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REVIEW ARTICLE

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REVIEW ON BOTANY, TRADITIONAL USES, PHYTOCHEMISTRY AND BIOLOGICAL ACTIVITIES OF *EUPHORBIA MICROSCIADIA* BOISS

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ABSTRACT

Background: In traditional medicine, Euphorbia was used to treat inflammations, tumors, gout, back pain, sciatica, arthritis, pneumonia, intestinal parasites, gonorrhea, and skin diseases. The species of this genus that distribute in most regions worldwide studied to discover and produce effective medicines because they contain valuable active compounds. In this study, we provided available evidence regarding *Euphorbia microsciadia* Boiss. as one of the main species of this genus.

Methods: For this purpose, we searched for relevant publications in scientific databases including PubMed, Web of Science, Google Scholar, Scopus, local herbal encyclopedias and textbooks.

Results: Certain chemical compounds, including flavonoids and terpenoids, have been isolated from *E. microsciadia*. Recent pharmacological investigations have demonstrated that its extracts and active compounds have a wide spectrum of pharmacological effects, such as antimicrobial, antiviral, anticancer and immunomodulatory.

Conclusion: This plant has a great potential and a broad spectrum of activities for treating different illnesses. Terpenes, as the main compounds of this plant, can be considered a potent source of natural compounds for discovering anticancer drugs.

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INTRODUCTION

Throughout the history, people have been used medicinal plants as a source of medicine. Also in the modern medicine, researchers have been evaluated their value as a source of new medicinal products or complimentary for discovering effective drugs (1-4). The plant-based medicine system plays an essential role in the health care (5-9).

Euphorbiaceae is one of the plant families whose various properties have been addressed both in traditional medicine and by experimental studies. Euphorbiaceae is a large family of the plants including 300 genera and over 7500 species. In most parts of the planet, except for the polar regions and peaks of the high mountains, this genus of this family distribute. Euphorbia is one of the most important genuses of the Euphorbiaceae family, which consists 2,000 species. The Euphorbia genus consists of one-base plants, one male floral flower with anthrax, female flowers with three-barrel ovary, a cyathium inflorescence and three-frame capsule fruit, and is divided into two categories of plants: Annual herbaceous plants with short lifespan and perennial plants (10-12). Euphorbia is well-known as producing milky irritant latex and produces secondary metabolites with considerable chemical variety (13, 14).

Screening studies on different species of Euphorbia show the beneficial therapeutic effects of these plants for the treatment of various diseases such as cancer, rheumatism, jaundice, toothache, earache, pertussis, asthma, splenomegaly, liver diseases, diarrhea, nerve pains and bacterial and viral infections (15, 16). *Euphorbia microsciadia* Boiss. is one of the important species of Euphorbia whose compounds and properties have been frequently studied. In this review, an overview of the current evidence about traditional uses and phytochemical and biological properties of *E. microsciadia* was presented.

To conduct this review, Euphorbia, *Euphorbia microsciadia* and Farfion were used as search terms to retrieve relevant publications indexed in the *Pubmed*, *Google Scholar*, *Scopus* and *Web of Science* databases. The books on traditional medicine were also manually searched for relevant information. Only studies that directly examined the species of interest were selected. The articles without abstract in English language were excluded from the study. A total of 36 articles that fulfilled inclusion criteria were selected and their findings were analyzed.

Scientific name and synonyms

Euphorbia microsciadia Boiss. (figure 1) has many synonyms such as; *Euphorbia isophylla* Bornm, *Euphorbia kazerouni* Parsa, *Euphorbia kazerouni* var. *stricta*, *Euphorbia persepolitana* Boiss, *Euphorbia striata* Boiss, *Euphorbia striatella* Boiss, *Euphorbia striatella* var. *microsciadia*, *Euphorbia striatella* var. *persepolitana*, *Euphorbia yamashitae* Kitam, *Tithymalus microsciadius*, *Tithymalus persepolitanus*, *Tithymalus yamashitae*.

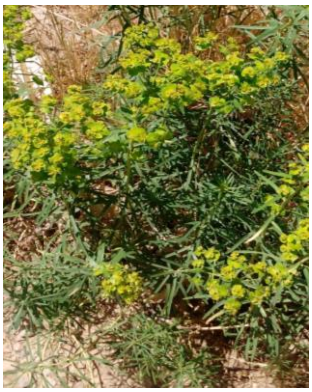


Figure 1. *Euphorbia microsciadia* Boiss (By author).

