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Antifungal Activity of the Secondary Metabolites Extracted from *Carthamus tinctorius* L. against *Aspergillus* Species Isolated from Stored Medicinal Plants Seeds in the Iraqi Markets

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Abstract

The present study, was conducted to investigate the effect of the crude alkaloids, flavonoids, and terpenoids compounds extract from seeds of (*Carthamus tinctorius* L.) against *Aspergillus* species isolated from stored medicinal plants seeds collected from different local markets in the province of Babil 2020 in Iraq. Antifungal activity was achieved *in vitro* by using food poisoning method against *Aspergillus* species by preparing three concentrations for each crude compound (5,10 and 20) mg/ml and compared with positive control represented by fungicide Quinoleine 50% and negative control represented by 10% dimethyl sulfoxide. The aim of this study was to control of *Aspergillus* species isolated form stored medicinal plants seeds by using secondary metabolites extracted from seeds of *Carthamus tinctorius* L. The data collected from the study revealed that, the crude alkaloids, flavonoids, and terpenoids compounds extract from seeds of (*Carthamus tinctorius* L.) showed significant reduction at $P \leq 0.05$ in the growth of *Aspergillus* species especially at 20 mg/ml compared with negative control. Finally, it can be concluded that *Carthamus tinctorius* L. is most effective in controlling *Aspergillus* species, especially terpenoids compounds.

Keywords: Alkaloids • Flavonoids • Terpenoids • *Carthamus tinctorius* L. • Antifungal

Introduction

Carthamus tinctorius L. (Safflower) of family Asteraceae is a medicinal plant with great potential. Its extract and oil have many therapeutic uses and having great pharmacological importance. Safflower is mainly cultivated for its seeds, oil and flowers. It is to cure many day-to-day ailments, and has proved importance as purgative, analgesic, anti-inflammatory, antipyretic, menstrual problems, post-partum hemorrhage, osteoporosis, diabetes, hepatoprotection, cancer, fibrosis and antioxidant. Carthamine, hydroxyl safflower yellow-A, carthamidine, luteolin are the main phytoactive principles of this plant. Flavonoid derivatives and Furanocoumarins are a target for inflammatory, antimicrobial, anticancer, antidiarrheal drugs [1]. *Carthamus tinctorius* L. commonly known as Safflower or false saffron is a thistle like, self-compatible, annual, diploid (2n=24) herbaceous crop that thrives in hot and dry climates and is believed to have been domesticated somewhere in the Fertile Crescent region over 4,000 years ago [2]. *Carthamus* species probably originate from Southern Asia and is known to have been cultivated in China, India, Iran and Egypt almost from prehistoric times. During middle ages it was cultivated in Italy, France, and Spain, and was introduced into United States in 1925 from the Mediterranean region [3]. More than 200 compounds have been isolated from C. tinctorius and the commonly known ones are flavonoids, phenylethanoid glycosides, coumarins, fatty acids, steroids and polysaccharides [4]. Oil content of the seeds is similar to that of olive and includes linoleic acid (63%-72%), oleic acid (16%-25%) and (1%-6%) of linolenic acid [5]. Phytochemical are secondary plants metabolites includes (a) Alkaloids, having the characteristics of antispasmodic, antimalarial, analgesic, diuretic activities, (b)Terpenoids, having the properties of antiviral, anthelmintic, antibacterial, anticancer, antimalarial, anti-inflammatory ,(c) Glycosides are known for its antifungal and antibacterial properties, (d) Phenols and flavonoids are reported to have an antioxidant, anti-allergic, antibacterial properties etc. and (e) Saponins have the properties of anti-inflammatory, antiviral, plant defence activities [6,7]. The resistance of pathogenic fungi to antifungal drugs is one of the major public health problems. Plant extracts have shown inhibitory effect on the growth of wide range of fungi. They are represented a good alternative for prevention and treatment of fungal diseases [8]. From this standpoint, humans should search for natural sources that are less harmful and environmentally friendly in order to control fungi and reduce as much as possible the use of fungicides and pesticides. However, the aim of this study was to control of *Aspergillus* species isolated form medicinal plants seeds by using secondary metabolites extracted from *Carthamus tinctorius* L. seeds.

Materials and Methods

Plant material

Safflower seeds (*Carthamus tinctorius* L), had been purchased from local markets, identified based on the taxonomic features in Iraqi Flora (Table 1) [9]. Seeds of these plants were cleaned, dried, and kept according to Figure 1 [10].

Table 1. Scientific, Local, English name, Family, and active parts.

Scientific name	Local name	English name	Family	Active part used
Carthamus tinctorius L.	Asfur, Asfoor, Usfur	Safflower	Asteraceae	Seeds

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Figure 1. Seeds of *Carthamus tinctorius* L.

