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A PHYTOCHEMICAL AND PHARMACOLOGICAL REVIEW ON *TREMA ORIENTALIS*: A POTENTIAL MEDICINAL PLANT

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Abstract

This review presents up-to-date phytochemical information and pharmacological activities of a potent medicinal plant named *Trema orientalis* (Linn.). The leaves, stems, flowers, fruits, and essential oils of the plant possess a variety of important phytochemical moieties and momentous biological activities including antimicrobial, antiplasmodial, antioxidant, anti-inflammatory, thrombolytic, anticancer, and antidiabetic activities. The plant has potential pharmacological values and has been reported to be used traditionally in the treatment and management of diabetes, respiratory and inflammatory diseases, malaria, diarrhea and muscular pain. Crude extract of different part of *T. orientalis* showed antibacterial activity against both gram positive and very strong gram-negative bacteria including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus, Plesiomonas shigelloides*, *Shigella dysenteriae*, *Staphylococcus aureus, Vibrio cholerae Shigella sonnei* and *Pseudomonas aeruginosa*. The Anti-inflammatory and analgesic activity of *T. orientalis* may be due to presence of polyphenols, saponins, flavonoids that linked to the inhibition of inflammatory mediators such as cyclooxygenases, interleukins, or prostaglandins. Chloroform fractions of *T. orientalis* showed highest significant ($P < 0.05$ and $P < 0.001$) clot lysis activity, 46.44 ± 2.44% respectively compared with positive control standard streptokinase (80.77 ± 1.12%) and negative control sterile distilled water (5.69 ± 3.09%) whereas other fractions showed modest to low clot lysis activity. In the prophylactic experiment, dichloromethane (DCMF), methanol fraction (MF) and extract (ME) showed significant antiplasmodial effects. The roots extract in cytotoxic study by brine shrimp lethality bioassay, the lethal concentration-50 (LC50) value of the n-hexane, ethyl acetate and hydro-methanol fraction was 1377.03 µg/ml, 11.67 µg/ml and 48.62 µg/ml respectively. These fractions are highly promising for further exploration to identify the bioactive compounds and eventually discover new drugs.

Keywords: *Trema orientalis; antiplasmodial; prophylactic; cytotoxic; bioactive*

Introduction

Starting from the stone-age, medicinal plants are major source of bioactive compounds with various pharmacological activities [1]. *Trema orientalis* (Bengali name - Jibon or Chikon), is a fast-growing medicinal shrub or tree belonging to the family Ulmaceae (Table 1) disseminated all over the world including Bangladesh [2,3]. It is a shrub or small to medium size tree and its height varies depending on the location and climatic conditions. It can grow up to 18 m high in forest regions, and up to 1.5 m tall in the savannah [4]. The plant has potential pharmacological qualities and has been accounted for to be utilized customarily in the treatment of diabetes, respiratory and fiery illnesses, intestinal sickness, looseness of the bowels and solid torment [5]. The helpful naturally dynamic mixes got from the green leaves of this oriental plant incorporate polyphenols, saponins, flavonoids, tannins and triterpenoids, which have a few pharmacological properties, for example, antibacterial, antipyretic, cell reinforcement, anticonvulsant, antiplasmodial, antidiabetic and pain relieving properties [6,7]. It's likewise utilized as inhalant, fume shower for hacks, against helminthic, remedy to general harming, febrifuge, hostile to loose bowels, anticonvulsion, hostile to diabetic, pain relieving, hostile to sickling [8,9,10,11]. Both stem bark and leaf decoctions of T. orientalis are utilized to treat jungle fever, oversee torment in tired muscles and throbbing bones just as venereal illness while the hexane concentrate of stem bark of T. orientalis indicated antiplasmodial action [12]. The root is utilized in society medication for the treatment of injury, blood balance, hematuria, and seeping of digestive organs and stomach just as the stems and twigs implantation are utilized to treat fever and toothache [4].

This review aims to outline a current scenario on the phytochemical and pharmacological activities of *T. orientalis* on the basis of database (PubMed, Springer, Science Direct, MedLine, Scopus, and Google Scholar) information.