Botany and distribution

E. microsciadia has straight chamomile stems with two or very rarely three-branched divisions. This species is characterized by limited number of the end branches and the radii of the umbrellas are relatively short and the leaves around the umbrella appear to be thin. *E microsciadia* was utilized as a native plant from Iran. In Iran, this plant mainly distributes in the southern and central regions and occurs less frequently in northern Iran. It is found in highlands in northern Pakistan as well as in India (17, 18).

Traditional uses

In traditional medicine, plants from Euphorbia genus such as *E. microsciadia* was used as the treatment of inflammations, tumors, gout, back pain, arthritis, sciatica, pneumonia, intestinal parasites, gonorrhea, wart cures as a paste on sores, blister, and also in the treatment of skin diseases (18-20).

Biological activities

Antimicrobial and antifungal

Ghaedi and colleagues investigated the antimicrobial activity of euphol from *E. microsciadia* in the presence of nanoparticles ($ZnO/Zn(OH)_2$). The results of this research showed that methanolic extract of *E. microsciadia* had antibacterial effects on *Staphylococcus epidermidis*, *Escherichia coli*, and

Pseudomonas aeruginosa. In this study, antifungal activity of ZnO/Zn $(OH)_2$ nanoparticles covered with extract were tested against *Aspergillus oryzae*. Antifungal activities of constructed disks showed considerable difference for extract of *E. microsciadi* (21).

Antiviral

Antiviral activity of the some species of the genus *Euphorbia* against polio, coxsackie, and rhinoviruses has been reported (22). In Salmasi et al studies, the antiviral effect of *E microsciadia* was investigated using plaque reduction assay. This study indicated that the extracts of *E. microsciadia* have antiviral activities (23).

Immunomodulatory

E. microsciadia have shown to have immunomodulatory activity. Syed Mustafa Ghanadian et al. in their study, the human lymphocyte proliferation inhibitory effect of the isolated flavonol glycosides of *E. microsciadia*, showed flavonol glycosides from *E. microsciadia* could be used for the control of harmful immune responses and can show immunomodulatory activity (24).

Lymphocyte antiprolifeartive

The study of Ghannadian et al. on the activity of flavonoids isolated from *E. microsciadia*, showed that these flavonoids, particularly a quercetin called 3-O-β-D-galactopyranoside, has anti-lymphocyte proliferative activity. They argued that this activity could be due to the antioxidant role of flavonoids and inhibition of superoxide producing enzymes such as xanthine oxidase and protein kinase C, and that protein kinase C plays an important role in activating T lymphocytes. Therefore, this plant causes decrease in T lymphocyte activation by inhibiting protein kinase C (24).

Inhibiting tumor cell growth

The study of Amirghofran et al. (2011) on the inhibition of tumor cell growth and lymphocyte stimulation by Euphorbia species, showed that *E. microsciadia* could be used for inhibiting tumor cell growth (25).

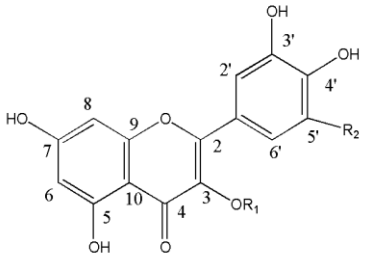
Antiangiogenic activity

E. microsciadia could serve as a natural source of chemical substances for treating diseases associated with pathological angiogenesis such as cancer disease. Ghannadian et al. studied anti-angiogenic activity of *E. microsciadia* in vascular endothelium growth factor (VEGF)-induced angiogenesis with cultured human umbilical vein endothelial cells through assessing capillary-like tube network formation, and were first to observe that a cyclomyrsinol diterpene acted as an inhibitor of angiogenesis (26).

Phytochemistery

E. microsciadia mainly contains flavonoids, terpenoids and other compounds. Also phorbol esters, steroidal saponins, cycloclarkeanol, β-sitosterol , and nonacosane reported in this plant. The major chemical structures of these compounds have shown in Figures 2, 3, 4.

One type of the important constituents of *E. microsciadia* is flavonoids. Four flavonoids (Figure 2) including, quercetin 3-O-β-D-glucopyranoside (Q3Glc), quercetin 3-O-β-D-galactopyranoside (Q3Gal), myricetin 3-O-β-D-galactopyranoside (M3Gal), and quercetin 3-O-β-D-rutinoside (Q3Rut) were isolated from aerial parts of *E. microsciadia* (24).



	R2	R1
1	*β*-D-glucopyranoside	H
2	*α*-L-rhamnopyranosy1 (1-6)-*β*-D-glucopyranosidc	H
3	*β*-D-galactopyranoside	OH
4	*β*-D-galactopyranoside	H

Figure 2. Flavonol glycosides (compounds 1-4) from *Euphorbia microsciadia* (24).

