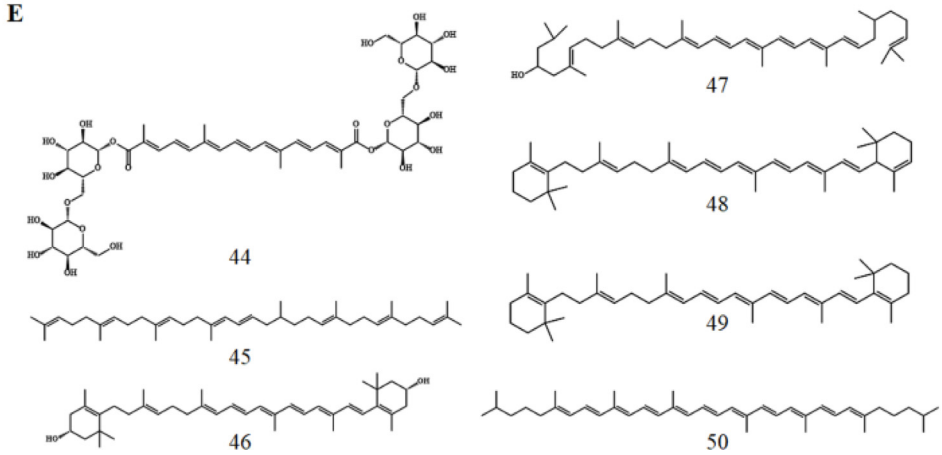


Fig. 1 Conjugated glycosyl structure (A) and Chemical Structures of terpenoids (B: sesquiterpenoids and monoterpenoids; C: *trans*-diterpenoid; D: *cis*-diterpenoid; E: tetraterpenoids).

3.1.2. Diterpenoids

Diterpenoids, one of the most important active components in *C. sativus*, refer to esters formed by the carboxyl group of crocetin (**26**) and the hydroxyl group of glucose, gentiobiose, and triglucose. A total of 18 compounds are summarized (Table 1).

Table 1 Sesquiterpenoids and Monoterpenoids isolated from *Crocus sativus* L.

Species	NO.	Compound	Molecular formula	Part of plant	Reference
Sesquiterpenoids					
	1	Cedrol	$C_{15}H_{26}O$	petals	(Wang et al., 2012)
Monoterpenoids					
	2	Safranal	$C_{10}H_{14}O$	stigmas	(Tarantilis and Polissiou 1997, Yu et al., 2008, Li et al., 2017)
	3	Picrocrocin	$C_{16}H_{26}O_7$	stigmas petals	(Rios et al., 1996, Zhou et al., 2011, Montoro et al., 2012, Christodoulou et al., 2015)
	4	(4R)-4-hydroxy-2,6,6-trimethylcyclohex-1-enecarbaldehyde 4-O-[β-D-glucopyranosyl (1 → 3)-β-D-glucopyranoside	$C_{22}H_{36}O_{12}$	stigmas	(Straubinger 1997)
	5	(4R)-4-hydroxy-2,6,6-trimethylcyclohex-1-enecarboxylicacid O-β-D-glucopyranoside	$C_{16}H_{26}O_8$	stigmas	(Straubinger 1997)
	6	6-hydroxy-3-(hydroxymethyl)-2,4,4-trimethylcyclohexa-2,5-dienone 6-O-β-D-glucopyranoside	$C_{16}H_{23}O_8$	stigmas	(Straubinger et al., 1998, Li et al., 2004)
	7	(5S)-5-hydroxy-7,7-dimethyl-4,5,6,7-tetrahydro-3Hisobenzofuran-1-one O-β-D-glucopyranoside	$C_{16}H_{24}O_8$	stigmas	(Straubinger 1997, Straubinger et al., 1998)
	8	(5S) -5-hydroxy-7,7-dimethyl-4,5,6,7-tetrahydro-3Hisobenzo-Furanone 5-O-β-D-gentibioside	$C_{22}H_{35}O_{13}$	stigmas	(Carmona et al., 2006)
	9	(4S) -4-hydroxymethyl-3,5,5-trimethyl-cyclohex-2-en-1-one 4-O-β-D-gentibioside	$C_{22}H_{36}O_{12}$	stigmas	(Carmona et al., 2006)
	10	(4R)-4-hydroxy-3,5,5-trimethylcyclohex-2-enone 4-O-β-D-glucopyranoside	$C_{15}H_{24}O_7$	stigmas	(Straubinger 1997, Straubinger et al., 1998)
	11	(4S)-4-hydroxy-3,5,5-trimethylcyclohex-2-enone 4-O-β-D-glucopyranoside	$C_{15}H_{24}O_7$	stigmas	(Straubinger 1997)
	12	(2Z)-3-methylpent-2-enedioic acid1-[1-(2,4,4-trimethyl-3,6-dioxocyclohexenyloxy)-O-β-D-glucopyranosid-6-yl] ester	$C_{21}H_{28}O_{11}$	stigmas	(Straubinger 1997)
	13	(1R)- 3,5,5-trimethylcyclohex-3-enol O-β-D-glucopyranoside	$C_{15}H_{26}O_6$	stigmas	(Straubinger 1997)
	14	(4S,3′R)-4-Hydroxy-4-(3′-hydroxy-1′-butenyl)-3,5,5-trimethyl-2-cyclohexen-1-one 3′-O-β-D-glucopyranoside	$C_{19}H_{30}O_8$	stigmas	(Straubinger 1997)
	15	2,6,6-trimethyl-1,4-cyclohexadiene-1-carboxaldehyde	$C_{10}H_{14}O$	stigmas	(Christodoulou et al., 2015)
	16	2,6,6-trimethyl-4-hydroxy-1-cyclohexen-1-carboxaldehyde	$C_{10}H_{16}O_2$	stigmas	(Zarghami and Heinz 1971)
	17	2,4,4-trimethyl-3-formyl-6-hydroxy-2,5-cylohexadien-1-one	$C_{10}H_{12}O_3$	stigmas	(Zarghami and Heinz 1971)
	18	4-hydroxymethyl-3,5,5-trimethylcyclohex-3-enol	$C_{10}H_{18}O_2$	stigmas	(Li and Wu 2002)
	19	3,5,5-trimethyl-4-hydroxy-1-cyclohexanon-2-ene	$C_9H_{14}O_2$	stigmas	(Zarghami and Heinz 1971)
	20	3,5,5-trimethyl-1,4-cyclohexadione	$C_9H_{14}O_2$	stigmas	(Zarghami and Heinz 1971)
	21	3,5,5-trimethyl-1,4-cyclohexadion-2-ene	$C_9H_{12}O_2$	stigmas	(Zarghami and Heinz 1971)
	22	3,5,5-trimethyl-2-hydroxy-1,4-cyclohexadion-2-ene	$C_9H_{12}O_3$	stigmas	(Zarghami and Heinz 1971)
	23	(4R) -4-Hydroxy-2,6,6-trimethylcyclohex-1-enecarbaldehyde-O-β-D-gentiobioside	$C_{26}H_{34}O_{11}$	stigmas	(Li and Wu 2002, Tung and Shoyama 2013)
	24	4-Hydroxy-2,6,6-trimethylcyclohex-1-enecarboxylic acid-O-β-D-glucopyranoside	$C_{16}H_{26}O_8$	stigmas	(Straubinger 1997)
	25	α-Pinene	$C_{10}H_{16}$	stigmas	(Mounira 2014)
Diterpenoids					
	26	Crocetin	$C_{20}H_{24}O_4$	stigmas petals	(Montoro et al., 2012, Christodoulou et al., 2015, Garcia-Rodriguez et al., 2016)
	27	crocetin-(β-D-gentiobiosyl)-(β-D-glucosyl)-ester	$C_{38}H_{54}O_{19}$	stigmas petals	(Pfander and Wittwer 1975, Pfister et al., 1996, Carmona et al., 2006, Montoro et al., 2012)
	28	crocetin di-(β-D-glucosyl) ester	$C_{32}H_{44}O_{14}$	stigmas petals	(Pfander and Wittwer 1975, Pfister et al., 1996, Rios et al., 1996, Montoro et al., 2012)

Table 1 (*continued*)

Species	NO.	Compound	Molecular formula	Part of plant	Reference
	29	*trans*-crocetin (β-D-glucosyl) ester	$C_{26}H_{34}O_9$	stigmas petals	(Montoro et al., 2012, García-Rodríguez et al., 2017)
	30	*cis*-crocetin (β-D-glucosyl) ester	$C_{26}H_{34}O_9$	stigmas petals	(Montoro et al., 2012, García-Rodríguez et al., 2017)
	31	crocetin-mono-(β-D-gentiobiosyl)-ester	$C_{32}H_{44}O_{14}$	stigmas	(Pfander and Wittwer 1975, Pfister et al., 1996)
	32	crocetin (β-D-triglucoside)-(β-D-gentibiosyl) ester	$C_{50}H_{74}O_{29}$	stigmas	(Carmona et al., 2006, Zhou et al., 2011)
	33	Methyl-crocetin	$C_{21}H_{26}O_4$	stigmas	(Christodoulou et al., 2015)
	34	crocetin di(β-D-gentabiosyl) ester	$C_{44}H_{64}O_{24}$	petals	(Montoro et al., 2012)
	35	*trans*-crocetin di-(β-D-gentiobiosil) ester	$C_{44}H_{64}O_{24}$	stigmas petals	(Tarantilis et al., 1995, Carmona et al., 2006, Montoro et al., 2012)
	36	*cis*-crocetin di-(β-D-gentiobiosil) ester	$C_{44}H_{64}O_{24}$	stigmas petals	(Tarantilis et al., 1995, Carmona et al., 2006, Montoro et al., 2012)
	37	crocetin β-D-glucopyranoylmethyl ester	$C_{27}H_{36}O_9$	stigmas	(Moraga et al., 2009, Rubio-Moraga et al., 2009, Zhou et al., 2011)
	38	Dimethylcrocetin	$C_{22}H_{28}O_4$	stigmas	(Zhou et al., 2011, García-Rodríguez et al., 2017)
	39	crocetin (β-D-neopolitanosyl)-(β-D-gentiobiosyl) ester	$C_{50}H_{74}O_{28}$	stigmas	(Carmona et al., 2006, Carmona et al., 2006)
	40	*cis*-crocetin di-(β-D-gentiobiosyl) ester	$C_{44}H_{64}O_{24}$	stigmas petals	(Tarantilis et al., 1995, Carmona et al., 2006, Carmona et al., 2006)
	41	*trans*-crocetin (β-D-gentiobiosil) ester	$C_{32}H_{44}O_{14}$	stigmas petals	(Tarantilis et al., 1995, Carmona et al., 2006, Carmona et al., 2006)
	42	*cis*-crocetin (β-D-gentiobiosil) ester	$C_{32}H_{44}O_{14}$	stigmas petals	(Tarantilis et al., 1995, Carmona et al., 2006, Carmona et al., 2006)
	43	crocetin-1-al 1-O-β-D-gentiobiosyl ester	$C_{31}H_{44}O_{13}$	stigmas	(Pfander and Schurtenberger 1982, Carmona et al., 2006)
Tetraterpenoids					
	44	Crocin	$C_{44}H_{64}O_{24}$	stigmas petals	(Termentzi and Kokkalou 2008, Georgiadou et al., 2012, Christodoulou et al., 2015, Shahi et al., 2016, Wang et al., 2019)
	45	Phytoene	$C_{40}H_{64}$	stigmas	(Wang et al., 2014, Andrade et al., 2016)
	46	Zeaxanthin	$C_{40}H_{56}O_2$	stigmas	(Pfander and Schurtenberger 1982, Andrade et al., 2016)
	47	Lycopene	$C_{40}H_{56}$	stigmas	(Wang et al., 2014, Andrade et al., 2016)
	48	α-carotene	$C_{40}H_{56}$	stigmas	(Pfander and Schurtenberger 1982, Pitsikas et al., 2008, Andrade et al., 2016)
	49	β-Carotene	$C_{40}H_{56}$	stigmas	(Pfander and Schurtenberger 1982, Andrade et al., 2016)
	50	Tetrahydrolycopene	$C_{40}H_{60}$	stigmas	(Pfander and Schurtenberger 1982, Andrade et al., 2016)

