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A REVIEW ON THERAPEUTIC POTENTIAL OF MEDICINAL PLANT *EUPHORBIA MACULATA* (EUPHORBIACEAE)

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ABSTRACT: Secondary metabolites are important source from plants which has huge therapeutic potential for human mankind. These phytoconstituents are present in different parts of the plant with varying amounts for different purposes when extracted. Different classes of secondary metabolites content are identified with preliminary phytochemical analysis which revealed to possess the properties for curing various ailments and may be the source for treatment. Among different types of plants, genus *Euphorbia* is one such class of plant comprising of large group of species distributed across the globe with diverse range of compounds which have pharmacological activities. *Euphorbia maculata* L (spotted spurge) is one plant belonging to *euphorbiaceae* family with tremendous value that have attracted human interest. Besides, Euphorbia derived compounds have great potential as a source of extracts and pure compounds, which prolongs the health of humans. The current review discusses the phytoconstituents, pharmacological and therapeutic potential of *Euphorbia maculata*.

Keywords: phytoconstituents, phytochemical, treatment, *Euphorbia maculata*, extracts and pharmacologic.

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1. INTRODUCTION

World plant biodiversity is the largest source of herbal medicine and still about 60 – 80% of the world's population depend on plant based medicines which are being used since the early ages as traditional health care system. [1] In order to identify and determine the presence of important chemical compounds in the plant, phytochemical screening is primarily an important aspect. Family *Euphorbiaceae* is one of the largest families of flowering plants comprising of over 300 genera and 8,000 species. [2] It consists of species of great economic importance like *Ricinus communis* L (Castor oil plant), *Manihot esculenta* crantz (cassava) and *Hevea brasiliensis* (rubber tree) among others but also noxious weeds like *Euphorbia esula* L and *Euphorbia maculata* L. [3] The inference is that *Euphorbiaceae* is a complex family with a lot of potential towards research which in turn benefits human mankind. Most of the species of *Euphorbia* (spurges) have been used as medicinal plants due to their therapeutic activity for the treatment of skin diseases, inflammation, intestinal parasites and wart cures. [4] Indeed, several studies on this genus proved to reveal the presence of diterpenoids, triterpenoids and steroids [4], alkaloids, flavonoids, coumarins, glycosides, polysaccharides, phenols, tannins and terpenoids [5] and macrocyclic diterpenes [6]. Apart from these compounds, plants contain other compounds that act as agents to prevent side effects or assists in the assimilation of the main substance. [7] Some of the compounds such as, umbelliferone and scopoletin were separated from *Euphorbia maculate* L. [8] Regarding umbelliferone compound, a recent study proved that it inhibits the release of Cyclin D1 which is overexpressed in many types of cancer. This concept may lead to its use in cancer therapy. [9] Extracts of *E. maculata* has antiplatelet activity by suppressing thromboxane B2 formation. [10] Therefore, the medicinal plants of *Euphorbia* (*Euphorbiaceae*) genus was chosen which contains triterpenoids to study their chemical compounds and pharmacological activities. [11] *Euphorbia maculata* L. (Figure 1) is a plant belonging to *Euphorbiacea*e family that is widely used as folk medicine throughout the world, especially in Northern America, Japan and Korea. [12] It is commonly used for the treatment of diarrhea, hemoptysis, hematuria and swollen sores. [13] Previous phytochemical investigations yielded tannins, flavonol glycoside and triterpenoids. [14, 12, 15, 16] Herein, we describe the pharmacological activities, traditional uses and effect of compounds (coumarins) of *Euphorbia maculata* L.

Fig 1. *Euphorbia maculata* – Plant. [17]

TAXONOMICAL CLASSIFICATION

Kingdom: Plantae

Clade: Tracheophytes

Clade: Angiosperms

Clade: Eudicots

Order: Malpighiales

Family: *Euphorbiaceae*

Genus: *Euphorbia*

Species: *E. maculate*

HABITAT

The Chamaesyce clade is probably best known for it's globally pervasive weedy species grown mainly in temperate regions with an affinity for sidewalk cracks. [18] Naturalized as a weed in lawns, ornamental gardens, forests and road sides. [19] It grows in open sunny locations and a variety of soils and especially found as a weed of gardens and fields. [20, 21]

GEOGRAPHICAL DISTRIBUTION

It's originated from North America and the chromosome number 2n = 42 as reported. [22, 23] Pahlevni and Riina (2011) reported that the plant *E. maculata* is geographically distributed across America and introduced to many parts of the world such as Europe (France, Austria, Switzerland, Bulgaria, Germany, Azores, Italy, Spain and Hungary) and Asia (China, Iran, Caucasus and Taiwan). [19] The species was first recorded for flora of Iran from the Mazandaran province. [24]