Methods

A search (till November 2019) was done in the following databases: PubMed, Springer, Science Direct, MedLine, Scopus, and Google Scholar with the keyword "*Trema orientalis*", pairing with 'phytochemicals', 'biological activities/effects', or 'pharmacological activities/effects'**.** No language limitations were forced. Articles were evaluated for the data about the concentrates or divisions and separated mixes of the plant or its parts, fixation or portion (course of organization), test frameworks, results or conceivable system of activity, and last end. Incorporation and avoidance criteria of confirmations found in databases have been given as follows.

Inclusion criteria:

1. Studies carried out in vitro, ex vivo or in vivo with or without using experimental animals, including humans and their consequent tissue and cells;
2. Studies with *Trema orientalis* and its other parts's crude extracts, isolated compounds or their derivatives or preparations;

3. Studies with or without recommending activity mechanisms;
4. Studies with extracts without phytochemical analysis, but having biological activities;
5. Studies with extracts, with phytochemical analysis, but having no report for biological activities.

Exclusion criteria:

1. Duplicate of any data and titles and/or abstracts not meeting the inclusion criteria;
2. *Trema orientalis* with other studies uncovering the current topic;
3. Studies conducted on other Genus or Species of the plant.

Findings

Among the enormous evidences, 65 published articles found in the databases that have screening reports on the phytochemical and/or pharmacological activities of *T. orientalis* or its crude extracts/fractions or isolated compounds have been given below:

Phytochemicals

The leaves of *T. orientalis* contain tannins, saponins, flavanoids, n-hexadecanoic acid, farnesylacetone, triterpenoid (simiarenol, simiarenone, trematol) fixed oils and mucilage [13,14,15,16]. Flavonoids, lignanes, essential oils, tannin, saponins, Cardiac glycosides were noticed in ethanolic extract of leafy stem of Trema orientalis [17]. The protuberant constituents in the leaf oil were tetradecanal (33.3%), hexadecanoic acid (19.5%), farnesylacetone (5.6%), heptacosane (4.6%) and linalool (4.3%) [18]. Octacosanoic acid, 1-octacosanyl acetate, simiarenone, simiarenol, episimiarenol, and a new triterpene alcohol, trematol has been isolated from stem bark as well as studies have also reported the presence of methylswertianin, decussatin, glycosides of decussatin, sweroside, scopoletin, (–)-epicatechin, lupeol, p-hydroxybenzoic acid, adian-5-en-3-one, 2α, 3ß-dihydroxyurs-12-en-28-oic acid in the stem bark [13,19,20]. Chemical analysis has directed to the identification and isolation of triterpenoids, sterols, fatty acids, and flavonoid glycosides, (–)-epicatechin, (+)-catechin , (+)-syringaresinol, and trans-4-hydroxy-cinnamic acid, (–)-ampelopsin F, N-(trans-p-coumaroyl) tyramine, N-(trans-p-coumaroyl)octopamin, and 3,5-dimethoxy-4-hydroxyphenyl-1-O-β-D-glucoside in the stem of *Trema orientalis* [21]. The trunk and root barks are great source of terpenoids, coumarins, tannins and flavonoids [22]. Chemical investigation of dichloromethane and ethyl acetate extracts from trunk and root barks of *T. orientalis* led to the seclusion of 16 compounds. Methylswertianin, decussatin, glycosides of decussatin, sweroside, scopoletin, (-)epicatechin, lupeol, p-hydroxybenzoic acid, 3,4-dihydroxybenzoic acid, adian-5-en-3-one, 2a, 3a, 23-trihydroxyurs12-en-28-oic acid, 2a, 3b-dihydroxyurs-12-en-28-oic acid, b-sitosterol, 3-O-b-glucopyranosyl-b-sitosterol and hexacosanoic acid were assessed by means of its spectral data. [23].

Pharmacological activities

Antibacterial activity

According to the report of World Health Organization (WHO), over 13 million people die each