It's reported that there are 4 kinds of crocetin compounds containing cis and trans, and the difference between trans (Fig. 1C) and cis (Fig. 1D) lies in the configuration of C-13 on crocetin (**26**). Tung and Shoyama isolated a special crocetin (**26**) ester compound, *trans*-crocetin di- (β-D-gentiobiosil) ester (**35**), from the stigma of *C. sativus* in 2012(Tung and Shoyama 2013). Among the 16 kinds of diterpenoids, 7 are commonly found in stigma and petal, and 8 are isolated and identified from the stigma, leaving crocetin di (β-D-gentabiosyl) ester (**34**) the only one isolated from petals.

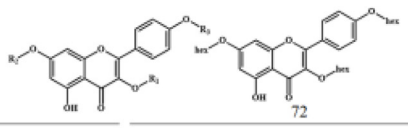
3.1.3. Tetraterpenoids

The various fat-soluble carotenoids that have been isolated and identified from the stigma and petals mainly include the following 7 compounds (Fig. 1E), crocin (**44**), phytoene (**45**), zeaxanthin (**46**), lycopene (**47**), α-carotene (**48**), β-carotene (**49**), and tetrahydrolycopene (**50**). The tetraterpenoids that mainly come from the stigma are represented by crocin (**44**), which is one of the main active components in the stigma (Maggi et al., 2022), and the only tetraterpenoid shared by stigma and petals (Table 1). Zeaxanthin (**46**) refers to the precursor compound of crocin (**44**), picrocrocin (**3**), and safranal (**2**) (Pfander and Schurtenberger 1982, Wang et al., 2014, Several 2016).

3.2. Flavonoids

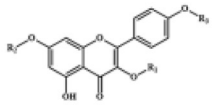
As the second most abundant bioactive in *C. sativus*, flavonoids perform anti-inflammatory, antioxidant, antibacterial, and cancer chemopreventive activities. They mainly consist

A



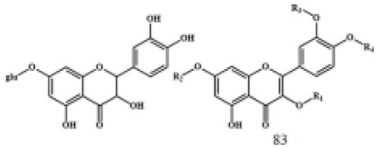
NO.	R_1	R_2	R_3
51	H	H	H
52	β-D-glucopyranoside	H	H
53	H	β-D-glucopyranoside	H
54	bi-hexoside	bi-hexoside	H
55	hexoside	(acetyl)-hexoside	H
56	β-D-glucopyranoside	β-D-glucopyranoside	H
57	(p-coumaroyl)-bihexoside	H	H
58	(acetyl-) hexoside	hexoside	H
59	H	hexoside	H
60	hexoside	H	H
61	(acetyl)- hexoside	H	H
62	β-D- (2-O-β-D-6-O-acetylglucosyl) - glucopyranoside	H	H
63	β-D-sophoroside	H	H
64	H	β-D-sophoroside	H
65	β-D- (2-O-β-D-glucosyl)glucopyranoside	H	H
66	β-D-glucopyranosyl-7-O-α-L-rhamnopyranoside	β-D-glucopyranoside	H
67	sophoroside	β-D-glucopyranoside	H
68	glucosid	glucosid	glucosid
69	β-D-(6-O-acetyl)-glucopyranoside	H	H
70	β-D-(6-O-acetyl)glucopyranoside	β-D-glucopyranoside	H
71	β-D-(2-O-β-D-6-acetylglucosyl)glucopyranoside	β-D-glucopyranoside	H
73	bi-hexoside	H	H
74	（2-O-β-D-glucopyranosyl）rhamnopyranoside	B-D-glucopyranoside	H
75	rutinoside	β-D-glucopyranoside	H

B



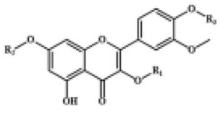
NO.	R_1	R_3	R_4
76	hexoside	H	H
77	deoxy hexoside	H	OCH_3

C



NO.	R_1	R_2	R_3	R_4
78	H	H	H	H
79	β-D-glucopyranoside	β-D-glucopyranoside	H	H
80	(p-coumaroyl)-hexoside	H	H	H
81	OCH3	bi-hexoside	OCH_3	OCH_3
82	β-D-glucopyranoside	H	H	H

D



NO.	R_1	R_2	R_3
85	H	H	H
86	β-D-glucopyranoside	β-D-glucopyranoside	H
87	β-D-glucopyranoside	H	H
88	glucoside	H	H
89	H	H	α-L-rhamnopyranosyl(1 →2)-β-D-glucopyranoside
90	glucoside	H	glucoside

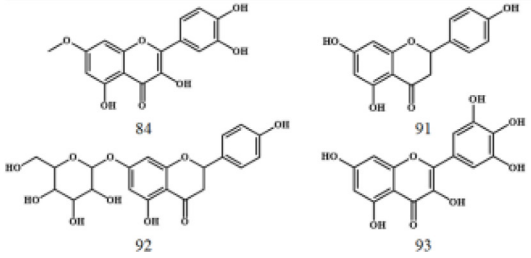


Fig. 2 Chemical structures of flavonoids and their glycosides (A: Kaempferol and its glycosides; B: Dihydrokaempferol and its glycosides; C: Quercetin and its glycosides; D: Isorhamnetin and its glycosides).

of flavonoids and their glycosides, flavonols, and their glycosides (Fig. 2), among which kaempferol and its glycosides abound (Fig. 2A) (Nørbæk et al., 2002, Li et al., 2004). Though distributed in both stigma and petals, the most abundant species are observed in petals (Yu et al., 2008, Moraga et al., 2009, Montoro et al., 2012). Among the 48 compounds (**51**–**93**) collected (Table 2), 24 are chemical constituents identified from petals, while 15 are common constituents.

3.3. Alkaloids

Alkaloid compounds are also shared by stigma and petals (Fig. 3A). Li et al. isolated and identified seven alkaloids (**94**–**100**) from both parts (Li and Wu 2002), among which 5-methyl uracil (**94**), pyridin-3-ylmethanol (**95**), and uracil (**96**) are only observed in stigma, while the other 4 (**97**–**100**) are shared (Table 3). As a result, no alkaloid is unique to petals.

Table 2 Flavonoids isolated from *Crocus sativus* L.

