The Potency of Safflower (*Carthamus tinctorius*) as an Antiviral Agent

Abd. Malik[1]*, Wisdawati Wisdawati[1], Aktsar Roskiana Ahmad[1]*
[1]Department of Pharmacognosy and Phytochemistry, Pharmacy Faculty, Universitas Muslim Indonesia, Makassar, Indonesia
E-mail: abd.malik@umi.ac.id
E-mail: aktsar.roskiana@umi.ac.id

Abstract
Carthamus tinctorius, extensively applied in curing diseases in many parts of the world, since it is known as fake saffron. Some etnopharmacology approaches relate the antioxidant properties of this plant, polyphenols especially flavonoids, with the antimicrobial and antiviral activities. This review provides a summary of the antioxidant, antimicrobial and antiviral effects of *C. tinctorius* with the latest reports on developing a new perception of safflower for its antiviral potency. Referring to some data regarding the phytochemical constituents of *C. tinctorius* which are substantial to give pharmacological effects. For instance, luteolin and its glucopyranosides, and dehydroabietylamine in leaves. Including hydroxysafflor yellow A, carthamin, isolated flavonoid compounds in flower, while seed oil is composed of serotonin derivatives. The interesting compounds are flavonoids, including carthamin, which have significant effects on bacteria, fungi as well as viruses. Hence, C. *tinctorius* has a promising constituent to be developed as an antiviral agent.
Keywords: *Carthamus tinctorius*, flavonoids, antioxidant, antimicrobial, antiviral.

1. Introduction

Carthamus tinctorius Linn (CT) is a member of the family Asteraceae/compositae and it has been widely used to treat diseases since thousand years ago. The English name of this plant is safflower, while people in Hindi mention this plant as kusumba. Honghua is the well-known name in China, whereas it is known as Kasumba turate (Makassar) or Ralle (Bugis) in South Sulawesi, Indonesia(1, 2).

Safflower has been applied differently in some countries depending on the culture and environment. For example, in China, to treat cardiovascular diseases, amenorrhea, gastric tumors, and for wound healing. People in India cure their scabies, arthritis, and breast pain with this plant. Iranians use it for colic, like skin patches, and baldness. It is used for anti-diabetes, phlegmatic fever, melancholia and dropsy in Persia (1, 2, 3). Despite its use for common diseases in many countries, in South Sulawesi, Indonesia, it has been used as an antiviral agent for Roseola infantum disease (measles), a common disease in children (4).

These ethnopharmacology findings lead to correlate between the phytochemical properties and the pharmacological effects over the years. The medicinal plants have variants of phytochemical secondary metabolites, including phenolics, alkaloids, flavonoids, and terpenoids and thus provide interest in new drug discoveries. Recently, some studies concluded that the potent antioxidant activity contributes to bioactive compounds existing in immense amounts in plants (5). Furthermore, in vitro and in vivo studies exhibit that antioxidant compounds; flavonoids and polyphenols, are responsible for several diseases. For instance, cardiovascular diseases, anti-inflammatory, anti-allergic, cytotoxic antitumor, neurodegenerative diseases, antimicrobial and antiviral activities (6, 7, 8, 9, 10, 11).

Based on this approach, in this review, we will summarize the antioxidant activities of safflower that contributed to antimicrobial and antiviral effects with the latest reports.

2. Methods

Articles were extracted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (12). Articles selected from year 2012 to 2022 with using keywords: *Carthamus tinctorius* and antioxidant, *Carthamus tinctorius* and antimicrobial, and *Carthamus tinctorius* and antiviral activity. Literature obtained from PubMed and Semantic Scholar is 144 and 200, respectively. Since duplication from both electronic databases browser, 47 articles were excluded and some not eligible articles found lead to only 21 reports were included in this review study (fig.1).