Extraction of the crude alkaloid compounds

Crude Alkaloid compounds were extracted according to Harborne [11].

Extraction of the crude flavonoid compounds

Crude flavonoid compounds were extracted according to Boham [12].

Extraction of the crude terpenoid compounds

Crude terpenoids compounds were extracted according to Harborne [13]. Stock solution of 200 mg/ml for Alkaloid, Flavonoid, and Terpenoid were prepared in 10% Dimethyl Sulfoxide (DMSO) then sterilized by Millipore filter (0.22 µm) and stored at (-20°C) until use [14].

Medicinal plants seeds collection

Medicinal plants seeds were collected from different regions of local markets in the province of Babil/Hillah City 2020 in Iraq.

Isolation and diagnosis of *Aspergillus* species

To isolate the *Aspergillus* fungus 100 seeds were taken randomly from each of the collected samples. It was sterilized using 2% sodium chlorate for 2 minutes and then washed with sterile distilled water twice to remove traces of sterile material and dried with sterile filter paper. It was transferred with sterile forceps to 9 cm petri dishes containing 20 ml of pre-prepared Potato Dextrose Agar(PDA) with (chloramphenicol) 50 mg/l to prevent bacterial growth [15], by 5 seeds per dish and three replicates per sample and then incubated in 25°C for 5-7 days. The fungi associated with the seeds were then purified by secondary cultures for identification. Isolated fungi were then diagnosed based on the taxonomic keys of both [16,17]. The fungal isolates were kept in clean, sterile glass containers containing the Nutrient Agar. Containers were incubated at 25°C for a week and then placed in the refrigerator at 4°C until it was used.

Antifungal activity assay of extract

PDA medium was prepared and autoclaved after that a known volume (2 ml) of the each plant extracts is placed in the center of the petri dishes and complete the volume to 20 ml with PDA medium to obtain the required final concentrations (5,10 and 20 mg/ml) of the medicinal plants after complete solidification of the medium, 5 mm disc of seven days old culture of the test fungus were placed aseptically in the center of the Petri plates and incubated at 25 ± 2°C for seven days, simultaneously 0.02 ml of antibiotic solution was added to each assay plate to check the bacterial contamination as suggested [18]. Fungicide Quinoleine 50% was used as positive control and dimethyl sulfoxide as negative control. Observations were recorded on seventh day. The colony diameter was recorded in terms of millimeters. PDA medium devoid of extract served as control. For each treatment three replicates were maintained. The fungi toxicity of extracts was calculated in terms of percent inhibition of mycelia growth by using the formula [19].

Percent Inhibition=(dc-dt/dc) × 100

where:

dc=Average increase in mycelia growth in control.

dt=Average increase in mycelia growth in treatment.

Statistical analysis

All data of treatments were dictated by three replicates. Data were subjected to an analysis of variance by using SPSS 16.0 program, a completely randomized design was used and Least Significant Difference (L.S.D) was performed at P ≤ 0.05.

Results

The results of antifungal activity of the crude Alkaloid compounds extracted from the seeds of (*Carthamus tinctorius* L.) against *Aspergillus* species isolated from stored medicinal plants seeds are presented in Table 2. The antifungal activity of Alkaloid secondary metabolites with three concentration (5,10 and 20 mg/ml) was screened by food poisoning methods. The results revealed that, the crude Alkaloid compounds extracted from the seeds of (*Carthamus tinctorius* L.) showed significant reduction at P ≤ 0.05 in the growth of *Aspergillus* species. Antifungal activity was applied at (5,10 and 20) mg/ml. mycelial inhibition ranging from (34.666% in 5 mg/ml, 78% in 10 mg/ ml, and 95% in 20 mg/ ml) compared with negative control and positive fungicide Quinoleine 50% control where inhibition percentage was 0.00% for negative control and 100% for positive control (Figures 2 and 3). On the other hand, the crude flavonoid compounds showed 71% mycelial inhibition at (5 mg/ml) and 88.16% at (10 mg/ml), and 91% at (20 mg/ml) concentration (Table 3). Thus, it differed significantly compared to the control treatment (Figures 4 and 5).

Table 2. Antifungal activity of the crude Alkaloid compounds extracted from seeds of (*Carthamus tinctorius* L.) against *Aspergillus* species isolated from stored medicinal plants seeds.

Concentrations (mg/ml)	Alkaloids compounds
	Inhibition percentage %
Negative Control	0 ± 0.00
5 mg/ml	34.666 ± 1.52
10 mg/ml	78.00± 2.00
20 mg/ml	95.000 ± 1.00
Positive Control	100 ± 0.00
L.S. D	2.203
Note: Mean ± standard deviation	

Table 3. Antifungal activity of the crude Flavonoid compounds extracted from seeds of (*Carthamus tinctorius* L.) against *Aspergillus* species isolated from stored medicinal plants seeds.