BOTANICAL DESCRIPTION AND MORPHOLOGY

It consists of prostrate pubescent annuals, usually much branched from the base; branches 10 – 45 cm long. The leaves are subfalcately elliptic oblong to linear oblong, 4 – 15 X 1.5 – 5 mm, obtuse,

assymetrical at the base, serrulate; stipules linear – lanceolate to linear or filiform, sometimes 2 – 3 partite, laciniate or fimbriate, 1.5 mm long. Glands transversely ovate, reddish brown with small white or pinkish petaloid appendages. Capsules 1.5 mm diameter, sparingly adpressed pubescent. Seeds 0.8 – 0.9 mm long, ovoid quadrangular, transversely grooved, brown colored and ecarunculate. The flowering and fruiting duration is between July – September. [19]

TRADITIONAL USES

E. maculata L. in Northern America is used for the treatment of corneal opacities and warts [25], whereas in China, it is used to treat blood disorders (i.e., haematuria, haemoptysis, epistaxis and hemafecia), carbuncles and wounds. [26] It is said to cure cholera, diarrhea and dysentery (www.botanical.com). The sap is applied externally to treat warts. [27] People of Cherokee tribe in North Carolina and Georgia were reported to use the infusion from the roots of *E. corollata* and *E. maculata* to treat haemorrhages [28] and decoction of the plant was used by Costanoan people in California to wash cuts. [29]

PHYTOCHEMISTRY

The phytochemical studies of *E. maculata* have been little reported. [16] Till date, several triterpenoids, flavonoids, tannins and related polyphenols were isolated and their antioxidant effects were also evaluated. [15, 12] The ethanolic extracts of *E. maculata* revealed the presence of quercetin, kaempferol, apigenin-7-O-glucoside, luteolin-7-O-glucoside, quercetin-3-O-arabinoside, ethyl gallate, scopoletin (Figure 2), umbelliferone (Figure 2) and ellagic acid. [30] The hexane extract of *E. maculata* showed isolation of two new triterpenoid compounds, a new spiro-triterpenoid and lanostane triterpenoid which showed anti-inflammatory activity. [31] Two new triterpenoid compounds were isolated from the whole herb of *E. maculata* which are characterized as gult-5-en-3β-yl acetate and ursa-9(11):12-dien-3β-ol on the basis of chemical and spectral evidence using benzene extract. [12]

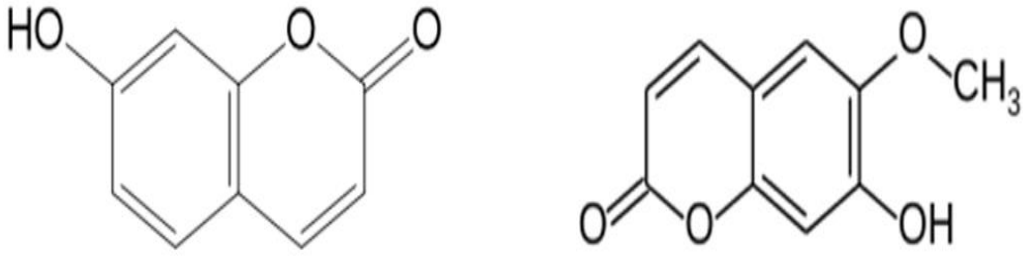

Fig 2. The chemical structures of umbelliferone and scopoletin (coumarins). [32, 33]

PHARMACOLOGICAL ACTIVITIES

The extracts of *Euphorbia* species as well as pure compounds isolated from them have been shown to reveal multiple pharmacological activities. In fact, *Euphorbia* extract and their compounds have been evaluated as potential natural drugs with other activities such as anti-inflammatory, anti-viral and anti- tumour. [34] According to literature reports, *E. maculata* is known to contain compounds (triterpenoids and coumarins) which possess activities against cancer and platelet inhibition.