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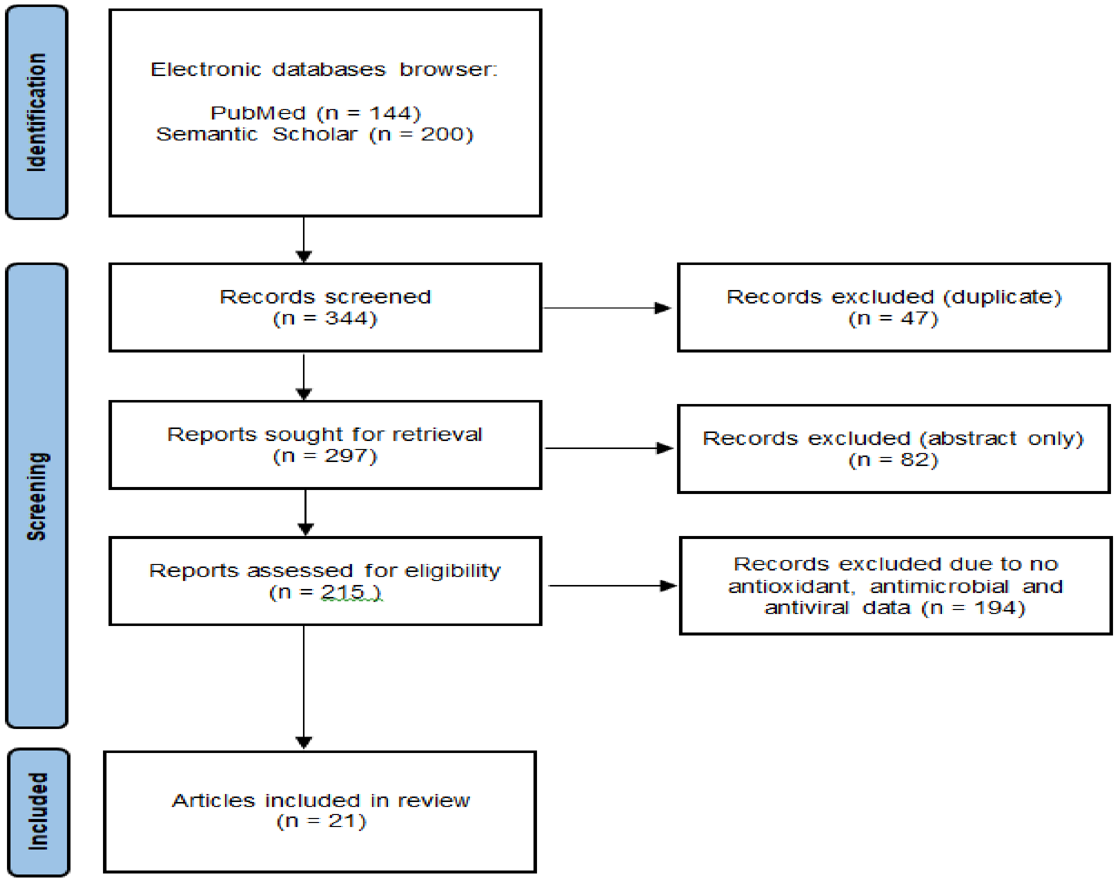

Fig 1. PRISMA flow-diagram for Carthamus tinctorius with antioxidant, antimicrobial, and antiviral activity.

3. Result

PHYTOCHEMICAL PROPERTIES of *C. tinctorius*	
Plant parts	Chemical compound
Leave	Luteolin and its glucopyranosides, dehydroabietylamine
Flower	Flavnoids: Carthamin; Heliaol; α-amyrin; β-amyrin; lupeol; cycloartenol; 24-methylenecycloartanol; tirucalla-7,24-dienol and dammaradienol(triterpene alcohol). carthamidin, isocarthamidin, quercetin, kaempferol, 6-hydroxykaempferol and its glycosides, chalcones including hydroxysafflor yellow A, safflor yellow A, safflor yellow B, saffloflavonesides A, saffloflavonesides B, safflamin C and safflamin A, and safflomin-A. carthamoside A1 and carthamoside A2 are acetylenic glucosides, , a new quinochalcone C-glycosides (tinctormine); safflor yellow B, nicotiflorin, alkane-1,3-diols, Caryophyllene, p-allyltoluene, 1- acetoxytetralin and heneicosane. The flavone luteolin and its glucopyranoside luteolin 7-O-beta-D-glucopyranoside and luteolin-7- O-(6''-O-acetyl)-beta-D-glucopyranosid. Other compounds : lauric acid, myristic acid, palmitic acid, linoleic acid, arachidic acid and oleic acid.
Seed Oil	Serotonin derivatives, N-[2(5-hydroxy-1H-indol-3-yl)ethyl]-ferulamide, N-[2(5-hydroxy-1H-indol-3-yl)ethyl]-p-coumaramide, N-[2,2'-(5,5-dihydroxy-4,4'-bi-1H-indol-3,3'-yl)diethyl]-di-pcomaramide, N-[[3'[2-(p-comaramido) ethyl]-5, 5'-dihydroxy-4,4'-bi-1H-indol-3-yl]ethyl] ferulamide, N,N'-[2,2'-(5,5'-dihydroxy-4,4'-1H-indol- 3,3'yl)diferulamide, N-[2[5-(beta-D-glucosyloxy)-1H- indol-3-ylethyl]-p-comatamide and N-[2-[5-(beta- D- glucosyloxy)-1H-indol-3-yl]-ethyl] ferumaramide, Serotomide(trans-N-caffeoylserotonin), safflomide (trans-N-caffeoyltryptamine),