Other compounds of the aerial parts of *E. microsciadia* include terpenoids, two diterpenes; 3, 5, 10, 14, 15-O-pentaacetyl-8-O-isobutanoyl-cyclomyrsinol and 3-O-propionyl-5, 10, 14-O-triacetyl-8-O-(20-methylbutanoyl)-cyclomyrsinol (Figure 3) and three triterpenes; ursolic acid (UA), betulinic acid, and oleanolic acid (OA) (Figure 4) have been isolated from the aerial parts of *E. microsciadia* (26, 27).

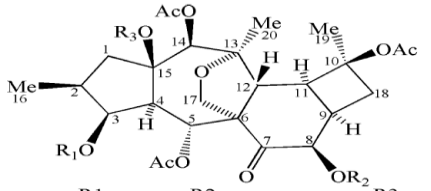


Figure 3. Cyclomyrsinol related diterpenes (1–2) from *Euphorbia microsciadia* Boiss (26).

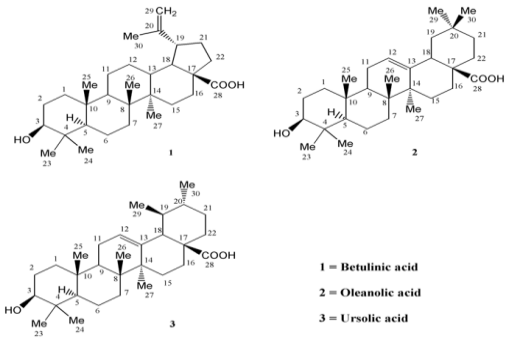


Figure 4. Pentacyclic triterpenes from *Euphorbia microsciadia* (27).

Pharmaceutical action mechanism and association chemical compounds and biological effects

Certain types of compounds in genus Euphorbia have very interesting immunomodulatory and anti-tumor properties (28, 29). Studies have also shown that *E. microsciadia* does not only lack these effects, but also can be addressed as a valuable agent for developing new anti-inflammatory and anti-cancer drugs.

Flavonoids (flavonol glycosides), diterpens (myrsinol) and triterpens (ursolic acid, oleanolic acid) are the main compounds that have so far been isolated from *E. microsciadia* (26).

Flavonoids have been reported to have many biological effects such as antioxidant, anti-inflammatory, anticancer, and anti-ischemic (30-32). Flavonoids present in human diet contain many polyphenolic secondary metabolites with a wide spectrum of pharmacological activities including anticancer. There is a positive correlation between flavonoids-rich diet (from vegetables and fruits) and lower risk of colon, prostate and breast cancers (33). Molecular mechanism of anticancer effect of flavonoids entails inhibition of pro oxidant enzymes, inhibition of PK_s, modulation of metabolism of carcinogen, inhibition of multidrug resistance, induction of apoptosis and cell cycle arrest, antioxidant properties and anti-angiogenic properties. In addition, flavonoids have the potential to modulate many biological processes in cancer such as cell differentiation, vascularization, cell proliferation, and apoptosis etc. A strong correlation persists between flavonoid-induced modulation of kinases with cell proliferation, apoptosis, and tumor cell invasive behavior in vitro. Moreover, some of the dietary flavonoids have been known to display anti-tumor activity and repress angiogenesis in vivo (33, 34). Because *E. microsciadia* is a source of flavonoids, it seems that this plant can be used in the treatment of breast cancer, anti-tumor activity and repress angiogenesis.

Terpenoids can be used as cancer chemopreventive agents (35). Terpenoids have been also reported to exert many biological activities, including antitumor, multidrug-resistance reversing, anti-inflammatory, and anti-HIV properties (36). Terpenes are secondary metabolites, which give the plant organoleptic properties (aroma and flavor), and comprise a large proportion of the essential oil produced by aromatic plants. Terpenes are known to exert for their lipophilic properties and their biosynthetic origin through the mevalonate and mevalonate-independent pathways. Structurally, terpenes are unsaturated cyclic or linear hydrocarbons with various degrees of oxygenation. They are classified by the number of five carbon units (isoprene) which are the building blocks of these compounds. It is known that isoprene occurs naturally but is not involved in the formation of these compounds, but instead by isomers of isopentenyl pyrophosphate and dimethylallyl pyrophosphate. Terpenes may vary from monoterpenoids (C10) to tertraterpenoids (C40), which are forty carbon molecules. Steroids are modified triterpenoids (C30) that are derived from squalene which is transformed into lanosterol. The basic structure of steroids is the well-known cholesterol molecule, with the typicall four fused cycloalkane rings. Substitutions in the functional groups surrounding the nucleus, formed by the fused rings, leads to a high metabolic activity to steroids, and therefore they can serve as hormones, drugs and anti-inflammatory medication (37-41).