year from infectious and parasitic diseases: one in two deaths in some developing countries [24]. Different parts of plant materials have been reported to exhibit anti-bacterial activities [25,26]. Crude methanol extract of *Trema orientalis* showed antibacterial activity (Figure 2) against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Plesiomonas shigelloides*, *Shigella dysenteriae*, and *Vibrio cholerae* on the other hand aqueous extract showed antibacterial activity against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Streptococcus pyogenes*, *Plesiomonas shigelloides*, *Shigella dysenteriae*, *Vibrio cholerae*, *Shigella Flexner*, *Shigella sonnei* and *Pseudomonas aeruginosa* [27]. The antibacterial study of the stem bark demonstrated action on both gram positive and exceptionally solid action on some gram-negative microscopic organisms. The water extract of stem bark showed zones of inhibition of 9 mm for *S. aureus*, 10 mm for *K. pneumoniae* at 100 mg/mL and 13 mm for both bacteria at 200 mg/mL and the chloroform extract showed zones of inhibition ranging from 15 mm- 30 mm *for P. flourescens*, 16 mm- 35 mm for *S. aureus*, 12 mm - 25 mm for *P. mirabili*, 12 mm- 24 mm *for K. pneumoniae* and 10 mm - 20 mm for *E. coli* [28]. 32Besides, the water, methanol, ethanol and acetone extracts of *T. orientalis* bark showed significant activity against *Klebsiella spp*, *Pseudomonas spp*, *Bacillus subtilis* and *Staphylococcus. aureus* [29]. Antibacterial compounds like octacosanoic acid, 1-octacosanyl acetate, simiarenone, simiarenol, episimiarenol and trematol have been isolated from stem bark of the plant [30]. Methanolic stem bark extract had a pronounced inhibitory effect on *Enterobacter cloaca* ATCC 13047 and *Enterococcus faecalis* ATCC 29212. *Serratia mercescens* ATCC 9986 and *Pseudomonas aeruginosa* ATCC 19582 were the most susceptible bacteria [25]. Besides, the aqueous and methanol root extracts showed antibacterial activity [18]. Another study showed that, based on concentration the methanol extract of the stalk was active against all the micro-organisms (*Escherichia coli*, *staphylocollus aureus*, *pseudomonas aeruginosa* and *klebsiella pneumonia*) than the corresponding ethyl acetate and hexane extracts of both plant parts investigated [31].

Antiplasmodial activity

In the prophylactic experiment, dichloromethane (DCMF), methanol fraction (MF) and extract (ME) (in this order) showed significant chemopreventive effects against *P. berghei* invasion of the red blood cells when compared with both Sulfadoxine-Pyrimethamine (SP) and untreated controls [32]. The herb extracts were significant ($p>0.05$) but with varying levels of antiplasmodal activity (*Plasmodium berghei*), as *Trema orientalis* has the highest (85%) suppression activity followed by *Morinda lucida* (83%) and *Alstonia soonei* (80%) [33]. The acetone leaf extract of T. orientalis has antiplasmodial activities and dosage of 800 mg/kg/day is the most effective dose. However, we observed that treatment at doses of 100 and 200 mg/kg/day were more effective than the dose at 400 mg/kg/day and statistically comparative activity to 600 mg/kg/day [34]. A similar observation has been reported in

literature where the methanolic bark extract of Chrysophyllum albidum produced a dose independent schizontocidal (chemosuppressive) effect of 74.20 and 62.90% for 1000 and 1500 mg/kg/day, respectively [35]. The results obtained in another study showed that purification enhanced the antiplasmodial activity of stem bark peel of *Trema orientalis* in Plasmodium berghei-induced malaria in mice [36].

Antioxidant activity:

Radicals may be envisioned as molecular sharks, which if not scavenged efficiently on time, are capable of damaging vital bio-molecules that linked to the pathogenesis of many disease conditions such as rheumatoid arthritis, hemorrhagic shock, cardiovascular disorders, cystic fibrosis, some metabolic disorders, and neurodegenerative diseases [37]. IC50 of the methanol extract of *T. orientalis* was 110.25 µg/ ml which designated the strong antioxidant activity of the plant extract. However the aqueous extract showed mild antioxidant activity [27]. The methanol extract, with an IC50 value of 48.40 µg/ml, exhibited a higher antioxidant activity than aqueous extract (IC50 value= 55.69 µg/mL). Although the obtained IC50 value of the methanol ($p<0.05$) and aqueous ($p<0.0001$) extracts are significantly different compared to the potency of ascorbic acid, results still indicate the potential of the plant extracts as an antioxidant [38]. Where methanol concentrate of T. orientalis leaves displayed higher rummaging movement contrasted with watery concentrate, with practically identical action to ascorbic corrosive. Henceforth, its rummaging action can be credited to high phenolics content and the nearness of flavonoids and tannins, as detailed prior [27]. The MeOH extract of T. orientalis flowers showed mild free radical scavenging activity (IC50: 131.2µg/ml) compared to ascorbic acid (IC50:12.4µg/ml) used as a standard [39]. The overall antioxidant activity of different solvent extracts of seed was observed to be very strong when compared to the standard, with the hexane extract recording the highest percentage inhibition of 87.14% at 0.125mg/g of the extract while ascorbic acid recorded 74.55% at the same concentration [40].

