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Echinophora platyloba DC. as a new natural antifungal agent

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PEER REVIEW

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Comments

The printing on the proposal of this manuscript is very interesting, although it has a fairly regional for the country from the plant. Thus, I also believe that there is significant potential for use of *Echinophora platyloba* DC, that makes me believe that the publication of the manuscript is a plausible option.
Details on Page 173

ABSTRACT

Echinophora platyloba DC. (Umbelliferae family) (*E. platyloba*) is a spiny plant with yellow flowers that in Iranian traditional medicine is used as an antifungal agent for preventing the dairy products and foods from fungi contaminations. This subject was the basis of an idea that has been supposed *E. platyloba* as an antifungal agent. This review investigates the studies that are designed on this idea. Also, it mentions other investigations that evaluate the other biological activities of this valuable plant. Literatures about *E. platyloba* were collected by electronic search and referred books on ethnopharmacology for receiving traditional records about this plant. Although, *E. platyloba* is a plant with many pharmacological effects but the main biological effect is their antifungal and synergistic effect with azole drugs against *Candida albicans* infections *in vitro* and *in vivo* studies. *E. platyloba* can be used as new candidates for treatment of *Candida albicans* infections. Other pharmacological effects should be more evaluated. Future studies should be directed on isolation and identification of antifungal sub-fractions by more precise investigations.

KEYWORDS

Echinophora platyloba, *Candida albicans*, Biological activity, Iranian traditional medicine

1. Introduction

Echinophora genus, a member of Umbelliferae family, has ten different species with white or yellow flowers that defined as *Echinophora tenuifolia*, *Echinophora platyloba* (*E. platyloba*), *Echinophora sibthorpiana*, *Echinophora anatolica*, *Echinophora cinera*, *Echinophora vadiaus*, *Echinophora orientalis*, *Echinophora tournefotti*, *Echinophora trichophylla* and *Echinophora spinosa*. Among ten species, *Echinophora orientalis*, *Echinophora sibthorpiana*, *Echinophora cinera* and *E. platyloba* are native to Iran and they are distributed in the west to western north of Iran[1]. From four native *Echinophora* sp., *E. platyloba* is an important traditional plant with a long history in Iranian traditional medicine[2,3]. In folklore, *E. platyloba* is commonly known as "Khosharuz", "Khusharizeh",

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"Tigh-Turagh", "Koshandar", "Tigh Masti", "Kouzang", "Tanghezand" and "Tologh-Oti".

E. platyloba is a spiny plant with yellow flowers and cylindrical fruits on a single stem and grows at 1400 to 2000 m above the sea level in sandy soils from early September to October and then it begins its sleeping season (Figure 1). The altitude and temperature change its growth season. *E. platyloba* is used as a folkloric medicinal herb in Iranian traditional medicine as a food flavoring in dairy products such as cheese and yoghurt[4]. And in the southwestern part of Iran (ChaharMahal-va-Bakhtiari Province), its main usage is as antifungal preservative agent for preventing the fungal growth on some traditional made foods like tomato paste and pickled cucumber[2,3].

Figure 1. *E. platyloba* DC.

For the first time, the preservative potency of *E. platyloba* in food products has been the basis of some studies about the antimicrobial activity of *E. platyloba* extracts by Prof. Avijgan and his colleagues[5-10], even though there are some researches on *E. platyloba* before Prof. Avijgan and his colleagues[11-13], which mainly focused on chemical composition of its essential oil, but the first idea of the antifungal activities of *E. platyloba* extracts was created by him[5]. In this article, we review the biological activities of *E. platyloba* with emphasis on its antifungal properties as its folkloric uses.

2. *E. platyloba* and its chemical composition

The first study, which has been conducted on phytochemical composition of *E. platyloba* reported this plant contained saponin, alkaloid and flavonoid but no tanin[12]. After a long time, another study on *E. platyloba* essential oil confirmed the presence of trans-β-ocimene (67.9%), 2-furanone (6.2%), myrcene (6.0%), linalool (3.1%) and β-ocimene (2.3%) as the main components of 10 identified components from *E. platyloba* aerial parts essential oil from Alvand Mountain, Golpaygan-Khomein Road. This oil was rich in monoterpenes (83.5%) with a predominance of hydrocarbons (80.4%)[11].