ANTI-INFLAMMATORY ACTIVITY

The 70% hydroethanolic extract of *E. supina* Raf. (Synonym of *E. maculata* L.), at 10 mg/mL is able to significantly minimize the ear thickness and number of inflammatory cells on the *Propioni bacterium* acnes-induced skin inflammation by inhibition of pro-inflammatory cytokines expression and the MAPK signaling pathway. [35] The hexane extract of whole plant of *E. maculata* inhibited the inflammatory ear edema induced by TPA (Tumour Promoting Activity) with ID50 (50% inhibitory dose) value of 0.8 mM and compared with indomethacin (commercial drug). Mostly, tetracyclic triterpenoids exhibited potent inhibitory activity, with ID50 values between 87.1 – 1087 nM/ear whereas compound 8 (Obtusifoliol – ID50 87.1 nM/ear) showed higher inhibitory activity than indomethacin (ID50 838 nM/ear). Hence, this compound is strong than other tetracyclic triterpenoids is because one methyl substitution at C-4 and a double bond at C-24 in the side chain possessed a stronger anti-inflammatory activity. [31]

ANTI-OXIDANT AND ANTI-OSTEOPOROSIS ACTIVITY

The methanolic extract (MeOH) as well as EtOAc and H_2O fractions of *E. maculata* showed potent anti-oxidant activity at concentrations of 1.0 µg/mL to 10.0 µg/mL. At 10.0 µg/mL, ORAC (Oxygen Radical Absorbance Capacity) values were 27.24±0.40, 28.47±0.36 and 27.07±0.31 whereas CUPRAC (Cupric ion Reducing Anti-oxidant Capacity) values were 46.67±0.34, 43.86±0.26 and 46.58±0.58 fold higher than 1.0 µM of Trolox. Among the compounds, Phlorizin (compound 12, 10.0 µM) exhibited highest ORAC value of 28.50±0.27. Compounds 1 – 8 and 13 – 19, at 10.0 µM showed reducing capacity with CUPRAC values 19.62±0.58 to 43.82±0.57 as reported. [16] In case of anti-osteoporosis activity, the MeOH and EtOAc fraction significantly inhibited with TRAP activities by 154.90±4.25 and 163.95±9.77% respectively at 10.0 µg/mL. Among the compounds, 1, 4, 7 and 14 showed significant TRAP inhibitory activities with values of 121.31±1.41% to 110.00±3.74% as reported. [16]

ANTI-PLATELET ACTIVITY

The anti-platelet activity *E. maculata* fractions on ADP (Adenosine Diphosphate)-induced platelet aggregation was evaluated *in vitro*. Among the fractions, chloroform fraction (CFEM) significantly inhibited ADP induced platelet aggregation. Oral administration of 50 mg/kg CFEM to rats reduced ADP without increasing tail bleeding time. Thromboxane B2 (TXB2) formation, coagulation time and rat tail bleeding time was also measured. [10] In particular, CFEM reduced the formation of

Thromboxane B2 in a dose dependent manner. ADP induced PRP produced 24.64±0.319 ng/mL of TXB2 and 10, 30 and 100 µg/mL of CFEM decreased TXB2 to 23.80±0.647, 21.48±1.337 and 13.73±0.432 ng/mL respectively. [10]

OTHER PHARMACOLOGICAL STUDIES

According to the literature, several reports on *E. maculata* stated the importance of phytochemical compounds present in the whole plant and their role in pharmacological activities as treatment or reduce the process of activity. Mainly it involves triterpenes and coumarins that could be the suitable candidates as preventive agents with enormous amount of therapeutic potential. *Euphorbia* plant possesses huge potential towards development of newer drugs for clinical use as a source from bioactive extracts. Pure compounds are identified and thoroughly isolated using various methods and can contribute to the research of other pharmacological activities too.

PHYTOCHEMICAL CONSTITUENTS IN PLANTS

Phytochemical compounds are the main ingredients in each part (leaf, stem, root, fruits and flowers) of plant species which constitute a total amount which are of huge therapeutic potential to human mankind. Many studies are conducted on chemical analysis of *Euphorbia* species which showed it contains many molecules that are used for encounter. [36] Secondary metabolites are necessary to counteract the pharmacological activity and each specific compound is identified when extracted from the plant. The chemical composition of essential oils from *Euphorbia* species revealed the presence of more than 80 compounds mainly, sesquiterpenes, sterols, diterpenes, flavonoids and other polyphenols. [34] *E. maculata* has been one such plant studied by various researchers and a number of active constituents have been isolated and identified with therapeutic activity.

COUMARINS

Coumarins (Figure 3) originate from the name ‘Coumarou’, the vernacular name of tonka bean from which coumarin is first isolated in 1820 as reported. [37] Coumarins are compounds that has a pleasant odor but has a bitter taste. Coumarins activity includes anti-HIV, anti-hypertension, anti-inflammatory, anti-tumour, anti-septic, anti-analgesic, anti-arrhythmia and anti-osteoporosis. [1] It is also used in the treatment of asthma and lymphedema. [38] These compounds have become important in recent years due to various biological activities.