Anti-inflammatory activity:

The methanolic concentrate of leaves of T. orientalis demonstrated a huge inhibitory impact on the edema arrangement from the main hour to fifth hour in the carrageenan instigated rodent paw edema model of mitigating action. The highest inhibitory effect was found during the third hour where the inhibition was 24.59% ($P < 0.001$) and 40.98% ($P < 0.001$) at the doses of 200 and 400 mg/kg respectively [41]. Another investigation directed on albino wistar rats showed that all three test groups of the ethanolic extract of leaves of T. orientalis L. exposed dose-dependent decrease in body temperature when compared against control and it can be due to inhibition of inflammatory mediator such as cyclooxygenases, interleukins, or prostaglandins [42].

Thrombolytic activity

Thrombosis, the blockage of veins with clusters, can prompt intense myocardial dead tissue and ischemic

stroke, the main sources of death [43]. In view of the inadequacies of the accessible thrombolytic drugs, endeavors are in progress to create improved recombinant variations of these medications [44]. . Various plants source particularly a few products of the soil have been read for their enhancements having against coagulant, hostile to platelet and fibrinolytic action and there is proof that devouring such nourishment prompts avoidance of coronary occasions and stroke [45]. Chloroform fractions of *T. orientalis* showed highest significant ($P < 0.05$ and $P < 0.001$) clot lysis activity, 46.44 ± 2.44% respectively compared with positive control standard streptokinase (80.77 ± 1.12%) and negative control sterile distilled water (5.69 ± 3.09%) whereas other fractions showed moderate to low clot lysis activity. Order of clot lysis activity was found to be: Streptokinase > Chloroform fractions > Methanol (crude) extract > Hydro-methanol fractions > Ethyl acetate fractions > n-hexane fractions > Water [46]. Both MeOH and EtOAc extract of *T. orientalis* flowers produced 21.4% and 21.5% clot lysis respectively compared to streptokinase used as a positive control that caused 51% clot lysis [39].

Antidiabetic activity:

Studies have indicated that HPA (human pancreatic α-amylase) movement in the small digestive tract relates to hyperglycemia, which is the most punctual metabolic imperfection to happen in diabetes mellitus [47]. One of the present methodologies in diabetes the board is the decrease of postprandial hyperglycemia (PPHG) through restraint of either αamylase or glucosidase compounds [48]. Over-generation (extreme hepatic glycogenolysis and gluconeogenesis) and diminished use of glucose by the tissues are the central premise of hyperglycemia in diabetes mellitus [49]. The study showed that, extract treatment in diabetic rats at two dose levels (250mg/kg and 500mg/kg) showed a decrease in fasting blood glucose levels. The total cholesterol and serum triglycerides levels were also reduced and the HDL cholesterol levels were increased upon treatment with the extract thus proving the potent antidiabetic property of the plant [50]. The methanolic bark extract has significantly higher α-amylase inhibition percentage per concentration than aqueous extract, with a low IC50 which is four-fold higher compared to the IC50 value of acarbose suggesting that α-amylase inhibitory activity of the *T. orientalis* bark tends to favor extraction in polar solvent which is similar to the results of other studies [38.51]. Aqueous stem bark extract of T. orientalis was reported to have hypoglycemic effects in induced diabetic rats by mechanism different from that of sulfonylurea agents [52]. In normoglycemic rats, the single oral administration of the aqueous stem bark extract of T. orientalis failed to reduce blood glucose levels while in STZ-diabetic rats, the plant extract (38–300 mg/kg) exhibited significant hypoglycaemic activity with a maximum effect of 29.67%, 5 hours after administration of the 75 mg/kg dose when compared with the diabetic untreated group. One week after repeated administration of T. orientalis extract, blood glucose levels were significantly

decreased ($p < 0.05$) and still remained low after 2 weeks ($p < 0.01$) [52].