Species	NO.	Compound	Molecular formula	Part of plant	Reference
Flavonoids					
	51	Kaempferol	$C_{15}H_{10}O_6$	stigmas petals	(Termentzi and Kokkalou 2008, Montoro et al., 2012, Ahrazem et al., 2015)
	52	kaempferol 3-O-β-D-glucopyranoside	$C_{21}H_{20}O_{11}$	stigmas petals	(Li et al., 2004, Montoro et al., 2012, Tung and Shoyama 2013, Liu et al., 2021)
	53	kaempferol 7-O-β-D-glucopyranoside	$C_{21}H_{20}O_{11}$	stigmas petals	(Montoro et al., 2012, Liu et al., 2021)
	54	kaempferol 7-O-bihexoside-3-O hexoside	$C_{33}H_{40}O_{21}$	petals	(Termentzi and Kokkalou 2008, Montoro et al., 2012)
	55	kaempferol 3-O-hexoside, 7-O-(acetyl)-hexoside	$C_{29}H_{33}O_{17}$	petals	(Termentzi and Kokkalou 2008, Montoro et al., 2012)
	56	kaempferol-3,7-di-O-β-D-glucopyranoside	$C_{27}H_{30}O_{16}$	petals	(Li et al., 2004, Termentzi and Kokkalou 2008, Montoro et al., 2012)
	57	kaempferol 3-O- (p-coumaroyl)-bihexoside	$C_{36}H_{36}O_{18}$	petals	(Termentzi and Kokkalou 2008, Montoro et al., 2012)
	58	kaempferol 3-O-(acetyl-) hexoside-7-O-hexoside	$C_{29}H_{33}O_{17}$	petals	(Termentzi and Kokkalou 2008, Montoro et al., 2012)
	59	kaempferol 7-O-hexoside	$C_{21}H_{20}O_{11}$	petals	(Termentzi and Kokkalou 2008)
	60	kaempferol 3-O-hexoside	$C_{21}H_{20}O_{11}$	petals	(Termentzi and Kokkalou 2008)
	61	kaempferol 3-O-(acetyl)- hexoside	$C_{23}H_{23}O_{12}$	petals	(Termentzi and Kokkalou 2008, Montoro et al., 2012)
	62	keampferol-3-O-β-D-(2-O-β-D-6-O-acetylglucosyl)-glucopyranoside	$C_{29}H_{32}O_{17}$	stigmas petals	(Li et al., 2004, Montoro et al., 2012)
	63	kaempferol-3-O-β-D-sophoroside	$C_{27}H_{30}O_{16}$	stigmas petals	(Moraga et al., 2009, Moraga et al., 2009, Tarantilis 2016)
	64	kaempferol 7-O-β-D-sophoroside	$C_{27}H_{30}O_{16}$	stigmas	(Tung and Shoyama 2013, Ahrazem et al., 2015, García-Rodríguez et al., 2017)
	65	kaempferol-3-O-β-D- (2-O-β-D-glucosyl) glucopyranoside	$C_{27}H_{30}O_{16}$	petals	(Li et al., 2004, Montoro et al., 2012)
	66	kaempferol-3-(O-β-D-glucopyranosyl-7-O-α-L-rhamnopyranoside)-7-O-β-D-glucopyranoside	$C_{33}H_{40}O_{20}$	petals	(Harborne and Williams 1984)
	67	kaempferol 3-O-sophoroside-7-O-β-D-glucopyranoside	$C_{33}H_{40}O_{21}$	stigmas	(Ahrazem et al., 2015, Christodoulou et al., 2015)
	68	kaempferol-3,7,4′-triglucosid	$C_{33}H_{40}O_{21}$	stigmas	(Ahrazem et al., 2015)
	69	kaempferol 3-O-β-D-(6-O-acetyl)-glucopyranoside	$C_{23}H_{22}O_{12}$	stigmas	(Slimestad et al., 1995, Li et al., 2004)
	70	kaempferol-3-O-β-D-(6-O-acetyl)glucopyranoside-7-O-β-D-glucopyranoside	$C_{29}H_{33}O_{17}$	stigmas	(Veit et al., 1995, Li et al., 2004)
	71	kaempferol-3-O-β-D-(2-O-β-D-6-acetylglucosyl) glucopyranoside-7-O-β-D-glucopyranoside	$C_{35}H_{43}O_{22}$	stigmas petals	(Han et al., 2001, Li et al., 2004, Montoro et al., 2008)
	72	kaempferol tetrahexoside	$C_{39}H_{50}O_{26}$	stigmas	(Carmona et al., 2007, Moraga et al., 2009, Moraga et al., 2009)
	73	kaempferol 3-O-bihexoside	$C_{27}H_{30}O_{16}$	stigmas petals	(Carmona et al., 2007, Termentzi and Kokkalou 2008, Montoro et al., 2012)
	74	Kaempferol-3-O-α-L-(2-O-β-D-glucopyranosyl) rhamnopyranoside-7-O-β-D-glucopyranoside	$C_{33}H_{40}O_{20}$	stigmas petals	(Harborne and Williams 1984, Li et al., 2004)
	75	kaempferol 3-O-rutinoside-7-O-β-D-glucopyranoside	$C_{33}H_{40}O_{20}$	petals	(Harborne and Williams 1984)
	76	Dihydrokaempferol 3-O hexoside	C21H22O11	petals	(Baba et al., 2015, Baba et al., 2015)
	77	4′ -Methyl ether dihydrokaempferol 3-O-deoxyhexoside	$C_{22}H_{24}O_{10}$	petals	(Termentzi and Kokkalou 2008)
	78	Quercetin	$C_{15}H_{10}O_7$	stigmas petals	(Harborne and Williams 1984, Bate-Smith 2008, Gismondi 2012)
	79	quercetin-3,7-di-O-β-D-glucopyranoside	$C_{27}H_{30}O_{17}$	petals	(Termentzi and Kokkalou 2008, Montoro et al., 2012)
	80	quercetin 3-O-(p-coumaroyl)-hexoside	$C_{30}H_{26}O_{14}$	petals	(Termentzi and Kokkalou 2008, Montoro et al., 2012)
	81	3,3′,4′ - trimethyl ether quercetin 7-O-bihexoside	$C_{30}H_{36}O_{17}$	petals	(Termentzi and Kokkalou 2008, Montoro et al., 2012)
	82	quercetin-3-O-β-D-glucopyranoside	$C_{21}H_{20}O_{12}$	petals	(Montoro et al., 2008, Montoro et al., 2012)
	83	Dihydroquercetin 7-glucoside	$C_{21}H_{22}O_{12}$	stigmas petals	(Montoro et al., 2008, Baba et al., 2015, Baba et al., 2015)

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Table 2 (*continued*)

Species	NO.	Compound	Molecular formula	Part of plant	Reference
	84	Rhamnetin	$C_{16}H_{12}O_7$	petals	(Termentzi and Kokkalou 2008, Montoro et al., 2012)
	85	Isoramnetin	$C_{16}H_{12}O_7$	petals	(Montoro et al., 2012)
	86	isorhamnetin-3,7-di-O-β-D-glucopyranoside	$C_{28}H_{32}O_{17}$	petals	(Montoro et al., 2012)
	87	isorhamnetin-3-O-β-D-glucopyranoside	$C_{22}H_{22}O_{12}$	stigmas petals	(Montoro et al., 2008, Baba et al., 2015, Baba et al., 2015)
	88	isorhamnetin-3-O-glucoside	$C_{22}H_{22}O_{12}$	stigmas petals	(Li and Wu 2002, Montoro et al., 2012)
	89	isorhamnetin-4′-O-α-L-rhamnopyranosyl(1 → 2)-β-D-glucopyranoside	$C_{28}H_{32}O_{16}$	stigmas	(Song and Xu 1991)
	90	isorhamnetin-3,4′-diglucoside	$C_{28}H_{32}O_{17}$	stigmas petals	(Li and Wu 2002, Montoro et al., 2008)
	91	Naringenin	$C_{15}H_{12}O_5$	petals	(Termentzi and Kokkalou 2008)
	92	Narinrenin 7-O-hexoside	$C_{21}H_{22}O_{10}$	petals	(Montoro et al., 2012)
	93	Myricetin	$C_{15}H_{10}O_8$	stigmas	(Gismondi 2012)

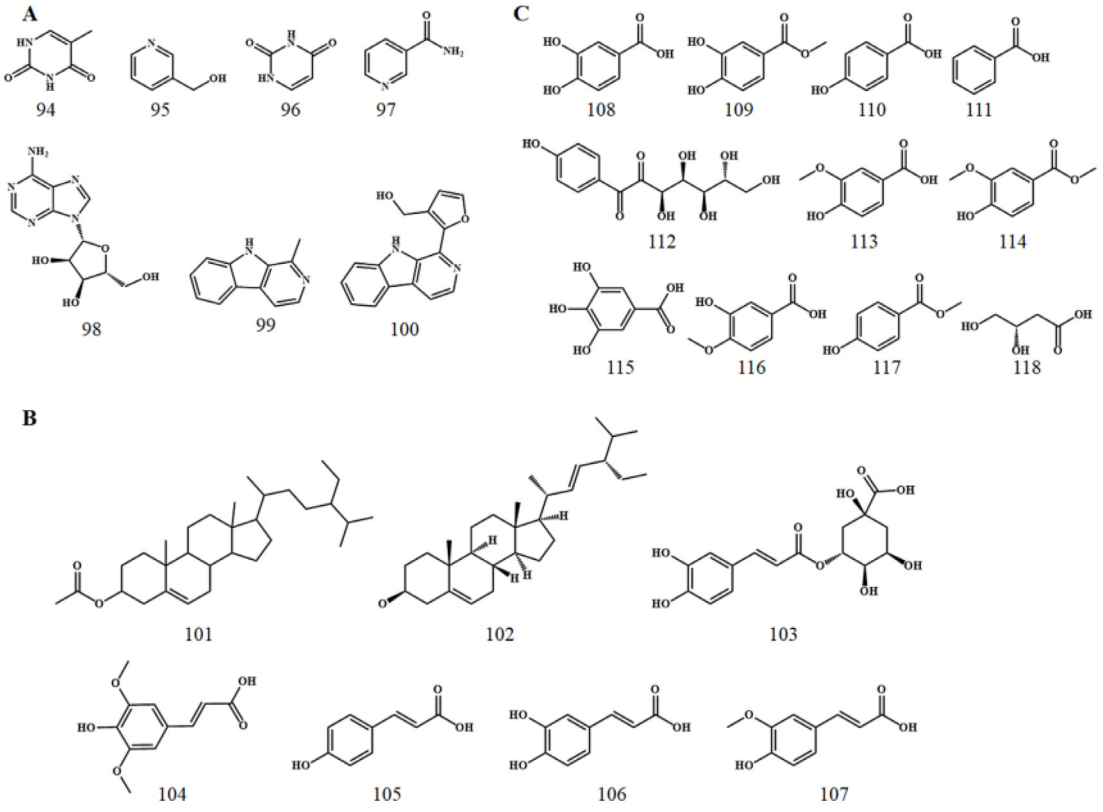

Fig. 3 Chemical structures of alkaloids (A), steroids and phenylpropanoids (B), and organic acids (C).

3.4. Steroids and phenylpropanoids

There exist fewer types of steroids in stigma and petals. Specifically, only two phytosterols, β-sitosterol (**101**) and stigmasterol (**102**), were isolated and identified from stigma (Table 3), while no steroids in petals were mentioned.

Phenylpropanoids refer to compounds in which a phenyl group is attached to three carbons. A total of four phenylpropionic acid compounds were isolated from stigma and petals, namely chlorogenic acid (**103**), sinapic acid (**104**), p-coumaric acid (**105**), caffeic acid (**106**), and ferulic acid (**107**). Among them, the first is an ester formed by the condensation of caffeic acid (**106**) and quinic acid (Fig. 3B). Such

Table 3 Alkaloids isolated from *Crocus sativus* L.