(E)-β-ocimene (49.9%), α-decalactone (8.4%), α-pinene (6%) and linalool (5.6%) were the main components of 29 components (93.5%) of *E. platyloba* aerial part essential oil from altitudes of Damavand, Tehran Province, Iran[3].

(Z)-β-ocimene (38.9%) and γ-phellandrene (24.2%) were the main composition of *E. platyloba* aerial parts oil from northwest of Iran, followed by p-cymene (7.4%), β-phellandrene (6.3%), α-pinene (3.4%), myrcene (1.6%), γ-decalactone (1.7%) and linalool (1.2%). Monoterpene hydrocarbons were 84.8% of total oil composition[13].

E. platyloba aerial parts oil from Shalamzar, Isfahan, Iran with yield 0.7% w/w exhibited 29 components that present 97.4% of total oil composition. (Z)-β-ocimene (26.7%), delta-3-carene (16.2%), limonene (6.6%) were found to be the main components of the oil. Other components were cis-3-hexyl benzoate (4.5%), spathunenol (4.6%), myristicin (4.5%), myrcene (4.3%), 4-decanolide (4.2%) and α-pinene (4.1%). This oil contains monoterpene hydrocarbons (62.1%), oxygenated monoterpenes (7.5%), sesquiterpene hydrocarbons (6.3%), and oxygenated sesquiterpenes (5.5%)[14].

E. platyloba aerial parts oil from ChaharMahal-va-Bakhtiari, Iran with yield 0.67% contained thymol (27.2%), trans-ocimene (20.9%), carvacrol (7.2%), E-sesqui-lavandulol (5.6%), limonene (4.5%) and geraniol (3%) as the most abundant compounds of 33 components that accounting for 95.7% of total oil composition. Monoterpenes (47.5%), oxygenated sesquiterpenes (8.1%) comprised the total amount of oil[15].

The essential oils from above studies were extracted from aerial parts of *E. platyloba* by hydrodistillation method. The chemical composition of oil and also its main components are affected by the altitude and environment.

There are many other techniques other than hydrodistillation method that is used for extraction of *E. platyloba* oils.

Asghari *et al.* (2012) extracted the essential oil from aerial parts of *E. platyloba* (Binaloud Mountain, Neishapor City) by microwave assisted hydrodistillation method[16]. The yield oil was about 40% higher than the hydrodistillation method and the extraction time was lower than hydrodistillation method (35 min *v.s.* 3 h). γ-decalactone (43.9%), trans-β-ocimene (21.6%) and cis-β-ocimene (4.2%) were the main components of 24 identified components from *E. platyloba* essential oil that accounts for 96.4% of total oil composition of microwave assisted hydrodistillation method, while E-β-ocimene (8.9%) and γ-decalactone (20.7%) were in the main components of 19 components (82.2%) of essential oil by hydrodistillation method[16].

Monoterpene hydrocarbons are prominent components of the *E. platyloba* oil. *E. platyloba* oil extracted by

hydrodistillation method is not an economic procedure due to low yield and time consuming procedure.

Besides altitude and growth condition, the development and different growth stage can change the quality and quantity of *E. platyloba* essential oil composition.

The composition of *E. platyloba* essential oil from aerial parts during different growth and developmental stages was the subject of another study. The yields of extraction (w/w) were 0.7%, 0.5% and 0.2% in rosette, floral butting and full flowering stages of *E. platyloba* essential oil, respectively. (Z)-β-ocimene was the major component of rosette stage, drastically decreased in floral budding and then slightly increased at the full flowering stage. E-β-ocimene was the main component of floral butting while its content decreased at the full flowering stage and was not detected at the rosette stage. Monoterpene hydrocarbons as main group compound were 71.6%, 64.8% and 69.8% at rosette, floral butting and full flowering stages, respectively[17].

3. Biological activity of *E. platyloba*

3.1. Antioxidant activity of E. platyloba

Free radicals are produced continuously in the body as normal cellular function but the increase in free radicals has an essential role in some coronary diseases, atherosclerosis, cancer and many other diseases. Antioxidants, especially natural ones are substances that prevent diseases by scavenging or neutralizing the free radicals.