Analgesic and anti-arthritic activities:

The methanolic extract of T. orientalis produced 32.00 and 51.34% writhing inhibition in test animals, respectively at the doses of 200 and 400 mg/kg on acetic acid induced writhing and thus Inhibition of prostaglandin synthesis could give rise to analgesic activity [41]. The leave concentrates of T. orientalis have noteworthy capacity to diminish torment in mice in acidic corrosive incited squirming test, and in rodents by the hot plate model [53]. The aqueous extract of leaves showed significant ($P < 0.001$) analgesic effect in acetic acid induced writhing in mice at a dose of 500 mg/kg body weight [54]. The Stem and root barks used in mixed preparations in the treatment of arthritis, fracture, and rheumatism [55]. The leaves extract have also been shown to have anti-arthritic effects in acute and chronic models in mice [56].

Anticancer activity:

Malignant growth has risen as one of the main executioner maladies all inclusive, guaranteeing more than 6 million lives each year [57]. The momentum choices for the treatment of this fatal ailment (for example Chemotherapy, radiotherapy and medical procedure) have a few disadvantages, for example, significant expense inaccessibility in the asset constrained nations, loss of typical cells, advancement of optional malignancies and genuine post-treatment intricacies, therefore expanding the interest for the presentation of novel medications [58]. The cytotoxic activity of *Trema orientalis* leaves crude methanol extract (TLME) was determined *in vitro* by the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay. The LD_{50} of was 3120.650 mg/kg body weight, and this extract was proven to be safe at a dose of as high as 800 mg/kg body weight. The oral administration at 400 mg/kg body weight resulted in approximately 59% tumor cell growth inhibition compared with the control mice, with considerable apoptotic features, including membrane blebbing, chromatin condensation, nuclear fragmentation and aggregation of the apoptotic bodies in DAPI staining under a fluorescence microscope [59]. The methanol extract of *Trema orientalis* leaves showed very low cytotoxicity (LC50, 170.215 µg/mL) in comparison with the standard vincristine sulphate having LC50 value 2.477 µg/Ml [60]. The roots extract in cytotoxic study by brine shrimp lethality bioassay, the lethal concentration-50 (LC50) value of the n-hexane, ethyl acetate and hydro-methanol fraction was 1377.03 µg/ml, 11.67 µg/ml and 48.62 µg/ml respectively [61]. These fractions are highly auspicious for further exploration to identify the bioactive compounds.

Miscellaneous effects

Diuretic activity

The impact of the methanolic concentrate of T. orientalis leaves on the pee of mice was watched for 5 h which uncovered that the concentrate has a checked diuretic impact in the guinea pigs [41]. *T. orientalis* is a strong wellspring of assortment of polyphenols which have potassium maintenance

capacity, and hence might be answerable for diuresis [54].

Anthelmintic activity:

Decoction arranged from the leaves and bark of T. orientalis has been utilized customarily in the treatment of infections brought about by hookworm, roundworm, and intestinal worms [62,63]. Likewise, as per Diehl et al. (2004), the leaf and root concentrate of T. orientalis indicated 100% death rate on Haemonchus contortus hatchlings species [64].

Antiulcer activity:

All three test doses (100 mg/kg; 150 mg/kg; 200 mg/kg) of the ethanolic extract of leaves of *T. orientalis* L. showed dose-dependent decrease in UI (Ulcer Index) when it was compared against control as well as against pantoprazole, which was used as a standard [42]. The bioactivity-guided phytochemical screening of ethanolic extract of *T. orientalis* revealed the presence of flavonoids, tannins, and triterpenoids, which may be responsible for the antiulcer effect and can be further fractionated and investigated for their role and utility in any of the antiulcer mechanisms.

Antidepressant and anxiolytic Activities:

The leaf extract exclusively decreases the duration of immobility in both animal models of antidepressant activity, forced swimming and tail suspension tests. In elevated plus mazes (EPM) test, the extract significantly increased time spent in open arms compared to control and in the hole board test, they also considerably increase in the number of head pokes in comparison to control [65].