Species	NO.	Compound	Molecular formula	Part of plant	Reference
Alkaloids					
	94	5-methyluracil	$C_5H_6N_2O_2$	stigmas	(Li and Wu 2002)
	95	pyridin-3-ylmethanol	C_6H_7NO	stigmas	(Li and Wu 2002)
	96	Uracil	$C_4H_4N_2O_2$	stigmas	(Li and Wu 2002)
	97	Nicotinamide	$C_6H_6N_2O$	stigmas petals	(Li and Wu 2002, Li et al., 2004)
	98	Adenosine	$C_{10}H_{13}N_5O_4$	stigmas petals	(Li et al., 2004, Termentzi and Kokkalou 2008)
	99	Harman	$C_{12}H_{10}N_2$	stigmas petals	(Li and Wu 2002, Li et al., 2004)
	100	Tribulusterine	$C_{16}H_{12}N_2O_2$	stigmas petals	(Li and Wu 2002, Li et al., 2004, Termentzi and Kokkalou 2008)
Sitosterol					
	101	β-Sitosterol	$C_{30}H_{52}O$	stigmas	(Zheng et al., 2011, Feizy and Reyhani 2016)
	102	Stigmasterol	$C_{29}H_{50}O$	stigmas	(Zheng et al., 2011, Feizy and Reyhani 2016)
Phenylpropanoids					
	103	Chlorogenic acid	$C_{16}H_{18}O_9$	stigmas	(Gismondi 2012)
	104	Sinapic acid	$C_{11}H_{12}O_5$	petals	(Termentzi and Kokkalou 2008, Montoro et al., 2012)
	105	p-coumaric acid	$C_9H_8O_3$	stigmas	(Li et al., 2004)
	106	Caffeic acid	$C_9H_8O_4$	stigmas	(Gismondi 2012, Loizzo et al., 2016)
	107	Ferulic acid	$C_{10}H_{10}O_4$	stigmas	(Loizzo et al., 2016)
Organic acid					
	108	Protocatechuic acid	$C_7H_6O_4$	stigmas petals	(Li et al., 2004)
	109	Protocatechuic acid methyl ester	$C_8H_8O_4$	stigmas petals	(Li and Wu 2002, Li et al., 2004)
	110	4-hydroxybenzoic acid	$C_7H_6O_3$	stigmas petals	(Li et al., 2004)
	111	benzoic acid	$C_7H_6O_2$	stigmas	(Li and Wu 2002)
	112	1-O-(4-hydroxybenzoyl)-β -D-glucose	$C_{13}H_{16}O_8$	stigmas	(Li and Wu 2002)
	113	vanillic acid	$C_8H_8O_4$	stigmas petals	(Li et al., 2004)
	114	methylvanillate	$C_9H_{10}O_4$	stigmas	(Li et al., 2004)
	115	gallic acid	$C_7H_6O_5$	stigmas	(Karimi et al., 2010, Gismondi 2012)
	116	3-Hydroxy-4-methoxybenzoic acid	$C_8H_8O_4$	petals	(Li et al., 2004)
	117	methylparaben	$C_8H_8O_3$	stigmas petals	(Li and Wu 2002, Li et al., 2004)
	118	(S)-3,4-dihydroxybutyric acid	$C_4H_8O_4$	petals	(Mounira 2014)
Amino acid					
	119	Asparagine	$C_4H_7NO_4$	stigmas petals	(Lv et al., 2021)
	120	Threonine	$C_4H_9NO_3$	stigmas petals	(Lv et al., 2021)
	121	Serine	$C_3H_7NO_3$	stigmas petals	(Lv et al., 2021)
	122	Glutamicacid	$C_5H_9NO_4$	stigmas petals	(Lv et al., 2021)
	123	Glycine	$C_2H_5NO_2$	stigmas petals	(Lv et al., 2021)
	124	Alanine	$C_3H_7NO_2$	stigmas petals	(Lv et al., 2021)
	125	Valine	$C_5H_{11}NO_2$	stigmas petals	(Lv et al., 2021)
	126	Methionine	$C_5H_{11}NO_2S$	stigmas petals	(Lv et al., 2021)
	127	Isoleucine	$C_6H_{13}NO_2$	stigmas petals	(Lv et al., 2021)
	128	Leucine	$C_6H_{13}NO_2$	stigmas petals	(Lv et al., 2021)

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Table 3 (*continued*)

Species	NO.	Compound	Molecular formula	Part of plant	Reference
	129	Tyrosine	$C_9H_{11}NO_3$	stigmas petals	(Lv et al., 2021)
	130	Phenylalanine	$C_9H_{11}NO_2$	stigmas petals	(Lv et al., 2021)
	131	Lysine	$C_6H_{14}N_2O_2$	stigmas petals	(Lv et al., 2021)
	132	Histidine	$C_6H_9N_3O_2$	stigmas petals	(Lv et al., 2021)
	133	Arginine	$C_6H_{14}N_4O_2$	stigmas petals	(Lv et al., 2021)
	134	Proline	$C_5H_9NO_2$	stigmas petals	(Lv et al., 2021)

compounds are mainly found in stigma, and only sinapic acid is obtained from petals, leaving no common chemical composition.

3.5. Others

Except for the above-mentioned material bases, the stigma and petals also include essential minerals such as magnesium, iron, manganese, copper, calcium, and zinc, high levels of amino acids (**119**–**134**) including aspartic acid (**119**), alanine (**124**), and proline (**134**), certain organic acids (**108**–**118**) (Fig. 3C), and protein. Accordingly, the protein content of *C. sativus* is as high as about 20% (Mykhailenko et al., 2019).

The stigma and petals are rich in amino acids, and 16 amino acids are isolated and identified, all of which are shared (Table 3). The hydrogen on the benzene ring of organic acids is mainly replaced by –OH, –COOH, –OCH3, and other groups, such as protocatechuic acid (**108**), benzoic acid (**111**), methylparaben (**114**), gallic acid (**115**), etc (Song et al., 2020). In some organic acid molecules, –OH, –COOH, and glycosyl are further condensed into glycosides or esters (Liu et al., 2022), such as protocatechuic acid methyl ester, and 1-O-(4-hydroxybenzoyl)-β-D-glucose. Such compounds are commonly found in stigma and petals (Mykhailenko et al., 2019). Of the 11 kinds of organic acids collected, 5 are common components, 4, that is, benzoic acid (**111**), 1-O-(4-h ydroxybenzoyl)-β-D-glucose (**112**), methylvanillate (**114**), and Gallic acid (**115**), are only observed in stigma, while the remaining 2, 3-Hydroxy-4-methoxybenzoic acid (**116**) and (S)-3,4-Dihydroxybutyric acid (**117**), are isolated and identified from petals.

4. Pharmacological activity

Given their shared chemical composition, the stigma and petals have similar pharmacological effects. In traditional Chinese medicine, stigma is frequently used to treat amenorrhea, postpartum stasis, depression, palpitations, and madness. Pharmacological studies clarified safranal (**2**), picrocrocin (**3**), crocetin (**26**), and crocin (**44**) as the primary material basis for pharmacological activity and confirmed the anti-psychiatric, neurodegeneration, anti-atherosclerosis, and anti-tumor effects of stigma (Abu-Izneid et al., 2022) (Fig. 4).Studies involving petals demonstrated the pharmacological activities of petal extracts in the nervous system, cardiovascular system, and antitumor role, which calls attention to their application as a potential drug source for illnesses such as neurodegenerative diseases, ischemia–reperfusion injury, and cancer (Khazdair et al., 2015).

4.1. Mental illness

C. sativus stigma reduces depression symptoms by regulating neurotransmitter levels and promoting neuroplasticity. For example, using the isolated depressed rat model, acute intraperitoneal injection of 50 mg/kg and oral administration of 200 mg/kg of stigma aqueous extract significantly increased the swimming time and climbing times and their preference for sucrose in comparison to the control group, confirming the antidepressant effects of stigma extract (Orio et al., 2020). The *C. sativus* stigma ethanol extract (0.2–0.8 g/kg) and its constituents, safranal (**2**) (0.15–0.5 mg/kg) and crocin (**44**) (50–600 mg/kg) increased swimming time in depressed mice, during the forced swim test (FST) of the depression mice model, confirming that stigma extract and its components had an antidepressant effect by activating serotonergic, noradrenergic and dopaminergic systems. These results indicate that stigma plays an anti-depression role by regulating neurotransmitter levels (Hosseinzadeh et al., 2004). Neuroplasticity is the ability of the nervous system to adapt to internal and external stimuli and adapt to future stimuli. The neuroplasticity function of the hippocampus and prefrontal cortex, which are involved in emotion regulation, is impaired in depressed patients, and this is reflected in the decline of neurotrophic factors and other growth factors (Jones 2016). Roustazade et al. found that both doses of stigma reduced anxiety in rats in the stress group when they orally administered low-dose (30 mg/kg) and high-dose (60 mg/kg) stigma aqueous extracts to rats, respectively. Its mechanism is related to the expression of brain-derived neurotrophic factor (BDNF) and tumor necrosis factor-α (TNF-α) genes (Roustazade et al., 2022). Stigma aqueous extracts (40 and 80 mg/kg/ day) were intraperitoneally injected into depressed rats for 21 days. According to a Western blot analysis of the levels of the proteins cAMP response element binding (CREB), nerve growth factor inducible (VGF), and BDNF in the rats cerebellum, 80 mg/kg/day can significantly increase the expression of

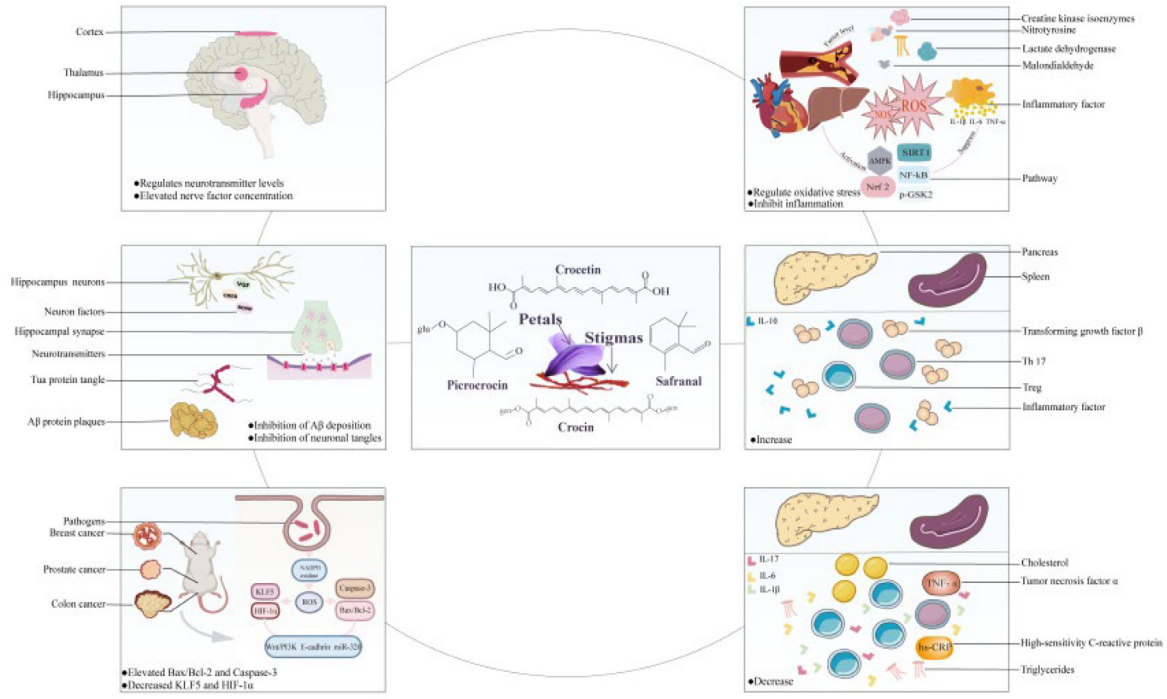

Fig. 4 Pharmacological activity of stigma and petals and their active ingredients.

CREB protein in the rats cerebellum (Asrari et al., 2018). Vahdati et al. studied crocin (**44**), an active ingredient of *C. sativus*, and found that the immotility time of rats was shortened on the 21st day following intraperitoneal injection of crocin (**44**) (12.5, 25 and 50 mg/kg). According to results from Western blotting and quantitative reverse transcription-polymerase chain reaction (qRT-PCR), crocin (**44**) increased VGF levels in a dose-dependent manner at all does. At doses of 25 and 50 mg/kg, CREB and BDNF levels were significantly increased in a dose-dependent manner. At a dose of 12.5 mg/kg, BDNF transcription level significantly increased. The results show that crocin (**44**), which has an antidepressant effect by enhancing neuroplasticity, can increase the concentration of CREB, BDNF and VGF neurofactors in the hippocampus (Vahdati Hassani et al., 2014).