From the table, as we can see, the leaves contain diterpene (dehydroabietylamine) and flavonoid (luteolin), glucopyranosides (13, 14). The most used part, flower or petal, is composed of numerous flavonoid compounds, including quercetin, carthamin, carthamidin, hydroxysafflor yellow A, etc (15, 16, 17, 18). Moreover, CT also has another bioactive compound, alkaloid (serotonin derivatives) that can be found in the seed oil. In summary, CT has substantial bioactive compounds that contribute to its significant pharmacological activities, namely antioxidant, antimicrobial and antiviral activities (19).

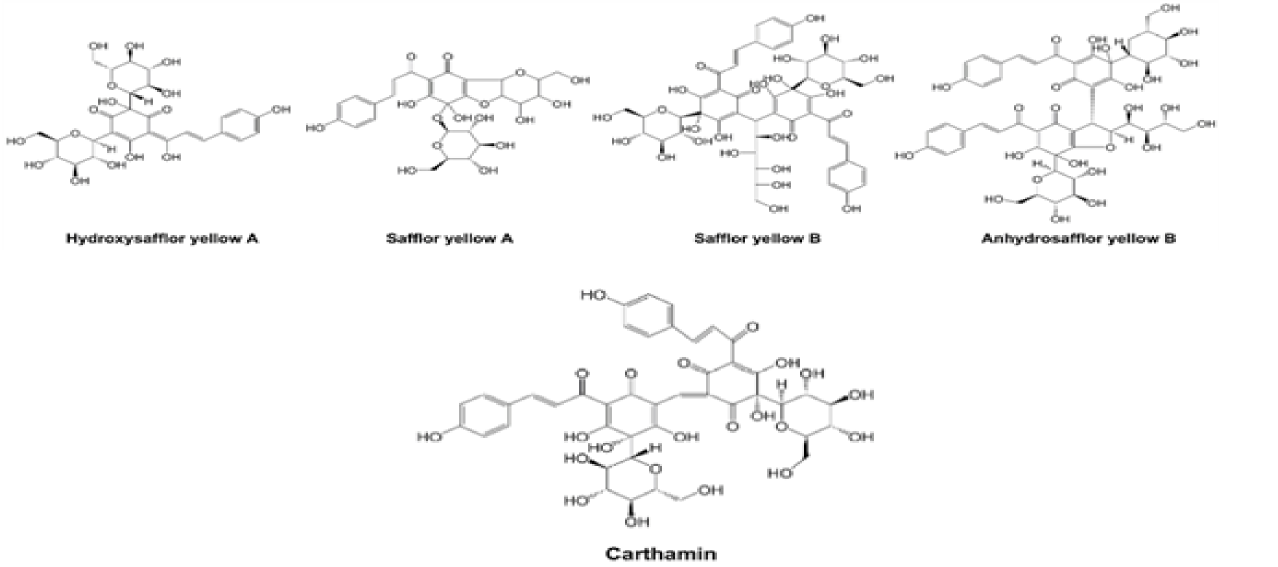

Fig. 2. Flavonoid compounds of Carthamus tinctorius

Antioxidant Activity

Oxidative stress is resulting from an excessive amount of free radicals which lead to damage to DNA, lipids, carbohydrates and proteins. Antioxidants, enzymes and non-enzymes play an important role in neutralizing this imbalance. In order to both prevent and treat some diseases, namely non-insulin dependent diabetes mellitus (NIDDM), hypertension, atherosclerosis, inflammation, cancer, Alzheimer, Parkinson, muscular dystrophy, antioxidants may act directly or indirectly to free radicals activity (6, 20). Some evidences of antioxidant activity of plants correlate with the bioactive compounds like polyphenols. Polyphenols act as antioxidant by reducing a numerous ROS, SOD and free radicals. Also, it is notable for the inhibition activity on oxidative damage in cells (21).