It is reported that *E. platyloba* essential oil acts as a natural antioxidant. Due to the main components of extracts or oils affecting on its biological activities, we report the biological activities along with identified components. The inhibitory concentration (IC_{50}) of *E. platyloba* essential oil with (Z)-β-ocimene, delta-3-carene, limonene and total phenolic content (83.3 μg/mL) was 1.10 mg/mL and its inhibition percent (I%) was 68% in β-carotene bleaching test. Polar sub fraction of methanol extract exhibited lower IC_{50} than that of its non-polar subtraction (71.2 μg/mL *v.s.* 331.4 μg/mL). Total phenolic content of polar sub fraction was higher than non-polar sub fraction (67.5 *v.s.* 35.3 μg gallic acid/mg) and was lower than that of essential oil, while the antioxidant activity of essential oil and sub fractions of methanol extract were lower than butylated hydroxytoluene and ascorbic acid. However, there was a positive relation between total phenolic content and its antioxidant activity[18].

E. platyloba essential oil with thymol, trans-ocimene, carvacrol and (E)-sesqui-lavandulol as the main components exhibited high scavenging activity with IC_{50}=49.7 μg/mL, but this activity was lower than butylated hydroxytoluene and ascorbic acid as a synthetic antioxidant[15].

Although, *E. platyloba* essential oils or extracts act as natural antioxidant, the antioxidant potency is weaker than synthetic antioxidant. Furthermore, increasing in phenolic compounds of extract may enhance its antioxidant activity. Therefore, the extraction solvent may improve the concentration of phenolic compounds and its antioxidant potency.

3.2. Antimicrobial activity

As mentioned before, the first antimicrobial screening according to its folkloric uses as anti-mold agents was performed by Prof. Avijgan and his colleagues from the years of 2005. He extracted different components from *E. platyloba* aerial parts in full flowering stage, including essential oil, ethanol extract and fat oil at the first study, but among these different extracts, ethanol extract was effective and more economical for further evaluations. Therefore, *E. platyloba* ethanol extract is the suitable candidate for their studies. In the first study, we evaluated the antimicrobial activity of *E. platyloba* ethanol extract and its essential oil with yield 0.3% against Gram positive bacteria [*Staphylococcus aureus* (*S. aureus*), *Staphylococcus epidermidis* and *Streptococcus pyogenes*] in comparison to cephalexin, cloxacilin and penicillin G by disc diffusion method. The inhibition zone diameter for extract and oil revealed the fact that the plant did not have any antibacterial effect. Because the results of antimicrobial effects were very weak, we did not publish the results as a full paper. Then, we evaluated the antifungal activity of *E. platyloba* extract against *Trichophyton schenlaini, Trichophyton verucosum, Trichophyton rubrum, Microsporum gypsum, Trichophyton violaseum, Trichophyton mentagrophytes, Microsporum canis* and *Epidermophyton flucosum* by agar dilution assay. The results exhibited that *Trichophyton schenlaini* and *Trichophyton verucosum* were more sensitive to *E. platyloba* extract than *Trichophyton violaseum* and *Trichophyton rubrum*. *Microsporum gypsum* was less sensitive than *Trichophyton mentagrophytes, Microsporum canis* and *Epidermophyton flucosum*[5].

The minimal inhibitory concentration (MIC) value for *E. platyloba* ethanol extract against *Candida albicans* (*C. albicans*) was 2 mg/mL by agar dilution technique[6]. The higher effectiveness of *E. platyloba* ethanol extract against *C. albicans* than the other fungi and the prevalence of this yeast were the basis of other investigations. *C. albicans* is a member of mucosal flora and in humans with impairment of the immune system can lead severe diseases. *C. albicans* is also an important agent of vaginitis.

Therefore, we investigated again the anti-fungal activity of *E. platyloba* ethanol extract against *C. albicans* ATCC 10231 by microbroth dilution assay. The difference of this study compared with previous study was in the strain and

