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A Review on Pharmacological Profile of *Pedilanthus Tithymaloides*

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ABSTRACT: *Euphorbia tithymaloides* (L.) Poit or *Pedilanthus tithymaloides*, (Family: Euphorbiaceae), is a tropical and subtropical succulent plant. This plant is available in various parts of India: Assam, Bihar, Gujarat, Madhya Pradesh, Maharashtra, Odisha, and Uttar Pradesh. The stem of this plant has morphological resemblance with spinal column due to zigzag structure. The fleshy tubular stems of this plant are thin pencil like which produce thick, dark-green or variegated, fleshy, ovate leaves and peculiar beak shaped flowers. *Pedilanthus tithymaloides* is mostly used as an ornamental plant and for making fencing in garden. It is latex producing plant and its latex has been traditionally used to treat various pathological conditions apart from latex its leaves, stem and roots also used to treat ear ache, insect stings, ringworm, skin cancer, toothache, umbilical hernias, and warts. This plant is reported to possess various phytochemicals viz. steroids, tannins, triterpenes, coumarins and saponins which have been shown to possess anti-diabetic, antioxidant, analgesic, stomachic, hemostatic, anti-microbial, antifungal, anti-helminthic, antimutagenic, anti-tubercular, antimalarial, anti-inflammatory, abortifacient, antivenom, antibiotic, antiseptic, antihemorrhagic, antiviral and antitumor effect and useful for venereal diseases. The isolated phytochemicals reported in this plant were cycloartenone, dammaronol A, dotriacontan-1-ol, friedelanol, hentriacontan-1-ol and sitosterol. Some of the antioxidant principles like Kaempferol, quercitrin, isoquercitrin, and scopoletin were isolated. The significant bioactive principles reported in *Pedilanthus tithymaloides* were diterpenoids, triterpene, flavonoids, carotenoids, pedilanthus coumarin A, pedilanthus coumarin B, 5,7-dihydroxy-8-(2-methylbutyryl)-4-phenylcoumarin, theraphin C, isodispar B, isodisparinol B and isomesuol. Recently silver nanoparticles of plant latex have been synthesized for their potential use as antibacterial agents. The aim of present review is an effort to provide coherent literature survey of plant *Euphorbia tithymaloides* or *Pedilanthus tithymaloides* in relation to its phyto-pharmacological, ethnobotanical and therapeutical uses that would pave the way for development of phytopharmaceuticals.

KEYWORDS: *Pedilanthus tithymaloides*, euphorbiaceae, pharmacological, profile, medicinal, bioactive, succulent, tropical and subtropical

I.INTRODUCTION

Medicinal plants are used to produce new antimicrobial drugs due to increased bacterial resistance of antibiotics.



Pedilanthus tithymaloides

The plant *Pedilanthus tithymaloides* said to possess the wide range of medicinal properties which were confirmed through previous studies. The present study was to determine its antimicrobial activity using its leaves extract and also analysing whether their phytochemical constituents are responsible for its anti-microbial activities. *Pedilanthus tithymaloides* leaves extract was obtained and tested for antimicrobial activities and analysed for the presence of chemical constituents by preliminary phytochemical analysis[1,2] and by FTIR analysis. The antimicrobial susceptibility studies were conducted against gram (-) bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa* and gram (+) bacteria such as *Staphylococcus aureus*. This supports the medicinal use of the leaf which acts as an antimicrobial agent. However further studies are needed to isolate the active compound from the leaf and to study the antimicrobial activity of that active compound. *Pedilanthus tithymaloides* leaves are widely used in Indian medicine to heal wounds, burn, mouth ulcers. However, systematic evaluation of these activities is lacking. Thus, the present study aimed to assess the wound healing activity of *Pedilanthus* leaves and its isolated constituents in topical ointment formulation.[3,4]