Currently, numerous studies have indicated that antioxidants extracted from many plants have minor undesired effects, including safflower extract. The hot aqueous CT seed extract have a good performance to reduce the free radical and oxidants effects based on in vitro test (DPPH and ABTS radical scavenging, the FRAP assay, and the reducing power assay) (22). Similarly result for Heok Hong study, CT hot water extract demonstrated higher ability to prevent oxidation (5.81-10.66%), following the increasing of total phenolic and total flavonoid content (23). Moreover, the water extract revealed the antioxidant capacity for total antioxidant capacity (TAC), oxygen radical absorbance capacity (ORAC) was scavenging hydroxyl radical capacity (SHRC) and scavenging superoxide anion radical capacity (SSARC) at 885.1 ± 5.5 U/g, 67.38 ± 0.12 TE/g, 1020.3 ± 3.8 U/g, and 636.5 ± 5.3 U/g, respectively (24). Compared to known antioxidant compound, Vitamin C, CT seed oil introduced the potent antioxidant power (FRAP; 247.5 ± 0.034 µmol Fe^{2+}/kg oil) as well scavenging effect on DPPH (89.41 ± 0.38 Vit. C eq/g oil) and ABTS radicals (88.52 ± 0.45 Vit. C eq/g oil) (25). The notable inhibitory capacity (IC_{50}) to diminish free radicals performed by CT flower extracts at 96.65%. This finding correlates with the numerous phenolic compounds in flower part of CT both in methanol and water extracts (2.12 and 1.32 g/100 g, respectively)(15). In addition, Bacchetti's study revealed radical scavenging activity not only the CT extract (EC50; 0.17 ± 0.01 µg GAE/ µg DPPH) (26).

According to Zhang's report, the antioxidant capacity was linked with the content of HSYA and AHSYB. It was found that as increasing of the concentration of safflower extract following the increasing of antioxidant effect. Furthermore, the contents of HSYA and AHSYB in high concentration safflower extracts were also relatively high. It was predicted that HSYA and AHSYB responsible for the inhibition of free radical DPPH (27). Further information of the antioxidant activity of the isolated compounds, HSYA and SYA, expressed as EC_{50} (0.09 ± 0.01 µg HSYA/ µg DPPH and 0.38 ± 0.06 µg HSYA/ µg DPPH, respectively). Trolox index for HSYA and SYA are 7.1 ± 0.3 and 2.1 ± 0.1 respectively compare to Quercetin (10.7) (26). Other reported for HSYA antioxidant effect in scavenging radical (ABTS) by comparing to Vitamin C, SC_{50} values of HSYA was 44.39 ± 1.62 µg/mL than vitamin C with SC_{50} of 4.87 ± 2.22 µg/mL (28).

The other polyphenol compounds of CT, *carthamin* and *precarthamin*, have been determined for antioxidant capacity using three different assays (FRAP, DPPH, and chelating power). It was found that fructification stage has the highest *carthamin* content and the strongest antioxidant as well (29, 30). Additionally, several polyphenolic compounds of CT, safflomin C, isosafflomin C, methylsafflomin C, and methylisosafflomin C, have a similar EC_{50} yield with caffeic acid and ascorbic acid expressed as Trolox Equivalent (1.34) as determined by ABAP/ABTS assay, and showed strong antioxidant activities against the ABTS radical system (28). Not only HSYA and AHSYB, but also 6-hydroxykaempferol-3, 6-di-O-glucoside-7-O-glucuronide were the potential antioxidant (31). The evidence of HSYC as antioxidant against H_2O_2 induced cytotoxicity in cultured H9c2 cells in vitro was active significantly active. Therefore it suggests that the potential used for treatment of cardiovascular diseases (30).

The excessive free radicals and oxidants in cells lead to cause various disorders. Cell line cultures support the antioxidant capacity of safflower by anticipating the oxidative affliction in cells, such as lowering the lipid accumulation in 3T3-L1 cells (22). Moreover, in vivo study, CT extract decreased the MDA serum level and the level of SOD and GSH-Px levels in hyperlipidemia rats (24). Thus, CT extract act as antioxidant that relate to obesity. Safflower extract also give a protection in cells against LPS-induced damage by mitigate the intracellular ROS levels linked with α-glucosidase and lipase inhibitory (23). In addition, it can be decreasing ROS concentration in BJ cells (fibroblast skin) at the concentration of 500 µg/mL (32). The antioxidant activity of HSYA expressed as the high ratio of GSH/GSSG which represented the reducing formation of free radicals to traumatic brain injury (24). Rich of polyphenols, CT also has alkaloids that give a significant antioxidant effect, including N-feruloylserotonin, N-feruloyltryptamine and serotonin derivatives (19).