technique. The MIC and minimal fungicidal concentration values of *E. platyloba* ethanol extract against *C. albicans* ATCC 10231 were 1.560 and 3.125 mg/mL, respectively. The synergistic activity of *E. platyloba* extract and amphotericin B showed that *E. platyloba* extract decreased the MIC and minimal fungicidal concentration values of amphotericin B from 2, 8 mg/mL to 1, 2 mg/mL, respectively. The antifungal activity of *E. platyloba* ethanol extract was 780 folds weaker than amphotericin B and also this extract increased the potency of amphotericin B almost two-folds[7]. Since the satisfied results from antifungal activity screenings of *E. platyloba* extract against American Type Culture Collection of *C. albicans*, we continue our studies on synergistic effects of *E. platyloba* ethanol extract and azole drugs against clinical isolates of *C. albicans* from women suffering recurrent vaginitis. At first, we isolated 27 clinical isolates of *C. albicans* from vaginal samples of women with recurrent vaginitis during Jan 2011 to Jan 2012. Then, the antifungal activity of ethanol extract from dried aerial parts of *E. platyloba* was determined by microbroth dilution assay. The synergistic effect of azole drugs and *E. platyloba* ethanol extract were also determined by disc diffusion method after determining the MIC_{90}. The results of this study demonstrated the synergistic effect of *E. platyloba* ethanol extract with itraconazol ($P<0.01$) and fluconazole ($P<0.001$) but an antagonistic effect with clotrimazole and miconazole against clinical isolates of *C. albicans*[10]. In this direction, from the above results, we planned a double blind, randomized clinical study on 60 women (two groups containing 30 cases) with chronic recurrent vaginitis for several years. One group was treated with cream containing 4.2% *E. platyloba* ethanol extract (*Echino cream*) plus fluconazole and others with fluconazole alone. *Echino cream* was administered at night before bed and one pill of fluconazole (150 mg) was eaten at night for 2 weeks. After treatment, culture of vaginal discharge was positive for 13 (43.3%) and 6 (20%) cases with a recurrence rate of 17 and 8 (56.7% *v.s.* 26.7%) in fluconazole and *Echino cream* plus fluconazole, respectively. The difference was significant between two groups ($P<0.05$)[9].

Therefore, the *E. platyloba* can be used as an alternative agent for lowering the dose of synthetic chemical antifungal agent in candidiasis infections especially in chronic recurrent vaginitis.

The identification of effective compounds in *E. platyloba* is useful for exploring newer antifungal agent. The extracting of antifungal compounds is possible by sub fractioning of *E. platyloba* ethanol extract and evaluating the antifungal efficacies of different fractions against fungi. After defining the effective fraction, identifying the chemical structure of antifungal agent is possible by different chemical methods.

There are other studies conducted on antimicrobial activity of *E. platyloba* extracts by Saei-Dehkordi *et al*[15,19,20].

E. platyloba methanol extracts from leaves and stems showed antibacterial activity against *S. aureus* and *Pseudomonas aeruginosa* (*P. aeruginosa*) while this extract showed no activity against *C. albicans, Aspergillus flavus* and *Aspergillus niger*. The authors have been mentioned that this antimicrobial activity relates to trans-ocimene (67.9%), 2-furanone (6.2%), myrcene (6.0%) and linalool (3.1%) as the main components of essential oil that present in *E. platyloba* methanol extract[20]. On the basis of our investigation, we did not accept this study as a scientific research, because this study is full of defaults about the scientific names of microorganisms and there are not any logical relation between the antimicrobial activity and chemical composition of methanol extract.

In another study, *E. platyloba* ethanol extract showed the best antibacterial activity against *Listeria monocytogenes* while *Alcaligenes faecalis* was more sensitive to aqueous extract. *Serratia marscescenes* and *Providencia rettgeri* were found to be sensitive to *E. platyloba* ethanol extract[19].

E. platyloba essential oil with thymol, trans-ocimene, carvacrol and (E)-sesqui-lavandulol as major components exhibited antimicrobial activity against *Listeria monocytogenes, Bacillus cereus, Bacillus subtilis, S. aureus, Escherichia coli* $O_{157}H_7$, *P. aeruginosa, C. albicans, Candida tropicalis, Rhodotorula rubra* (*R. rubra*) and *Rhodotorula mucilaginosa* (*R. mucilaginosa*). *R. rubra* and *R. mucilaginosa* were the most sensitive microorganisms to *E. platyloba* essential oil. Gram positive bacteria and *C. albicans* were more sensitive than that of Gram negative ones. *P. aeruginosa* showed less sensitivity to *E. platyloba* oil. Antimicrobial interactions of *E. platyloba* and nisin, chitosan, monolarin, and amphotericin B were determined by assessing the fractional inhibitory concentration indices for Gram negative, Gram positive and yeast by checkboard micro titer method. The synergistic activity was observed by *E. platyloba* oil-monolarin against *Escherichia coli* $O_{157}H_7$, oil-nisin against *Bacillus cereus*, oil-chitosan against *R. rubra* and *R. mucilaginosa*. The fractional inhibitory concentration indices of oil with nisin and chitosan against Gram negative bacteria were lower than Gram positive bacteria. All combinations of oil-amphotericin B showed the synergistic effect against yeast, but the combination of oil-chitosan showed synergistic activity against only *C. albicans* and *Candida tropicalis*. This study illustrates that *E. platyloba* oil is effective against food-born microorganisms[15].