The presence or generation of free radicals plays a vital role in several diseases like cancer, diabetes, sclerosis, Alzheimer's and Parkinson's [1]. An optimal dose of antioxidants is required so as to maintain a healthy system. Plants are a major source of antioxidants and they are exploited widely in the field of pharmaceutical and food industries. Hence, there is an increasing urge to detect natural resources for potent antioxidants. Antioxidant activity of several plants across different Nations such as Croatia [2], Egypt [3], Finland [4], Greece [5], India [6-10], Iran [11], Thailand[12], Turkey [13] etc., has been reported. However, in plants, complex system and diverse mechanisms owe to their antioxidant properties. Different reactive oxygen species may target different biomolecules, upon generation. Hence, characterization of plants through a variety of antioxidant assays is of importance [14] for their potential exploitation in industries. In this study, the plant, *Pedilanthus tithymaloides* was evaluated for its total antioxidant content, total phenolics and total flavonoids. Further, its free radical scavenging activity was determined through FTC, TBA, FRAP and ABTS assays. The phytoconstituents of the methanolic extract of the leaf are detected using GC-MS.

Pedilanthus tithymaloides (L.) Poit., belonging to Euphorbiaceae, is an erect shrub originating from Tropical America. Indian folklore uses *Pedilanthus tithymaloides* as antiviral, antibacterial, antihemorrhagic, antitumor, abortive, anticancer and anti-inflammatory agent [15]. Though the



antibacterial [16], larvicidal [17], anti-inflammatory and antioxidant activities [18] of *Pedilanthus tithymaloides* have been reported, an extensive study dealing with different assays against free radicals and detection of constituents has not been analysed. Hence, the present study was carried.

II. REVIEW OF LITERATURE

Euphorbia tithymaloides is a perennial succulent spurge.^[1] An erect shrub,^[2] the plant is also known by the scientific name *Pedilanthus tithymaloides*. However, the genus *Pedilanthus* has been submerged into the genus *Euphorbia*, and is more correctly known by its new name (*Euphorbia tithymaloides*).^{[3][4]} *Euphorbia tithymaloides* has a large number of household names used by gardeners and the public. Among them are **redbird flower**,^[5] **devil's-backbone**,^[6] **redbird cactus**, **Jewbush**, **buck-thorn**, **cimora misha**, **Christmas candle**, **fiddle flower**, **ipecacuahana**, **Jacob's ladder**, **Japanese poinsettia**, **Jew's slipper**, **milk-hedge**, **myrtle-leaved spurge**, **Padus-leaved clipper plant**, **red slipper spurge**, **slipper flower**, **slipper plant**, **slipper spurge**, **timora misha**, and **zig-zag plant**.^{[4][7][8]} In other parts of the world, it is known as **gin-ryu** (Japan); **pokok lipan** and **penawar lipan** (Indonesia); **airi**, **baire**, and **agia** "rang chita" (Bengal), (India); **aperejo** (Yoruba); **sapatinho do diabo** (Brazil); **ítamo real** (Cuba and Puerto Rico); **pantoufle** (France); and **zapatilla del diablo** (Mexico). *Euphorbia tithymaloides* is native to tropical and subtropical North America and Central America. It prefers soil that is sandy, well-drained, and nutrient-rich, particularly with higher concentrations of boron, copper, iron, manganese, molybdenum, and zinc.^{[11][12]} It is relatively intolerant of high soil salinity levels, but exhibits saline tolerance if well fertilized.^[12] The plant tends to be taller and have more biomass if it is well-watered.^[12] The plant requires a sunny area to grow in.^[11]

The shrub can grow to 1.8 to 2.4 metres (6 to 8 ft) in height and generally is about 45 to 60 cm (18 to 24 in) in width.^[13] The leaf is a simple angiosperm leaf, arranged oppositely on the stem.^{[2][13]} Each leaf is sessile (attaching directly to the plant), and about 35 to 75 mm (1.4 to 3 in) in length.^{[2][13]} The leaves are glabrous (smooth) and acuminate in shape, with entire (smooth) edges.^{[2][13]} The veins in the leaves are pinnate.^{[2][13]}