There is extensive clinical research on the study of *C. sativus* stigma to treat depression. In a randomized, double-blind, placebo-controlled trial, Lopresti et al. gave stigma extract (14 mg bid) or placebo to 80 adolescents with mild to moderate depression. The average internalization of the 17% total score on the Revised Child Anxiety and Depression Scale (RCADS) was 33% lower in the treatment group than in the placebo group. Stigma extract showed mild to moderate improvement of depressive symptoms in adolescents (Lopresti et al., 2018). In a *meta*-analysis of 12 studies on stigma's role in the treatment of depression, Dai et al. found no appreciable distinction between the effects of stigma and antidepressants (Dai et al., 2020). In a randomized, double-blind, placebo-controlled trial for major depression, 123 patients with major depressive disorder were randomly assigned to receive placebo, low-dose curcumin extract (250 mg b.i.d.), high-dose curcumin extract (500 mg b.i.d.), or combined low-dose curcumin extract plus stigma (15 mg b.i.d.). After 12 weeks, the combination therapy had a significantly greater improvement effect than the placebo, but there was no difference between the treatment groups receiving additional active drugs, and the combination therapy can effectively reduce the depressive and anxiolytic symptoms in patients with major depressive disorder (Lopresti and Drummond 2017). The combination of stigma and other antidepressants can improve severe depression. Many *meta*-analyses have concluded that *C. sativus* helps improve depressive symptoms with minimal side effects (Lu et al., 2021, Musazadeh et al., 2022, Zhang et al., 2022). Table 4 displays the clinical studies on anti-depression and anxiolytic effects of *C. sativus* stigma in recent 5 years. In conclusion, one of the hotspots in clinical research is the use of *C. sativus* to alleviate and treat mental illness, which may open up a new field for *C. sativus* to prevent negative emotions or as an adjuvant therapy for depression.

4.2. Alzheimer disease

Alzheimer disease (AD) can be treat with *C. sativus* stigma extract and its active ingredients by improving amyloid β-protein (Aβ) and neurofibrillary tangles (Finley and Gao 2017, Ghosh et al., 2020, Koulakiotis et al., 2020). For example, stigma aqueous alcohol extract showed anti-AD effects in 5XFAD mice by upregulating synaptic proteins and attenuating Aβ pathologically related neuroinflammation (Batarseh et al., 2017). Crocetin (**26**) and crocin (**44**) are terpenoid active components in *C. sativus* with antioxidant activity. After one month of oral crocetin (**26**) (10 mg/kg/day) treatment for wild-type male C57BL/6AD mice, Wani et al. found that there was a significant 45% decrease in total Aβ levels in the mouse brains. It was found that in the crocetin (**26**) (25 μM) treatment

Table 4 Antidepressant clinical studies of *Crocus sativus* L. stigma (Randomized, Double-blind, Controlled).

NO.	Administration group (dose)	Control group	Subjects	Participate in case/ Complete case	Indicators	Conclusion	Reference
1	Stigma capsule (30 mg/d)	Placebo	Overweight women with mild to moderate depression.	73/52	BDI-II Weight	Stigma capsules as a safe over-the-counter supplement, it may help reduce the symptoms of depression in patients who experience mild or moderate depression and are overweight.	(Akhondzadeh et al., 2020)
2	Stigma capsule (30 mg/d)	Citalopram (40 mg/d)	Major depressive disorder accompanied by anxious distress	66/60	HDRS HARS	Stigma as a potential efficacious and tolerable treatment for major depressive disorder with anxious distress.	(Ghajar et al., 2017)
3	Stigma alcohol extract (30 mg/d)	Placebo	Type 2 diabetes patients with mild to moderate depression and anxiety	54/54	HDRS HARS PSQI SLS	The results indicate the beneficial effect of Stigma on the mild to moderate comorbid depression-anxiety in type 2 diabetic patients.	(Milajerdi et al., 2018)
4	Stigma tablet (28 mg/d、22 mg/d)	Placebo	Healthy adults	128/128	POM PANAS DASS PSQI	Stigma increased mood, reduced anxiety and managed stress without side effects, offering a natural alternative to standard treatments.	(Kell et al., 2017)
5	Stigma tablet (14 mg bid)	Placebo	Adults with persistent depression who are taking medication antidepressants	160/139	MADRS	The experimental results are insufficient to support the clinical benefit of stigma as an adjunctive treatment for adults with persistent depressive symptoms after antidepressant treatment, and further research is needed to clarify.	(Lopresti et al., 2019)
6	Stigma extract tablet (14 mg bid)	Placebo	Youth with mild to moderate anxiety and depression	80/68	RCADS	Mild to moderate symptoms of depression and anxiety improved in adolescent patients after 8 weeks of treatment with stigma extract tablets.	(Lopresti et al., 2018)
7	Combined low-dose curcumin extract plus stigma (15 mg bid)	Placebo	Major depression	123/123	IDS-SR STAI	Curcumin/ stigma combination therapy is effective in reducing depression and anxiety symptoms in patients with major depressive disorder.	(Lopresti and Drummond 2017)
8	Combined Rhodiola tablet (154 mg) plus stigma extract tablet (15 mg)	/	Mild-moderate depression	45/45	HDRS	As a primary care study, rhodiola and stigma testing may be useful in managing mild to moderate depression and improving symptoms of depression and anxiety.	(Bangratz et al., 2018)
9	Stigma (15 mg capsule) or fluoxetine (20 mg capsule)	/	Mild to moderate postpartum depression	29/29	HDRS	Preliminary studies show that stigma is a safe alternative medication for improving depressive symptoms of postpartum depression.	(Kashani et al., 2017)
10	Luoxetine (20 mg/day) and stigma (30 mg / day)	Placebo	Major depression	40/40	HCY levels BDI	Stigma has beneficial effects on depression and homocysteine level in patients with major depression.	(Jelodar et al., 2018)
11	Crocin tablet (30 mg)	Placebo	Depression in subjects with metabolic syndrome	34/33	BDI	Crocin reduced depressive symptoms in subjects and this effect was independent of its effect on the serum pro-oxidant/anti-oxidant balance.	(Jelodar et al., 2018)
12	Stigma tablet (15 mg/Bid)	Placebo	New mothers with mild to moderate postpartum depression	60/60	BDI-II	When administered to nursing mothers for mild postpartum depression, stigma had a more significant effect on depressive	(Tabeshpour et al., 2017)

Table 4 (*continued*)

NO.	Administration group (dose)	Control group	Subjects	Participate in case/ Complete case	Indicators	Conclusion	Reference
						symptoms than placebo.	
13	Stigma capsule (30 mg/d)	Placebo	Major depressive disorder associated with post-menopausal hot flashes	60/56	HFRDIS HDRS	Stigma is a safe and effective treatment in improving hot flashes and depressive symptoms in post-menopausal healthy women, and with fewer adverse effects, may offer a non-hormonal and alternative herbal medicine option in treatment of women with hot flashes.	(Kashani et al., 2018)
14	Stigma capsule (60 mg/d)	Sertraline (100 mg/d)	older people with major depressive	50/50	HDRS	Both stigma and sertraline have the potential to significantly decrease symptoms of depression.	(Ahmadpanah et al., 2019)
15	Crocin tablet (30 mg/d)	Placebo	Major depression	40/40	BDI GHQ MDQ	Crocin can be used to treat patients with major depression.	(Talaei et al., 2015)
16	Stigma capsule (30 mg/d)	Placebo	Healthy adults	73/56	POMS	Stigma extract appears to improve subclinical depressive symptoms in healthy individuals and may contribute to increased resilience against the development of stress-related psychiatric disorders.	(Jackson et al., 2020)
17	Stigma extract (15.5 mg/d)	Placebo	Mild to moderate sleep disorder associated with anxiety	66/66	LSEQ PSQI	The results suggest that a saffron extract could be a natural and safe nutritional strategy to improve sleep duration and quality.	(Pachikian et al., 2021)
18	Stigma capsule (100 mg/d)	Placebo	Adult patients with anxiety and depression	60/54	BDI BAI	Stigma appears to have a significant impact in the treatment of anxiety and depression disorder. Side effects were rare.	(Mazidi et al., 2016)

group, the expression of STK11/LKB1 and CAMKK2/CAMKβ kinase was increased in N9 microglia and primary neuronal cells, and the red fluorescence of fluorescently labeled $A\beta_{42}$-Hilyte Fluor 555 was significantly decreased. These results indicated that the increase in Aβ clearance rate was promoted by the activation of autophagy. To prevent and treat AD, crocetin (**26**) induces autophagy, promoting the clearance of Aβ (Wani et al., 2021). Hadipour et al. found that intraperitoneal injection of crocin (**44**) (30 mg/kg) into AD rat model preserved the number of viable cells in hippocampal pyramidal neurons and granule cells in DG area in CA3 of AD rats and reversed the reduction of axons, spines and dendritic dendritic structures (Hadipour et al., 2021). Reducing neuronal apoptosis appears to improves synaptic loss and neuronal death in AD rats, which in turn improve their capacity for learning and memory (Lin et al., 2019). Stigma extract and its active components improve protein plaque accumulation and Aβ plaque clearance (Wani et al., 2021), showing a promising future for the treatment of AD (Wang et al., 2019).

Clinical research has demonstrated that *C. sativus* is effective in treating AD. In a randomized, double-blind, controlled trial, 54 patients with mild to moderate AD were given either 30 mg/day of *C. sativus* stigma or 10 mg/day of donepezil. After 22 weeks, the stigma capsule group experienced fewer adverse events than the control group and similar effects to donepezil in mild-to-moderate AD. There is preliminary evidence that *C. sativus* extract can help patients with mild to moderate AD (Akhondzadeh et al., 2010). In a double-blind, parallel study, 68 patients with moderate-to-severe AD were divided two group and given either memantine (20 mg/day) or *C. sativus* extract (30 mg/day) for a 12-months period. Comparable effectiveness to memantine was seen in the *C. sativus* capsule group (Farokhnia et al., 2014). In another randomized, placebo-controlled trial, 46 mild-to-moderate patients were given a daily 30mg*C. sativus* capsule or a placebo. After 16 weeks, *C. sativus* produced cognitive effects that were superior to placebo while having no negative side. The results suggest that *C. sativus* is, at least temporarily, a safe and effective treatment for mild to moderate AD (Akhondzadeh et al., 2010). *C. sativus* has a therapeutic effect on mild cognitive impairment and cognitive decline in AD patients and frequently has a synergistic effect with other nutritional supplements, suggesting that *C. sativus* can be used as a natural source of medicine for the prevention and treatment of AD (Tsolaki et al., 2016, Cicero et al., 2017).