Concentrations (mg/ml)	Flavonoid compounds
	Inhibition percentage %
Negative Control	0 ± 0.00
5 mg/ml	71.000 ± 1.000
10 mg/ml	88.166± 0.763
20 mg/ml	91.000 ± 1.000
Positive Control	100 ± 0.00
L.S. D	0.767
Note: Mean ± standard deviation	

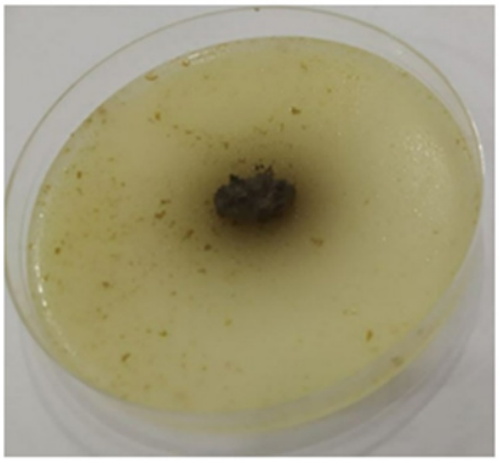

Figure 2. Antifungal activity of the crude Alkaloid compounds at 20 mg/ml against *Aspergillus* species.

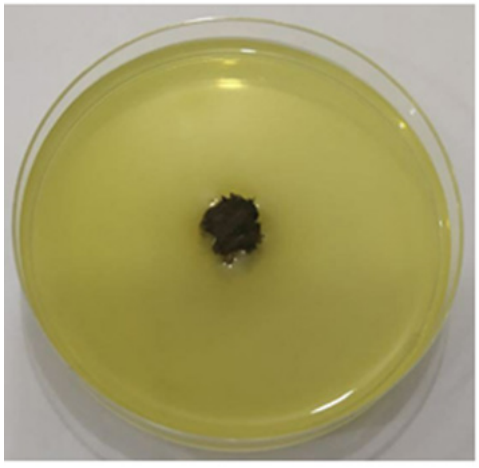

Figure 3. Growth of *Aspergillus* species in the fungicide Quinoleine 50% treatment.

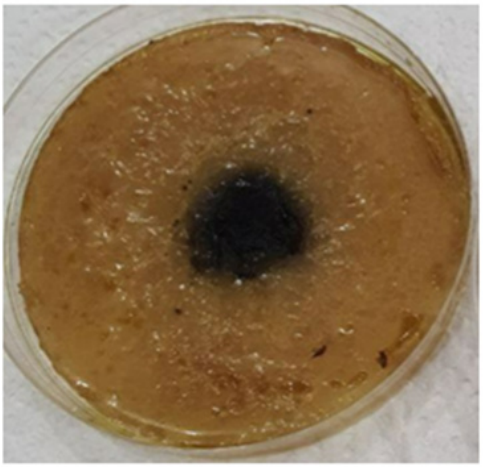

Figure 4. Antifungal activity of the crude Flavonoid compounds at 10 mg/ml against *Aspergillus* species.

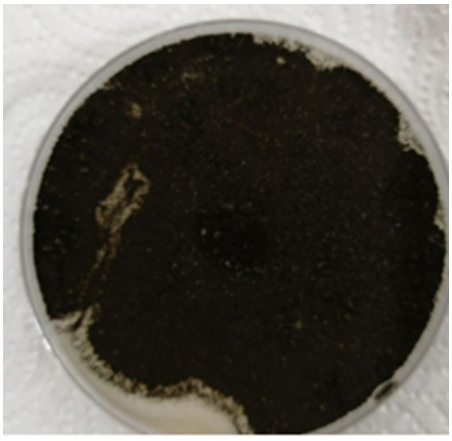

Figure 5. The growth of *Aspergillus* species in control treatment

In the same context, the crude terpenoid compounds showed significant activity at three concentrations (5,10 and 20 mg/ml) compared with negative control against *Aspergillus* species isolated from stored medicinal plants seeds (Table 4). The highest percentage of inhibition (96%) was recorded at 20 mg/ml and (84%) was recorded at 10 mg/ml (Figure 6). While the highest percentage of inhibition in the crude alkaloid compounds was reached up to (95%) at 20 mg/ml concentration and the highest percentage of inhibition in the crude flavonoid compounds was reached up to (91%) at 20 mg/ml concentration.

Table 4. Antifungal activity of the crude Terpenoid compounds extracted from seeds of (*Carthamus tinctorius* L.) against *Aspergillus* species isolated from stored medicinal plants seeds.