The plant terminates in a dichotomous cyme, with a peduncle supporting each flower.^{[2][13]} The floral leaves are bifid (split in two parts) and ovate, while the involucre bracts are bright red, irregularly acuminate in shape (e.g., like a slipper), and about 1.1 to 1.3 mm (0.043 to 0.051 in) in length with a long, thin tube.^{[2][13]} The flower is void of scent.^[14] The male pedicel is hairy, while the female is glabrous.^[13] The seed pod is about 7.5 mm (0.30 in) long and 9 mm (0.35 in) wide, and ovoid in shape (with truncated ends).^[13]

The plant generally flowers in mid-spring.^[2]

Euphorbia tithymaloides was introduced as a garden plant prior to 1688.^[17] The first record of it growing in a garden was in Amsterdam.^[17] It is primarily used as an outdoor garden border plant,^[10] but certain varieties do well indoors.^[11] Because of the plant's toxicity, gardeners are cautioned to wear goggles, gloves, long-sleeved shirts, and long pants.^[18] Propagation may be by seed or cutting. Cuttings should be made above a joint, be 5 to 6 inches (13 to 15 cm) long, and planted in



sandy, nutrient-rich soil and allowed to root before planting.^[14] Cuttings should be made in March – April or June – July, and from the middle or top of the main stem.^[19]

Hummingbirds are attracted to the plant's flowers.^[18] Cabbage worms are particularly fond of the plant's leaves.

Municipalities have planted *Euphorbia tithymaloides* in landfills, toxic waste sites, and along roadsides because it is one of the few plants which can thrive in these more difficult environments.^{[10][12]}

The root is known to be a powerful emetic.^{[2][18]} A proteolytic enzyme known as pedilanthain can be extracted from the plant's latex, and has been shown in experiments to be effective against intestinal worms and to reduce inflammation when ingested.^{[18][20]} In 1995, a galactose-specific lectin was purified from the plant's latex, and indications are that it might be useful in combatting diabetes mellitus.^[21]

In folk medicine, tea has been brewed from the leaves which has been used to treat asthma, persistent coughing, laryngitis, mouth ulcers, and venereal disease.^[18] Tea brewed from the root has been used as an abortifacient.^[18] The latex has been used topically to treat calluses, ear ache, insect stings, ringworm, skin cancer, toothache, umbilical hernias, and warts.^[18] None of these uses has been scientifically verified as effective.^[18] In the West Indies, a few drops of the latex is added to milk and used as an emetic.

In Peru, the plant is known as "cimora misha", "timora misha", or "planta magica". It is sometimes added to drinks made from mescaline-containing *Trichocereus* cacti (although *Euphorbia tithymaloides* has no known psychoactive properties).^[22] In Bengal, India, the species has been known as "rang chita".<ref.> Kumudranjan Naskar, Plant Wealth of the Lower Ganga Delta: An Eco-taxonomical Approach, Volume2,p. 589.

The fast-growing nature of the plant, coupled with its ability to grow in relatively toxic soils, had led scientists in India to investigate its usefulness as a "petrocrop", a plant which could yield biofuel compounds for internal combustion engines.^{[12][23]}

III.MATERIALS AND METHODS

Bioassay-guided chromatographic fractionation of the methanol extract of leaves resulted in the isolation of 2-(3,4-dihydroxy-phenyl)-5,7-dihydroxy-chromen-4-one and 1, 2-tetradecanediol, 1-(hydrogen sulfate), sodium salt. The ointment formulation of methanol extract (2.5%, 5% w/w) and isolated compounds (0.25% w/w) was prepared and evaluated on excision, incision and dead space wound models in rats. The effects of formulations on wound healing were assessed by the rate of wound closure, period of epithelialization, tensile strength, granulation tissue weight, hydroxyproline content and histopathology. Significant wound healing activity was observed with methanol extract and isolated constituents. Topical application of isolated compound ointments caused faster epithelialization, significant wound contraction (95.41%), and better tensile strength (565.33 g) on 16 post-wounding day, while 5% extract showed wound epithelialization with 95.55% contraction on 18th post-wounding day, better than the control group (76.39% on 22 day). The tensile strength of incision wound was significantly increased in extract and compound treated animals. Moreover, in dead space model the extract significantly increased granuloma tissue weight, tensile