4.3. Cardiovascular diseases

Similar to AD, the incidence of cardiovascular disease is age-related, manifested as ischemia–reperfusion injury and atherosclerosis. Reactive Oxygen-nitrogen Species (RONS) are a by-product of cellular metabolic redox reactions which must be controlled in order to reduce tissue damage and treating cardiovascular diseases (Fig. 5) (Speer and McKune 2021).

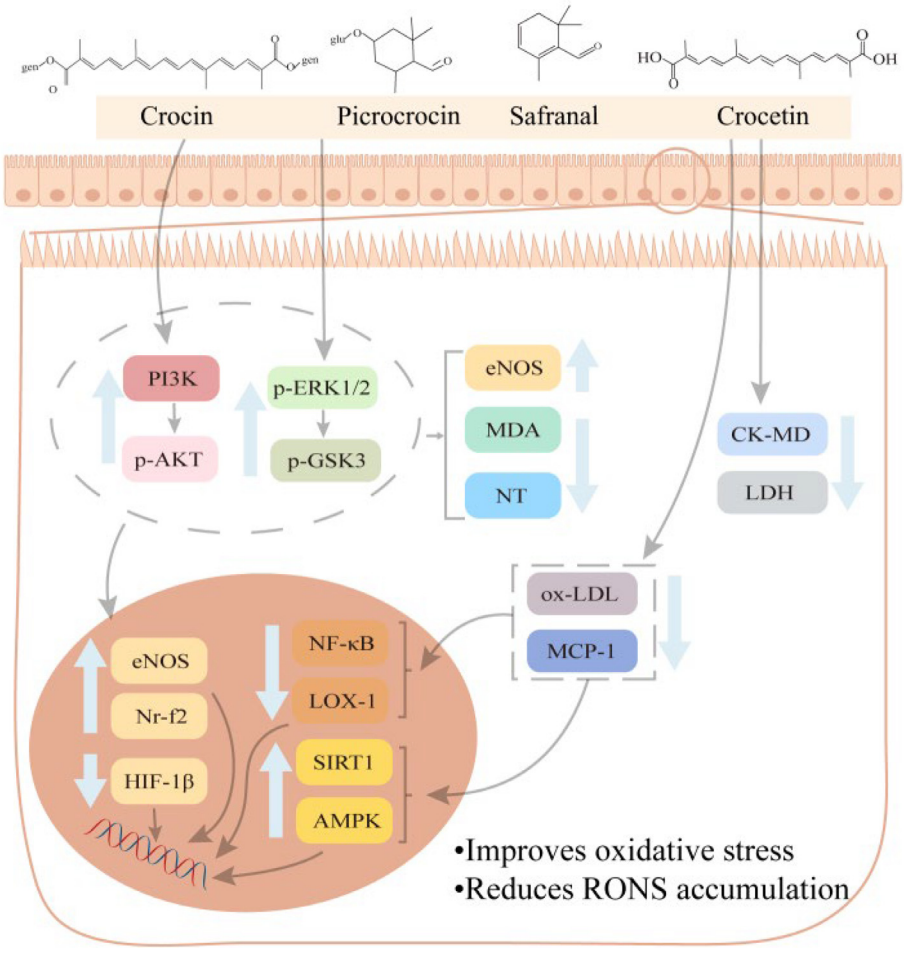

Fig. 5 Anti-cardiovascular mechanism of *Crocus sativus* L. and its active components.

In *C. sativus* extract, safranal (**2**), crocetin (**26**), and crocin (**44**) demonstrate the positive effects of oxidative stress and have potential to prevent age-related diseases (Su et al., 2021).

C. sativus plays a protective role in ischemia–reperfusion injury by regulating oxidative stress. For example, *C. sativus* aqueous extract (60 mg/kg/d) can decrease the size of myocardial infarctions, lower levels of malondialdehyde (MDA) and nitrotyrosine (NT), and increase levels of eNOS, p-Akt, P-ERK1/2 and P-GSK3 in Wild Type and ApoE mice with myocardial ischemia–reperfusion injury models. The Akt/eNOS/ERK1/2/GSK3-β and Nrf2 pathways are activated by stigma aqueous extracts to provide antioxidant protection against myocardial ischemia–reperfusion injury (Efentakis et al., 2017). Arrhythmia is brought on by excessive ROS production and an excess of calcium in the early stages of reperfusion. After intragastric administration of safranal (**2**) (0.025 mL/kg/d), the activities of creatine kinase (CK-MB), lactate dehydrogenase (LDH) and the oxidative stress factor MDA in serum decreased, while the activity of superoxide dismutase (SOD) increased in the rat model of myocardial ischemia injury. Its mechanism of action may involve inhibiting ROS accumulation, myocardial contractility, and calcium influx, according to speculations (Xue et al., 2020). In another study, administration of an ethanol extract of stigma significantly increased antioxidant enzyme content and decreased ROS concentration in rats with hepatic ischemia–reperfusion injury. By regulating protein oxidation, the ethanol extract of stigma can lessen ischemia and perfusion injury, which aids in the development of new therapeutic strategies for diseases caused by ROS (Pan et al., 2013).

C. sativus stigma extract and its active components can improve atherosclerosis by regulating ROS levels and improving inflammation (Rahman et al., 2016, Li et al., 2018). For example, gavage stigma aqueous extract (60, 90 mg/kg/day) for 4 weeks improved aortic stenosis and triglyceride levels and significantly decreased the proinflammatory factor il-6 in the dosing group in a high-fat diet apolipoprotein E (ApoE) mouse model. Antiatherogenic effects of *C. sativus* were dose-dependent and probably resulted from improvements in inflammatory mechanisms (Christodoulou et al., 2018). One of the pharmacologically active components of *C. sativus*, crocin (**44**), can regulate eNOS levels and is beneficial for atherosclerosis (Hatziagapiou and Lambrou 2018). Crocin (**44**) (100 mg/kg/day) was gavaged to atherosclerotic apolipoprotein E knockout (ApoE-/-) mice. In the mice, eNOS expression significantly increased after 16 weeks, while HIF −1α expression significantly reduced. Crocin (**44**) may reduce atherosclerosis in ApoE-/- mice by modifying eNOS and HIF-1α expression (Makaritsis et al., 2022). The levels of low-density cholesterol (ox-LDL) and monocyte chemoattrac-

tant protein 1 (MCP-1) were lower in crocin **(44)** (30 mg/d) group than in the placebo group after 8 weeks of treatment in a clinical trial. Crocin (**44**) may have beneficial effects in atherosclerotic patients by modulating atherogenic genes (increasing SIRT1 and AMPK gene expression and decreasing LOX1 and NF-κB expression (Abedimanesh et al., 2020). In another randomized, double-blind, placebo-controlled clinical trial, 63 atherosclerotic patients were randomly assigned to receive *C. sativus* stigma capsule (100 mg/day) or placebo, the results showed significantly greater Macnew scores (<0.001), physical domains ($=0.025$), and social domains (<0.001) after receiving the stigma capsule (Ahmadikhatir et al., 2022). *C. sativus*, which is a potential treatment strategy for coronary atherosclerosis, can effectively improve the quality of life of patients with atherosclerosis.

4.4. Anti-diabetic

The active components in *C. sativus* stigma extract lower blood sugar by reducing insulin resistance, are anti-inflammatory, and anti-oxidation, and can help with hypertension, hyperlipidemia, and other complications associated with diabetes (Jiang and Zhu 2019, Lingli and Wenfang 2022). In rats with streptozotocin-induced diabetes, Samarghandian et al. administrated stigma aqueous extract (20, 40, and 80 mg/kg),they found that the rats gained weight and had lower serum levels of TNF-α blood glucose, cholesterol, and triglyceride. The results indicated that stigma extract could lower blood glucose and hyperlipidemia risks and that it could help treat chemoinduced diabetes mellitus and its complications (Samarghandian et al., 2014). Jiang et al. administered stigma aqueous extract (100 mg/kg) intravenously to diabetic mice by streptozotocin. Water intake, fasting blood glucose, and the area under the stigma aqueous extract curve were all significantly lower than in the homologous diabetes group. Total cholesterol was also lower, but high-density lipoprotein cholesterol and insulin were both significantly higher (Jiang et al., 2018). In streptozotocin induced diabetic mice, *C. sativus* aqueous extract can reduce blood glucose and blood lipid levels, suggesting that *C. sativus* may be useful in the treatment of diabetes. In another study, C57BL/6 mice with streptozocin-induced autoimmune diabetes received an oral administration of an aqueous alcohol extract of stigma (500 mg/kg) for 3 weeks. The incidence of hypoglycemia and proinflammatory interleukin-17 (il-17) production were decreased, and the production of the anti-inflammatory factors molecules IL-10 and transforming growth factor-β (TGF-β) was increased in pancreatic cell populations. It has been provided that *C. sativus* stigma extract has a hypoglycemic effect and can be used to treat diabetes (Faridi et al., 2019). Crocin (**44**), picrocrocin (**3**), crocetin (**26**), safranal (**2**), and other compounds that are the primary anti-diabetic active ingredients in *C. sativus*, of which crocin (**44**) is the representative (Delkhosh-Kasmaie et al., 2018, Yaribeygi et al., 2019, Sepahi et al., 2022). In diabetes rats induced by nicotinamide and streptozotocin, the levels of aspartate aminotransferase (AST), superoxide dismutase (SOD), glutathione (GSH), creatinine, cholesterol and triglyceride were measured in kidney and blood. After diabetes is induced, treatment with 50 mg/kg crocin(**44**) helps to restore blood glucose, reduce blood lipid, cholesterol and other parameters, and alleviate some complications of diabetes (Margaritis et al., 2020).

C. sativus has been shown to be effective in treating type 2 diabetes by recent clinical evidence. In a triple-blind trial, 54 patients with type 2 diabetes were randomly assigned to receive either *C. sativus* stigma extract capsules (15 mg/kg) or placebo. After 8 weeks, the stigma group's fasting blood glucose levels were significantly lower than those of the placebo group. Aqueous alcohol extract of *C. sativus* improves glycemic control in T2D patients by reducing serum levels of LDL and HDL, total cholesterol, and triglycerides (TG), as well as glycosylated hemoglobin (HbA1c) (Milajerdi et al., 2018). In another clinical trial, the mean differences in fasting blood glucose (FPG), cholesterol, LDL C, and LDL/HDL ratio were significantly lower in 64 patients with type 2 diabetes who were randomized to receive *C. sativus* capsules (15 mg/day) or placebo after 3 months (Moravej Aleali et al., 2019). There is no lack of clinical use of *C. sativus* as a supplement in the treatment of type 2 diabetes. For example, in a clinical trial of *C. sativus* as a supplement, 60 obese patients with type 2 diabetes received *C. sativus* (100 mg/d), training (resistance + aerobic), and placebo. Patients with type 2 diabetes mellitus who lost weight after training experienced significant reductions in insulin, high activity cytokine (TNF-α), C-reactive protein (hs-CRP) and inflammatory factors such as IL-6, IL-1β and IL-10 (Hooshmand Moghadam et al., 2022). Supplemental *C. sativus* has an adjuvant effect on diabetes and a strong anti-inflammatory effect.