Concentrations (mg/ml)	Terpenoid compounds
	Inhibition percentage %
Negative Control	0 ± 0.00
5 mg/ml	72.000 ± 2.000
10 mg/ml	84.000 ± 1.000
20 mg/ml	96.000 ± 1.000
Positive Control	100 ± 0.00
L.S.D	1.992
Note: Mean ± standard deviation	

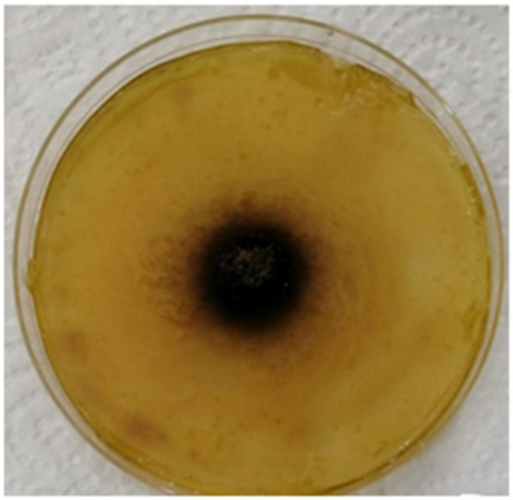

Figure 6. Antifungal activity of the crude Terpenoid compounds at 10 mg/ml against Aspergillus species.

Discussion

The present study was proved that, the secondary metabolites include alkaloids, flavonoids, and terpenoids extracted from the seeds of (*Carthamus tinctorius* L.) have powerful antifungal activity against *Aspergillus* species isolated from stored medicinal plants seeds. The plant kingdom provided and is still providing endless sources of medicinal plants of various uses for example, Bioactive compounds such as phenolic, terpenoids, and alkaloids extracted from several medicinal plants like *Lactuca serriola* L., *Lepidium sativum* L., *Myrtus Communis* L., *Cassia senna* L., *Ricinus communis* L., *Cassia didymobotrya* (*Fresenius*) Irwin & Barneby, *Melia azedarach* L., *Dianthus caryophyllus* L., and *Salvia hispanica* L. have antibacterial efficacy against different pathogenic microorganisms. [20-28]. Hussein used primitive plant like *Chlorella* vulgaris as antibacterial [29]. Kamal used *Hibiscus sabdarifa* extracts against member of Enterobacteriaceae microorganisms [30]. Kamal used leaves of *Ficus carica* Linn against pathogenic bacteria [31]. AL-Masoodi used *Curcuma longa* L. and Boswellia carteri Birdwood against Fusarium species isolated from maize seeds [32]. The antifungal activity of the carthamin natural pigment of safflower was more active against Candida albicans than precarthamin [33]. The chemical groups isolated from *Carthamus tinctorius* were included, oils, proteins, minerals, phenolics, flavonoids, alkaloids, lignans, carboxylic acids, steroids, polysaccharides, quinochalcone C-glycosides and quinone-containing chalcones [34]. Safflower oil extracted from seeds exhibited a significant antifungal activity against *Candida parapsilosis*, *Candida sake*, and three fungal species *aspergillus niger*, *Penicillium digitatum*, and *Fusarium oxysporum* [35]. On the other hands, the mode of the antifungal action of the Alkaloids is usually pleiotropic, where protein synthesis is inhibited, and the fungal DNA is intercalated or by boosting the development of fungi inhibitors [36]. Terpenoids reduced the mitochondrial content, thus modified the level of reactive oxygen species (ROS) and ATP generation. It is also reported that triterpenoid possesses more potent antifungal activity as compared to the tetraterpenoid [37]. Terpenoids and flavonoids make their effects by disruption of microbial membranes [38]. Medicinal plant possessed antifungal effects by many mechanisms, they caused membrane disturbance resulting in the loss of membrane integrity, inhibited DNA transcription and reduced the cell populations, inhibited the activity of fungal antioxidant enzymes and inhibited fungal biofilm formation [39,40].

Conclusion

Antifungal activity of *Carthamus tinctorius* L. might be belonging to secondary metabolites like alkaloids, flavonoids, and terpenoids and their effect in proteins and DNA synthesis and disruption in membranes permeability or disturbance in metabolic activity. Alkaloids, flavonoids, and terpenoids extracted from the seeds of (*Carthamus tinctorius* L.) have powerful antifungal activity against *Aspergillus* species. *Carthamus tinctorius* L. The data collected from the study revealed that, the crude alkaloids, flavonoids, and terpenoids compounds extract from seeds of (*Carthamus tinctorius* L.) showed significant reduction at $P \leq 0.05$ in the growth of *Aspergillus* species especially at 20 mg/ml compared with negative control. Finally, it can be concluded that *Carthamus tinctorius* L. is most effective in controlling *Aspergillus* species, especially terpenoids compounds.

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