The plants from the Euphorbia genus are mainly characterized by diterpenoids (13). Many secondary metabolites, which have chemotaxonomial significance, have been isolated from different parts of the species of the Euphorbia genus based on specific types of diterpene skeletons (e.g. jatrophane, etc.) (42). These diterpenoids can be formed in different steps of intramolecular cyclization of a casbene precursor, many of which retain the gem-dimethylcyclopropane ring in their final structures, such as lathyranes, tiglianes and ingenanes

(43). A casbene synthase has also been found to cyclize geranylgeranyl pyrophosphate (GGPP) to casbene (44). Moreover, Euphorbia diterpenoids have been demonstrated to exert many biological activities, including antitumor, multidrug-resistancereversing, anti-inflammatory, and anti-HIV properties (36). Diterpenoid have also been shown to inhibit cell proliferation and induce apoptosis (45, 46).

Myrsinol is a diterpenoid compound that is abundantly found in *E. microsciadia* with a wide range of biological activities. In a study in 2014, myrsinane-type diterpenes were evaluated for cytotoxic activities on human breast cancer cell lines. Myrsinane-type compounds exhibited moderate inhibitory effects, with IC50 values against the MDA-MB and MCF7 cell lines. Diterpenes may be one of the lead molecules in the treatment of cancer (26). Thus, *E. microsciadia* can be used to treat breast cancer due to a source of myrsinol-type diterpenes.

Triterpenes are highly capable of modulating multiple cancer-related signaling pathways and processes, including PI3K/Akt, Wnt/β-catenin, NF-κB, and many other routes related to proliferation or cell death (47-49). UA and OA are two triterpenes that have been isolated from *E. microsciadia*. UA is a pentacyclic triterpenoid compound which has a broad range of biological effects. UA has been shown to suppress tumorigenesis and inhibit tumor promotion (50). It has been observed that UA activates the immune system via activating the cell-mediated immune responses *in vivo*. UA with dose 50 μmol/kg BW for five consecutive days led to increased NK cell activity in animal models. Administration of UA obviously enhanced the ADCC. Treated animals with UA was also found to enhance ACC. The elevated level of GM-CSF in the control animals treated with tumor alone was reduced after UA treatment. The markedly increased level of interleukin 6 was also reduced by UA treatment. The level of interleukin 2 was enhanced by UA treatment when compared with untreated tumor-bearing control animals (51). Besides that, UA has been found to exhibit a wide range of pharmacological properties and is likely to become one of the most potent chemopreventive agents (52). OA, another triterpene of *E. microsciadi*a, has been demonstrated to be active ingredient in producing biological effects. It has been reported that OA exerts a wide variety of antitumor activities, including decrease in both the incidence and the multiplicity of azoxymethane-induced intestinal tumors. Treated rats with 200 ppm of OA in diet for 3 weeks decreased the incidence and multiplicity of intestinal tumor (53). OA has been recommended for treating skin cancer in Japan (54). Pharmaceutical preparation containing OA has also been patented for the treatment of nonlymphatic leukemia (55). In the study of Hua et al. in 2011, the effect of dextrose–OA on apoptosis and cell cycle of osteosarcoma cells was evaluated. OA had good inhibitory effect on the proliferation of the cells (56). Since triterpenes such as UA and OA represent major compounds of *E. microsciadia*, this plant can be used to treat melanoma, intestinal tumor, skin cancer and osteosarcoma.

Toxicity and dosage

Studies with *E. microsciadia* have not reported any toxicity. The lethal dose of this plant has not get been specifically determined. However, for the other Euphorbia species, this dose has been reported. For example, the study of Sultan et al. with rats to investigate the acute toxicity of *Euphorbia heliscopia*, showed that its oral LD50 was 1211.7 mg/kg body weight (57).

CONCLUSION

In alternative medicine, medicinal plant-derived preparations have recently been used to serve various purposes for diseases that cannot been effectively treated by modern approaches. Latex of *E. microsciadia* seems to have magical activities that have been extensively studied. Chemical and phytochemical analyses of *E. microsciadia* have revealed the existence of numerous important active compounds including flavonoids and terpenes. This plant has great potential and a broad spectrum of activities for several illnesses. Since anticancer effects of terpenes such as diterpenes and triterpenes have been confirmed, *E. microsciadia* can be considered a resource of natural compounds for discovering anticancer drugs.

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