4.5. Anticancer effect

It's been proved that safranal (**2**), picrocrocin (**3**), crocetin (**26**), and crocin (**44**) in stigma exhibit obvious anti-tumour effect, particularly the therapeutic effect on breast cancer, colon cancer, gastric cancer, uterine cancer, lung cancer, cervical cancer and other cancers (Liu and Mao 2014, Bhandari 2015, Colapietro et al., 2019). The possible anticancer mechanisms of *C. sativus* include promoting cancer cell apoptosis, inhibiting cell proliferation, migration, and invasion to play preventive and therapeutic roles (Fig. 6) (Hu et al., 2014, Naeimi et al., 2019). Considering antitumor activity and toxicity, crocin (**44**) has become one of the most promising anticancer drugs among the active components of *C. sativus* (Veisi et al., 2020).

Research in vitro and in vivo studies have shown that the active components in *C. sativus* have anti-cancer effects by promoting apoptosis and inhibiting cell proliferation, migration, and invasion. Oral administration of *C. sativus* stigma extract (200 mg/kg) extended the lives of mice with endoperitoneal metastases of Sarcoma-180 (S-180), Ehrlich AScites Carcinoma (EAC), and Dalton's ASCITES (DLA), by 111.0%, 83.5%, and 112.5%, respectively. Hematological and biochemical parameters in toxicology studies were within normal ranges, indicating the potential value of *C. sativus* as an anticancer agent (Nair et al., 1991). Bax/Bcl-2 and caspase-3 levels in stigma aqueous extract-treated mice were significantly higher than those in other controls in the 4 T1 cell line-induced breast cancer experiment in female mice, indicating that stigma extract may mediate cancer cell apoptosis by rasing Bax/Bcl-2 and caspase-3 levels in breast cancer mice (Ahmadabadi et al., 2021). At different concentrations (100,

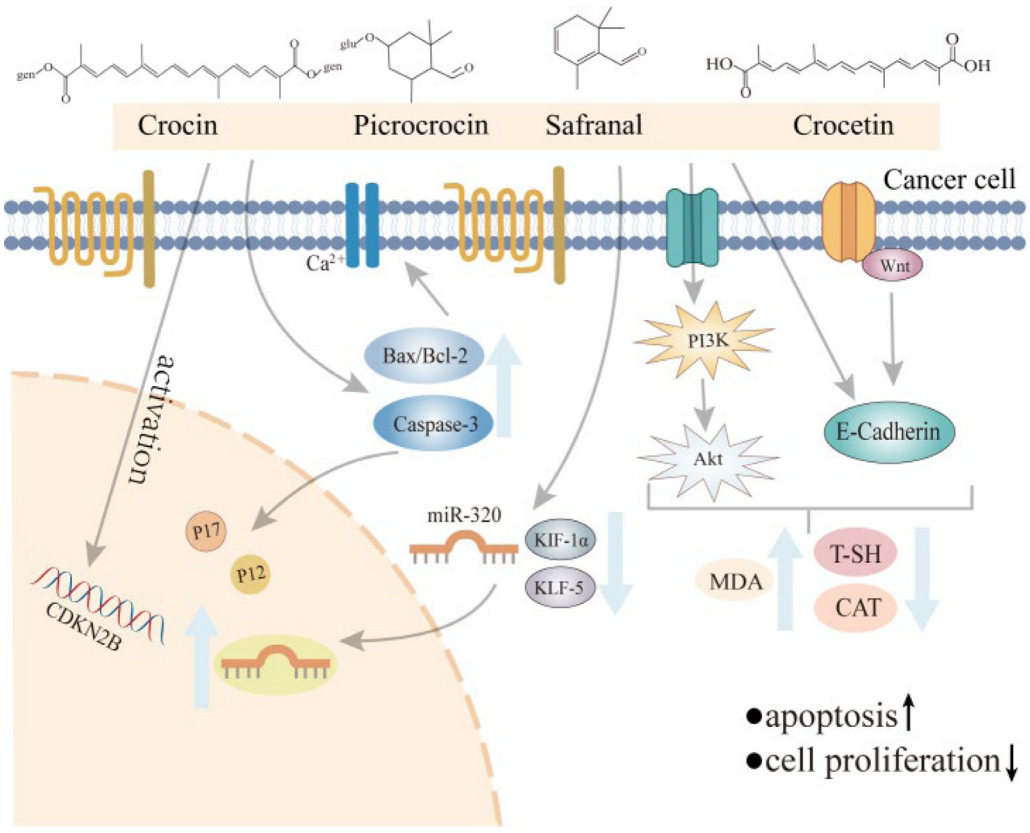

Fig. 6 Anticancer mechanism of *Crocus sativus* L. and its active components.

200, 400, 600, 800, 1600 and 3200 μg/mL), stigma aqueous extract was applied to human prostate cancer cells (PC3). The 1600 μg/mL group manifested severe granulation, a reduction in cell volume, and partial cell death after 72 h. Inhibited human prostate cells by stigma aqueous extract was dose-dependent (Ahmadnia et al., 2020). In colorectal cancer (CRC) rat experiments, long-term treatment with crocin (**44**) (400 mg/kg) improved the survival rate of female colon cancer rats without causeing significant toxic effects (García-Olmo et al., 1999). Amerizadeh et al. discussed the effect of crocin (**44**) (200 ppm in drinking water) on a mouse model of colon cancer (Amerizadeh et al., 2018). The results reveal that total thiol (T-SH) and catalase (CAT) levels were decreased, and MDA activity was increased, while the size and number of colon tumors were smaller and fewer in treated mice than in the control group. By using flow cytometry, the inhibition of crocin (**44**) on the proliferation of HCT116 cells was identified, and the expression levels of several genes were evaluated. Both the release of the P-STAT3/STAT3 ratio and cytokine were decreased. Crocin (**44**) has antitumor activity in CRC and may play a role in reducing inflammation in mucosal ulcers and highly dysplastic crypts. Crocin (**44**) inhibits the growth and invasion of CRC cells by regulating the Wnt pathway and E-cadherin, as well as colonic inflammation (Wang et al., 2020). Crocetin (**26**) can induce apoptosis in gastric cancer cells (He et al., 2014, Naeimi et al., 2019). The mechanism of action of crocetin (**26**) on gastric cancer cells demonstrated that crocetin (2 or 3 μm) inhibited the migration, invasion and epithelial-mesenchymal transition of gastric cancer cells, and the expression of KLF5 and HIF-1α decreased, while Mir-320 expression increased. Crocetin (**26**) prevents gastric cancer cells from migrating, invading, and undergoing the epithelial-mesenchymal transition, which is mediated by Wnt/PI3K, Mir-320 / KLF5 / HIF-1α (Khodir et al., 2019, Zhou et al., 2019). Liu et al. found that *C. sativus* extract and its active components protect against cancer organ damage by inhibiting oxidative stress (Liu et al., 2022), and activating the Wnt/PI3K and miR-320 / KLF5 / HIF-1α signalling pathways (Amerizadeh et al., 2018). The cell inhibition of cancer cells is more active than that of non-cancer cells, which may be regarded as a successful anticancer agent with broad clinical implications for cancer treatment (Hire et al., 2017).

4.6. Other activities

In addition to the pharmacology listed above, *C. sativus* also have antiasthmatic, memory-enhancing and diuretic activities. In a clinical trial, 80 patients with mild to severe allergic asthma were randomized to receive either *C. sativus* capsules or a placebo. When compared to the placebo group, the *C. sativus* group's clinical sympotoms and asthma severity were significantly reduced (Zilaee et al., 2019). Many studies have shown that *C. sativus* has the effect of enhancing memory. It has been demonstrated that morphine-induced memory deficits in mice can be avoided by using *C. sativus* aqueous extracts (Naghibi et al., 2012). *C. sativus* extract can improve learning and memory impairment brought on by AD and cerebral ischemia–reperfusion injury (Ghadrdoost et al., 2011). According to Shariatifar N et al., gaving rats oral doses of *C. sativus* aqueous extracts (60 mg/kg, 120 mg/kg, 240 mg/kg) produced

diuretic effects comparable to those of the commonly prescribed diuretic hydrochlorothiazide (10 mg/kg B.W., i.p.) (Shariatifar et al., 2014). Additionally, more research is required to determine the mechanisms of action, possibly other side effects, and interactions with other medications.

5. Safety and/or toxicity of *Crocus sativus* L.

Although *C. sativus* and its active ingredients are widely used in food and medicine, more research is required to determine the safety and toxicity of the medicinal herbs. The stigma and petals of *C. sativus* had different toxicological effects. In a subacute toxicity test, the stigma (1.2–3.6 g/kg) and the petal ethanol extract (0.16–0.48 g/kg) both coused anemia and pulmonary and hepatocytosis in rats after intraperitoneal administration, respectively. The LD_{50} values of stigma and petals were 1.6 and 6.0 g/kg, respectively, indicating that the toxicity of petals was lesser than that of stigma (Mohajeri et al., 2007). There are a variety of toxicological literature reports on the stigma of *C. sativus*. The LD_{50} value of stigma aqueous extract to CCD-18LU human normal lung cells was 50–400 mg/mL in the toxicity study, and there was no cytotoxicity (Abdullaev et al., 2003). The mice showed symptoms of nausea, vomiting, diarrhea and bleeding after receiving an intraperitoneal injection of stigma aqueous extract at the dose of 1.2–2 g/kg (Schmidt et al., 2007). In another study, oral administration of stigma aqueous extract (4 g/kg/d) to mice did not result in any negative side effects (Melnyk et al., 2010). Bahmani et al. invesrigated the toxicity of stigma aqueous extract on lactating mice and neonatal mice, and found that the LD_{50} value of lactating mice after oral administration (500, 1000 or 2000 mg/ kg/ day) was 4120 ± 556 mg/kg, did not show any toxic effects on the liver, but at high doses (2000 mg/kg/d) neonatal mouse kidneys showed morphological changes (Bahmani et al., 2014). In the subacute toxicity test of stigma ethanol extract in rats, intraperitoneal injection of 0.35, 0.70, and 1.05 g/kg/d increased the damage of liver and kidney tissue in a dose-dependent manner (Mohajeri et al., 2007). Compared with ethanol extract, aqueous extract may have lower toxicity. It's possible that oral administration damages tissue less than intraperitoneal administration.