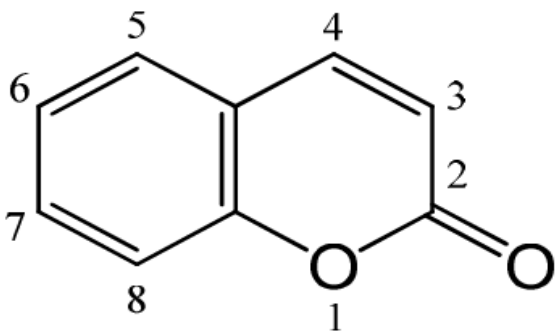

Fig 3. The basic chemical structure of coumarin compound. [43]

Jain and Joshi in 2012 reported that coumarins are of 4 subtypes, the simple coumarins, furanocoumarins, pyranocoumarins and pyrone substituted coumarins. [39] Most prevalent hydroxylated coumarins are umbelliferone, esculetin, herniarin, fraxetin, isoscopoletin, daphnetin and scoparone. [40] The compound umbelliferone (7-hydroxycoumarin) receives the attention of researchers due to it's diverse bioactivities in different applications in numerous therapeutic fields. [41] Overall, these compounds as medicinal drugs have been increasingly attracting special interest due to their underlying outstanding contributions in the prevention and treatment of diseases and the related researches have become one of the extremely attractive highlighted area. [42]

BIOSYNTHETIC PATHWAY OF COUMARINS

Most importantly, biosynthesis of secondary metabolites take place in the cytosol of the plant cell. Despite the importance of coumarins for plant life and human uses major facts of their biosynthesis have remained unresolved. [40] These compounds are biosynthesized from phenylalanine via the shikimic acid pathway. [44] The pathway of coumarin biosynthesis has been largely outlined during the '60s and '70s, with the help of tracer feeding experiments. [45]

CINNAMIC ACID TO UMBELLIFERONE AND OTHER COUMARINS

The formation of umbelliferone proceeds from 4-coumaric acid or it's ester derivatives. Teutsch et al. (1993) reported that conversion of cinnamic acid to 4-coumaric acid is catalyzed by cinnamte 4-hydroxylase. [46] According to literature, 4-coumaric acid is *ortho*-hydroxylated to 2,4-dihydroxycinnamic acid. This enzyme fraction was demonstrated to slowly convert cinnamic acid to *o*-coumaric acid but was more active to transform *p*-coumaric acid and ferulic acid respectively to umbellifrone and scopoletin. [40]

FUTURE SCOPE AND PROSPECTS

The extract of the plant is known to contain a lot of compounds and each target compound is isolated depending on the nature of the solvent used. Phytochemical analysis of *E. maculata* extract confirms the presence of active secondary metabolites and quantitative analysis of the extract can also be estimated. These secondary metabolites can be identified and confirmed through GC analysis and further can be produced in *in vitro* studies that indicate it's activity through *in vivo* studies too. The role and mechanism of compounds against the target is to be known and substantiated. The apical part of the plant contains huge amount of compounds which can be used for the extraction studies. A lot of research work related to *in vitro* studies has to be proved in case of *E. maculata*. Biosynthesis of compounds has to be studied through the application of enzymes, precursors or elicitors for the production of important compounds which are in huge demand. Finally, the amount of secondary metabolite content present in the extract is estimated and compared with *in vitro* studies and it's mode of action is proved through *in vivo* studies using mice models.

2. CONCLUSION

In summary, traditional medicinal practice is widely distributed in India and across the globe. These different traditional uses clearly attracted the attention of researchers on the need to investigate chemical compounds and evaluate their activity in plant. From the available literature, it clearly shows that *Euphorbia maculata* L serve as an important source of many therapeutic potential compounds. This review discusses the role of plant extract of *E. maculata* with various pharmacological activities and effects of compounds for treatment and other disorders. Secondary metabolites are important composition in plant species and constitute a major part in treatment which can indicate through *in vivo* studies. Preliminary phytochemical analysis of the plant extract is important to identify different group of secondary metabolites and quantitatively analyzed using the standard. Biosynthesis of compounds are essential phase in research where the target is achieved through precursors or enzymes under *in vitro* conditions. Moreover, further research is required to establish the *in vivo* activities with respect to various diseases and improve the health with the use of compounds isolated from the extracts of *Euphorbia maculata* L.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The author confirms that the data supporting the findings of this research are available within the article.

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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