Antimicrobial Activity

Because the drawbacks of antibiotics are widely used, and the resistance to microbial strains, a new alternative of antimicrobial agent from natural products attracts many researchers (33). The antibacterial activity from extracted compounds of various plants is widely studied due to in vitro evidence of the potency of antimicrobial properties of some phytochemical compounds, namely tannins, terpenoids, alkaloids, flavonoids, and glycosides (34).

CT water extract possess a significant antimicrobial activity in a number of bacteria (*Bacillus subtilis*, *Bacillus cereus*, and *Bacillus mycoides, Proteus vulgaris, and Klebsiella pneumonia, S. aureus, E. coli, P. aeruginosa, and K. pneumonia*) and also in fungi (*Aspergillus niger*, *Penicillium expansum*, *Geotrichum candidum*, *Aspergillus fumigatus*, *Candida albicans*, and *Rhodotorula rubra*) (19, 35, 36).

Furthermore, an antibacterial effect also performed by safflower methanolic extracts in different cultivars (IL111, Padide, Isfahan-28, and Mahali). It was found that Isfahan-28 cultivar presented the best inhibition against Staphylococcus aureus and Salmonella enterica serovar Typhi at concentration 30 and 60 mg/ml, respectively (36). Seed oil of safflower also gives an impressive inhibition result against E.coli, S. aureus Streptococcus agalactiae, and Enterobacter cloacae and for the fungicidal activity against Candida parapsilosis, Candida sake, Aspergillus niger, Penicillium digitatum, and Fusarium oxysporum (25, 36). The volatile oil of C. tinctorius L. revealed the potent activity against the Cryptococcus neoformans with IC50 20.41 µg/mL (37). Interestingly, the nanoparticles of CT extract indicated an excellent antimicrobial activity against several bacteria which are promising methods for the development of newer pharmaceuticals (19).

However, the flavonoid extract inhibit more effective than the oil extract to some bacteria, both Gram-positive and Gram-negative bacteria (36). The high antibacterial activity introduced by the chalcone compound of CT flower extract, carthamin, following the more compound in flowering stages against E. coli, which was similar to gentamicin (iz = 26) (29). The isolated compound, Dehydroabetilamine, a diterpene, has the same trend for the bacterial effects in S.aureus and P.aeruginosa with a notable MIC at 12.5 µg/mL and 6.25 µg/mL, respectively(13). Nevertheless, precarthamin performed the contrast effect (iz = 17.56mm) (29).

Antiviral activity

The antioxidant compound polyphenols, especially flavonoid, is considered to have an antiviral effect against such RNA viruses as poliovirus, *sindbis* virus, respiratory syncytial virus (RSV), and DNA virus, Herpes simplex virus (HSV). The antiviral mechanism of flavonoids is to inhibit viral polymerase and bind with DNA viruses or viral capsid proteins (38).

In addition, an antiviral study of CT extract reported by Lee et al, that it has a strong cytotoxicity against KSHV (Kaposi's Sarcoma Associated Herpesvirus) (39).

Anti-HIV activity introduced by SH formula (combination of 5 plants: *Morus alba*, *Glycyrrhiza glabra*, *Artemisia capillaris*, *Astragalus membranaceus* and *Carthamus tinctorius*) at IC_{50} was 217 µg/mL. Furthermore, the combination between SH formula and ATV (Antiretroviral) exhibited the enhancement activity against HIV protease. Therefore, this study demonstrated the potency of combinational used of anti-HIV drug between ATV and SH formula (40).

An antiviral candidate via enzyme–based inhibition of SARS-CoV-2 was demonstrated by CT hot water extract. This activity in COVID-19 signaling by kinase and other pathways in both the large compound and nanoparticle of CT, which the CT hot water extract shows the higher binding activity than the nanoparticle (41).

4. Conclusion

Since safflower has antioxidant compounds and has been proved in many studies, it is considered to relate to other activities, like antimicrobial and antiviral effects. Therefore, it can be concluded that it has a promising potency to be developed as an antiviral agent.

5. Acknowledgments

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