Safranal (**2**) has been reported to have more toxic effects than other active ingredients in *C. sativus* (Hosseinzadeh et al., 2010). Rat mortality was decreased when *C. sativus* aqueous extract (25–100 mg /kg, IP) and safranal **(2)** (1.2 mL /kg, IP) were combined as opposed to when safranal **(2)** was used alone, and no deaths were observed when *C. sativus* aqueous extract was used at a dosage of 10 mg/kg. Safranal (**2**) can be made less toxic when when combined with aqueous extract of *C. sativus* (Ziaee et al., 2014). According to Hosseinzadeh et al., crocin (**44**) had a low toxicity for acute intraperitoneal administration and was nearly non-toxic for acute oral administration. Safranal (**2**) was given intraperitoneally, resulting in LD_{50} values for male mice of 1.48 mL/kg, female mice of 1.88 mL/kg, and rats of 1.50 mL/kg, all of which were < 5.0 mg/kg. Oral administration resulted in LD_{50} values of 21.42 mL/kg in male mice, 11.42 mL/kg in female mice, and 5.53 mL/kg in rats, all of which were higher than 5.0 mg/kg (Hosseinzadeh et al., 2013). However, the results of acute and subacute trials using intraperitoneal and oral doses of 3 g/kg crocin (**44**) showed no mortality and no negative effects on organs in experimental rats and mice (Hosseinzadeh et al., 2010). In the studier by Moallem et al., pregnant mice were given intraperitoneal doses of crocin (**44**) (200 mg/kg or 600 mg/kg) or safranal (**2**) (0.075 mL/kg or 0.225 mL/kg), which led to skeletal malformation and growth retardation in newborn mice. Additionally, the severity of embryo malformation induced by the two is similar (Moallem et al., 2016). This result suggests that pregnant women should use *C. sativus*-related products with caution because *C. sativus* has a strong blood-activating effect. Other blood-activating and anticoagulant drugs, such as Chuanxiong rhizoma, Salvia miltiorrhiza, enteric-coated aspirin, warfarin, heparin, etc., should generally be avoided during the period of *C. sativus*, (Qiu et al., 2021), and pregnant women should be cautious to avoid bleeding risks. To sum up, studies on the long-term toxicity of *C. sativus* in vivo as well as studies to establish an effective dose are still lacking.

6. Potential medicinal source possibilities for petals

It was believed that the stigma and petals of *C. sativus* had comparable pharmacological activities on the basis of common material basis. Petal methanol extract on rat cardiomyocytes showed negligble inotropic and chronotropic intrinsic activity, but significant intrinsic activity on smooth muscle. Kaempferol (**51**) and crocin (**44**) were isolated and purified from petals and demonstrated selective negative inotropic activity (Zeka et al., 2020). Another study using angiotensin II and NG-nitro-L-arginine methyl ester (L-NAME, a NOS inhibitor) on anesthetized rats confirmed the significant attenuation of cardiovascular responses caused by AII and L-NAME in the petal pretreatment group, including the antihypertension effect and application prospect of hydroalcoholic extract petal in cardiovascular diseases (Mohebbati et al., 2021).

The *C. sativus* petals have antidepressant effects, according to in vivo tests. Karim et al. found that gavage administration of an aqueous and ethanol extract (30 mg/kg) from *C. sativus* petals significantly reduced immobilization time and had antidepressant effects in depressed mice (Karimi et al., 2001). In a randomized, double-blind, placebo-controlled clinical study, 40 depressed patients were given petals supplement (30 mg/ day). After 6 weeks, the petals group significantly outperformed the placebo group on the Hamilton Depression Rating Scale (HDRS) and the subjects' depressive mood (Akhondzadeh et al., 2005). In a randomized, double-blind, controlled trial, 40 moderately depressed patients received either petals capsules (15 mg bid) or fluoxetine (10 mg bid). HDRS significantly reduced by 25% in both groups after 8 weeks. The antidepressant effect of *C. sativus* petals was similar to fluoxetine, and the side effects were not significantly different. *C. sativus* petals may be used as a potential source of antidepressants (Akhondzadeh Basti et al., 2007). Another double-blind randomized clinical trial involved 40 patients with mild to moderate depression who were randomized to receive either *C. sativus* petals capsules (30 mg/day) or placebo. After 6 weeks, the HDRS results in the petals capsule group were significantly better than those in the placebo group, and there were no side effects, indicating that petals are very effective in the treatment of mild to moderate depression (Moshiri et al., 2006). *C. sativus* petals may be used as an adjuvant therapy for mild to moderate depression.

Table 5 Pharmacological effects of important active components in stigmas and petals.

Compounds	Petals	Stigmas	Effect	Reference
Safranal (**2**)	–	+	• AntidepressantReducing ROS accumulation, inhibiting myocardial contractility and reducing calcium influxAnti-diabetic	(Wang et al., 2015, Tabeshpour et al., 2017, Xue et al., 2020)
Picrocrocin (**3**)	+	+	• Anti-diabetic	(Roshanravan and Ghaffari 2022)
Crocetin (**26**)	+	+	• AntidepressantInhibit the aggregation of Aβ monomers into oligomers or fibers, and degrade the formed Aβ oligomers or fibersInhibit pancreatic lipase and improve hyperlipidemiaGastric cancer, hepatocellular carcinoma, cervical cancer	(Zhu 2019, Yu et al., 2020) (Chen et al., 2015, Wang et al., 2015, Mohan et al., 2021, Zang et al., 2021)
Crocin(**44**)	+	+	• AntidepressantInduces autophagy in N9 microglia and primary neuronal cells, promotes increased Aβ clearance and improves protein plaque accumulationAnti-atherosclerosisRestore some parameters after diabetes induction and relieve some complications of diabetesBreast cancer, colon cancer	(Li et al., 2018, Xiao et al., 2019, Margaritis et al., 2020, Farahi et al., 2021, Wani et al., 2021, Bakshi et al., 2022)
Kaempferol (**51**)	+	+	• Inhibits the inflammatory response and apoptosis of renal tissue in rats with diabetic nephropathy, and has a protective effect on renal function and histopathological damageAnti-atherosclerosisAnti-inflammatory and analgesic, hypoglycemic, anti-osteoporosis, anti-fertility. Immune regulation, disease prevention, protective effect on damaged tissueAntibacterialBreast cancer, lung cancer	(Kong 2014, Lei et al., 2017, Ming 2018, Tang et al., 2018, Li et al., 2020)
Quercetin (**78**)	+	+	• Treating Rheumatoid ArthritisAnti-fibrosisAntibacterialBreast cancer	(Wang et al., 2018, Ezzati et al., 2020, Chen et al., 2021, Jiang et al., 2021)

Note: + indicates that the site contains the compound; - Indicates that the site does not contain the compound.

Petal performance surpasses stigma in the areas of antibacterial, liver, and kidney protection in addition to the previously mentioned cardiovascular system and nervous system activities. With a 13–22 mm diameter inhibitory zone, the 1000 mg/mL methanol extract of petals has antibacterial activity against *Staphylococcus aureus*, *Bacillus cereus*, *Salmonella typhi*, *Escherichia coli*, and *Shigella dysenteriae* (Asgarpanah et al., 2013). Rats were intraperitoneally injected daily with low-dose (40 mg/kg) and high-dose (80 mg/kg) petal extracts to test for gentamicin sulphate-induced nephrotoxicity. The serum blood urea nitrogen (BUN) and creatinine levels of rats were decreased at the dose of 40 mg/kg. The damaging effects of gentamicin sulfate (GM) on the kidney can be lessened by an ethanol extract of petals (Omidi and Totrabi 2016). In the acetaminophen-induced liver and kidney injury experiment, rats pretreated with low-dose (10 mg/kg) of hydroalcoholic extract of petals showed mild necrosis in the hepatic lobule area, but rats pretreated with high dose (20 mg/kg) showed only modest hepatocyte degeneration (Omidi et al., 2014). Increased serum creatinine and uric acid are signs acute nephrotoxicity from acetaminophen, which were significantly reduced by a 20 mg/kg dose of *C. sativus* hydroalcoholic extract (Omidi et al., 2015). As a result, liver and kidney damage brought on by gentamicin sulfate and acetaminophen can be made up for by the hydroalcoholic extract of petals.

Despite the evidence that stigma and petals both have similar pharmacological effects, stigma has been the subject of more extensive and in-depth pharmacological research than petals. This paper summarized and analyzed the connection between the common and different main active ingredients of stigma and petals and their pharmacological effects based on the study of the chemical constituents of petals and stigma, as shown in Table 5.

7. Remaining problems and trends

As a by-product, there are some limitations in the exploitation and utilization of petal. By comparing the metabolites in the stigma and petals, Zhou et al. discovered that the composition of the metabolites in the stigma and petals was essentially the same. The petals contained flavonoids, alkaloids, coumarins, and other medicinal components, which were of great development value to medicine and food (Zhou et al., 2022). The remaining petals must be dried quickly once the stigma has been collected to prevent spoiling. For the purpose of controlling the quality of fresh petals, some rapid drying techniques, such as infrared drying and microwave drying, can be applied (Zhao et al., 2019, Qiu et al., 2022). In addition, although the petals are valuable for medicine and foods and have potential utility in multiple areas such as the natural spice, cosmetic, health drink, and natural health product industries, it lacks in necessary safety measures, and further studies of the mechanism of action and toxicological properties of petals are also required, especially research to establish an effective dose and its long-term toxicity in vivo.

8. Conclusion

Modern chemical and pharmacological studies have clarified the relationship between complex chemical composition and clinical application of *C. sativus*. Terpenoids, flavonoids and their derivatives are the main material basis for pharmacological effects in *C. sativus*(Liu

et al., 2020), accounting for 69.39% of the total compounds. The stigma and petals contain a large number of chemical compounds that are chemically similar and make up 33.57% of the total compounds. Flavonoids and their derivatives account 31.25% of all flavonoids and their derivatives, making them the class with the most similar chemicals. The material basis overlap rate is extremely high. Besides, flavonoids with good antioxidant activity are proved to be the most abundant compounds in the stigma and petals(Hatziagapiou and Lambrou 2018), and kaempferol glycosides are abundant in dried petals with a concentration of up to 126 mg/g DW and crocin concentration of 6.4 mg/g DW (Zeka et al., 2020), which indicates the role of petals as a source of phytochemicals and their application prospect in adjuvant treatment of various diseases, especially depression. Therefore, we believe it's necessary to review it, which will help to provide ideas for the development and utilization of petals.

9. Authors'contributions

Hongyan Ma and Jin Pei conceived and designed all the review. Xue Li, Jin Xie and Hong Fan wrote and edited the review. Jin Tan and Yang Bao completed data analysis and graphing. Funeng Geng and Dingkun Zhang collected documents and literatures.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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