strength and hydroxyproline content. The tissue histology of ointment treated groups showed complete epithelialization with increased collagenation, compared to the povidone–iodine group. The results validated the traditional use of *Pedilanthus tithymaloides* for cutaneous wound management.[19]

Plant source

Healthy, uninfected and undamaged leaves of *Pedilanthus tithymaloides* were collected from Thiruvallur district of Tamil Nadu, India. The leaves were cleaned, washed and allowed to dry in shade. The dried leaves were pulverized using an electric blender and stored for further use.

Preparation of plant extract

The methanolic extract of the plant was prepared by cold percolation method. The pulverized plant material (20 g) was mixed with methanol (200 mL) and maintained for 48 h at $30\pm 2^{\circ}\text{C}$, in a temperature controlled shaker. The crude extract obtained upon filtering and concentrating was reconstituted with the solvent for further analysis. The antioxidant potency of the plant was assessed by determining its phenolic, flavonoid and antioxidant content. The free radical scavenging ability was assessed by FTC, TBA,FRAP and ABTS assays. The experiments were performed in triplicates and the results are expressed as Mean \pm Standard Deviation.[20,21]

Determination of total phenolic content

The total phenolic content (TPC) was determined by Folin-Ciocalteu method [19]. To the plant extract (100 μL), 500 μL of distilled water and 100 μL of Folin-Ciocalteu reagent were added and incubated for 6 min at room temperature. Addition of 1.25 mL of 7% sodium carbonate was followed by making up the final volume of the solution to 3 mL. The mixture was incubated for 90 min and the absorbance was measured at 760 nm using UV- Visible spectrophotometer (Cyberlab, USA). The total phenolic content was expressed as mg TAE (Tannic acid equivalents) per g of the dry weight of the plant, using a standard plot of Tannic acid.

Determination of total flavonoid content

The total flavonoid content (TFC) of the plant was determined by the method described by Moussa *et al.*,[3]. Two hundred microlitre of the plant extract was taken in a test tube and the solvent was allowed to evaporate. To the residue, 5 mL of 0.1M aluminium chloride was added and shaken well. The absorbance value was measured at 415 nm after incubation of the solution for 40 min, at room temperature. Using a standard plot of Quercetin, the total flavonoid content was assessed and expressed as μg QE (Quercetin Equivalent) per gram dry weight of the plant material.

Determination of total antioxidants

Phosphomolybdenum method was employed for the estimation of total antioxidant activity [20]. Sulphuric acid (0.6 M), sodium phosphate (28 mM) and ammonium molybdate (4 mM) were used to



prepare the reagent solution. To 0.5 mL of the plant extracts, 4.5 mL of the reagent solution was added and maintained at 95°C, in a boiling water bath for 90 min. Upon cooling the solution at room temperature, the absorbance value was measured at 695 nm. The total content of antioxidants in the plant was expressed as mg TAE (Tannic acid equivalent) per g of the dry weight of the plant material. [22,23]

Gas Chromatography (GC) and Mass Spectroscopy (MS) analysis:

One μL of crude methanol extract of the plant was subjected to analysis of its constituents using Agilent Technologies 6890N GC system coupled with JEOL Mass spectroscopy. The sample was injected to the Agilent J&W HP-5 capillary column (30 m \times 0.2 mm \times 0.25 μm) fused with silica. The injection temperature was maintained at 220°C. The oven temperature of GC was programmed with an initial temperature of 50°C and increased up to 250°C at the rate of 10°C per min. Helium (He) was used as the carrier gas system with the flow rate of 1 mL/min. GC-MS interface temperature was maintained at 250°C. Identification of compounds was based on the comparison of the spectral values with the National Institute of Standards and Technology (NIST) Chemical Web book database. In addition, the peak area percentage contributed by each of the compounds detected was calculated. [24]

IV. DISCUSSION

The principle metabolites that play a vital role in antioxidant defence mechanism include flavonoids, polyphenols, tannins and saponins. Plants scavenge free radicals by donating electrons or transferring hydrogen atoms, thereby neutralizing free radicals [22]. Hence, the quantification of phenols, flavonoids and other antioxidant constituents is necessary. Prevention of radicals formed by oxidative stress is of utmost importance so as to maintain a healthy system. Several plants are being screened for potent antioxidative properties. Secondary metabolites of plants, differing in their structure, mechanism of action and biological properties, possess several medicinal attributes [23]. The crude, methanolic and chloroform extracts of *Pedilanthus tithymaloides* possessed good wound healing properties, which might be attributed to the action of phytoconstituents like, phytosterols, flavonoids, alkaloids, triterpenoids and tannins, either individually or in combination [24-26]. The potential antioxidant ability of the plant as assessed in the present study is in accordance with significant antioxidant activity evaluated by the DPPH method [7]. Several compositions comprising *Pedilanthus tithymaloides* have been formulated by Raula [27] for the prevention of gastrointestinal disorders.

Abreu *et al.*, [28] isolated flavonoids and coumarins from *Pedilanthus* sp. A major compound, cycloartanol triterpene, was isolated from the dichloromethane extract of *Pedilanthus tithymaloides* [26]. Similarly, Antimalarial and Antituberculous Poly-*O*-acylated Jatrophone diterpenoids have been isolated from *Pedilanthus tithymaloides* [27]. In the present study, GC-MS analysis revealed five different compounds, including three esters, an amine and an alkaloid in the methanolic extract of the plant. The results suggest the possible utilization of the plant against different radicals involved in oxidation processes.

**Table 2: GC-MS analysis of methanolic extract of *Pedilanthus tithymaloides***

Retention time	Name of the compound (IUPAC)	Molecular formula	Molecular weight (Da)	Peak Area (%)
17.43	Pentadecanoic acid, 14-methyl-, methyl ester	C ₁₇ H ₃₄ O ₂	270.45	5.14
19.1	10-Octadecenoic acid, methyl ester	C ₁₉ H ₃₆ O ₂	296.49	75.37
19.32	Cyclopropanebutanoic acid, 2-[[2-[[2-[(2-pentylcyclopropyl)methyl]cyclopropyl]methyl]cyclopropyl]methyl]-, methyl ester	C ₂₅ H ₄₂ O ₂	374.59	14.33
23.52	(4,4-Diphenyl-butyl)-(3-phenyl-piperidin-4-yl)-amine	C ₂₇ H ₃₂ N ₂	384.56	2.53
26.23	Rescinnamine	C ₃₅ H ₄₂ N ₂ O	634.72	2.61

V.RESULTS

The total phenolic content of *Pedilanthus tithymaloides* accounted to 10.98±0.08 mg TAE per gram dry weight of the plant. The total flavonoid content, as estimated by Aluminium chloride method, showed lower content (11.49±0.15 µg QE/g DW) than the phenolics. The total content of antioxidants, apart from phenols and flavonoids, accounted to 6.64±0.05 mg TAE/g DW of the plant. The plant is found to possess significant activity against the radicals of lipid peroxidation. This is evident from the results of TBA and FTC assays wherein the percentage inhibition was 99.73 and 87.25 respectively. Similarly, *Pedilanthus tithymaloides* inhibited the stable ABTS radical to 98.56%. However, the plant showed an average ability in reducing the ferric ions in the FRAP assay. The content of phenols, flavonoids and antioxidants is tabulated in table 1 and the percentage of inhibition acquired by the plants in TBA, FRAP, FTC and ABTS assays [27, 28]