3.3. Anti-parasitic activity

There is one study that evaluates the anti-parasitic activity of *E. platyloba* against *Trichomonas vaginalis*. The results

showed that *E. platyloba* did not have any anti-parasitic activity on *Trichomonas vaginalis* growth[21].

4. Other demonstrated beneficial effects

E. platyloba is traditionally used as an antispasmodic agent in dysmenorrheal and its efficacy was proven in clinical trials. The single blind clinical trial was conducted on single student with primary dysmenorrheal. Sixty students were randomly divided into two groups, receiving *E. platyloba* extract and placebo. *E. platyloba* extract decreases significantly the severity of dysmenorrheal in comparison to the placebo after 2-month intervention[22].

Other single blind, randomized clinical studies were conducted on 90 students with moderate to severe premenstrual syndrome. Three equal groups received the *E. platyloba* extract, fennel extracts (*Foeniculum vulgare*) and placebo. No significant differences were seen between fennel and *E. platyloba* groups ($P>0.05$). The results showed that administration of fennel and *E. platyloba* extract reduced the severity of premenstrual syndrome[23]. *E. platyloba* extract like fennel with identified estrogenic activity may be acting as phytostrogen and can be used as natural agent for treatment of different ailments related to estrogen deficits especially in women's diseases[24].

5. Safety

For confidence about the safety of *E. platyloba* extracts in pharmaceutical and food industries, the safety of *E. platyloba* was assessed by evaluation of its acute and sub chronic toxicity in male and female Wistar rats. Mortality, clinical signs, changing in body weight, hematological and biochemical parameters, gross findings, organ weights and histological markers were evaluated during the 45 d of the experiment. Acute toxicological evaluations for *E. platyloba* extracts exhibited no mortality and no abnormality in clinical signs, body weights and necropsy findings. Hematological parameters showed no significant difference in sub chronic studies. Lactate dehydrogenase and relative lung weights, congestion of alveolar capillaries in female groups and intra alveolar hemorrhage in male rats had a significant increase of 500 mg/kg of *E. platyloba* extract. At 200 mg/kg of *E. platyloba* extract, liver bridging necrosis was found in the female group. The safety level of *E. platyloba* total extract was 200 and 50 mg/kg for male and female, respectively. The female rats are more sensitive to extract than male ones. At oral LD_{50} (50, 200 mg/kg) value, *E. platyloba* is non-toxic plant[25].

6. Conclusion and future research perspectives

E. platyloba ethanol extract is economically superior to the other extracts (methanol) and essential oil. Also, the biological activities and safety of *E. platyloba* ethanol extract are higher than the others. *E. platyloba* ethanol extract has synergistic effects with some antifungal drugs such as azoles *in vitro* and *in vivo* studies. Therefore, it can be used as new candidates for treatment of *C. albicans* infections. Furthermore, other pharmacological effects such as antioxidant or antibacterial activity (preservative efficacy) and estrogenic effects should be evaluated. But the most finding of this review article is antifungal potency in clinics as its traditional uses[4]. Future studies should be directed on isolation and identification of antifungal sub-fractions by more precise investigations.

Conflict of interest statement

We declare that we have no conflict of interest.

Comments

Background

The manuscript is well founded in accordance with the popular use of this plant, which certainly increases the importance of the manuscript in question. The literatures used are recent.

Research frontiers

The manuscript presents preliminary results of research on the plant in question. However, I think it is an important contribution since it brings together the latest information on the subject.

Related reports

It is a manuscript review, whose obligation is only to describe the research conducted previously. However, it described the use of conventional techniques for such purposes, and therefore the reported results are reliable.

Innovations & breakthroughs

The innovation that is not possible to check is to give more emphasis to the plant *E. platyloba* DC, showing the great potential for a future. Perhaps next, a phytotherapic medicine is developed using it as raw material.

Applications

I think that innovation planned and/or proposed by manuscript is exactly the exploitation of plant *E. platyloba* DC.

Peer review

The printing on the proposal of this manuscript is very interesting, although it has a fairly regional for the country from the plant. Thus, I also believe that there is significant potential for use of *E. platyloba* DC, that makes me believe that the publication of the manuscript is a plausible option.

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