Table 1: Total Phenols, Total Flavonoids and Total Antioxidant content in the methanolic extract of *Pedilanthus tithymaloides*

	<i>Pedilanthus tithymaloides</i>
Total Phenolic Content (mg TAE/g DW)	10.98±0.0876
Total Flavonoid Content (µg QE/g DW)	11.49±0.15
Total Antioxidant Assay (mg TAE/g DW)	6.64±0.05

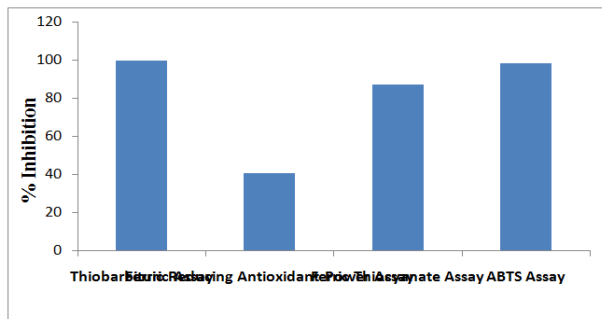


Fig. 1: Percent inhibition recorded by *Pedilanthus tithymaloides* through TBA, FRAP, FTC and ABTS assays.

The constituents of methanolic extract of *Pedilanthus tithymaloides* analysed by GC-MS resulted in the detection of 5 different compounds, of which three esters, an amine and an alkaloid. The maximum peak area was exhibited by 10-Octadecenoic acid, methyl ester with 75.37%. The lowest peak area with 2.53% was from (4,4-Diphenyl-butyl)-(3-phenyl-piperidin-4-yl)-amine.[28]

The alkaloid, Rescinnamine has also been detected at the retention time of 26.23. The GC-MS spectra obtained is depicted in Fig. 2 and the compounds detected by GC-MS are listed in table 2.

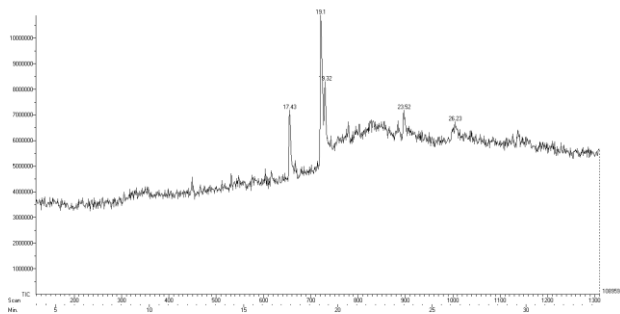


Fig. 2: GC-MS spectra of methanolic extract of *Pedilanthus tithymaloides*



VI.CONCLUSIONS

Leaf

Kind	Shape	Feature
Simple	Acuminate in shape, With entire (smooth) edges	The leaf is a simple angiosperm leaf, arranged oppositely on the stem. Each leaf is sessile and about 1.4 to 3 inches in length

Flower

Type	Size	Color and composition	Stamen	More information
Bisexual	Ovoid in shape	Pink		The seed pod is about 0.30 inches (7.6 mm) long and 0.35 inches (8.9 mm) wide, and ovoid in shape (with truncated ends)

The study on antioxidative properties of *Pedilanthus tithymaloides* has demonstrated significant ability as an antioxidant agent which can be used in pharmaceutical industries. Further, isolation of individual compounds responsible for such activity and their antioxidant potential as an individual compound is recommended. *Pedilanthus tithymaloides* houseplant likes bright indirect sunlight. Plant in direct sun in fall and winter, but give it a little protection from stinging hot rays in spring and summer[28]

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