In summary, the current research claims that *T. orientalis* is a valuable medicinal plant. This review combines phytochemical and pharmacological properties of the plant. The plant contains some potent bioactive phytoconstituents such as flavanoids, farnesylacetone, simiarenone, simiarenol, episimiarenol, methylswertianin, decussatin, glycosides of decussatin, sweroside and a new triterpene alcohol, trematol. The plant exhibits momentous biological activities including antimicrobial, antiplasmodial, antioxidant, anti-inflammatory, thrombolytic, anticancer, and antidiabetic activities. The anticancer properties of the root extracts are highly promising for further exploration to identify the bioactive compounds and eventually discover new drugs. Besides, the thrombolytic activity of the plant is also significant.

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Conflict of Interest

Authors declared no conflict of interest.

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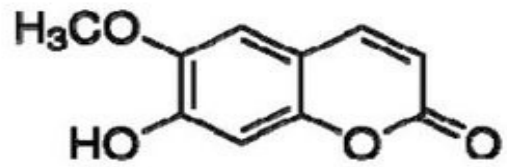
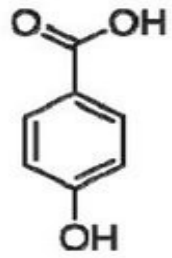
Table 1: Taxonomic Hierarchy of *Trema orientalis* (L.) Blume

Kingdom	**Plantae – Plants**
Subkingdom	Tracheobionta – Vascular plants
Superdivision	Spermatophyta – Seed plants
Division	Magnoliophyta – Flowering plants
Class	Magnoliopsida – Dicotyledons
Subclass	Hamamelididae
Order	Urticales
Family	Ulmaceae – Elm family
Genus	Trema Lour. – trema
Species	*Trema orientalis* (L.) Blume – Oriental trema

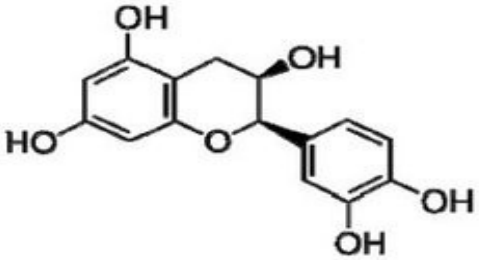
Figure 1: Structure of some important phytochemicals isolated from *T. orientalis*



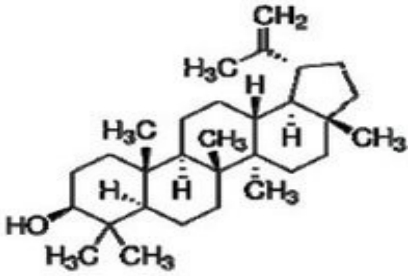
Scopoletin



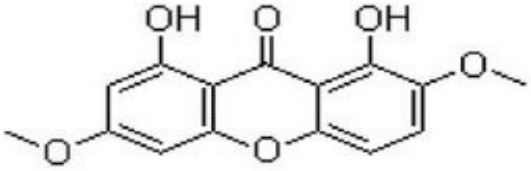
4-Hydroxybenzoic acid



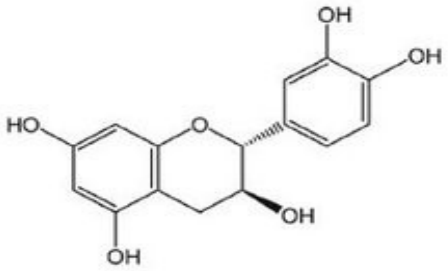
Epicatechin



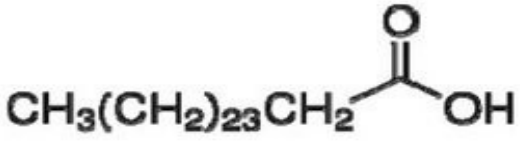
Lupeol



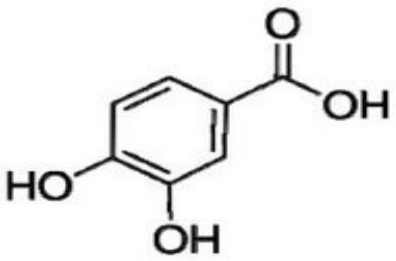
Methylswertianin



Catechin



Hexacosanoic acid



3, 4-Dihydroxybenzoic acid

Table 2: Preliminary phytochemical screening of leafy stem extracts of *T. orientalis*

Phytochemicals	Reagents	*T. orientalis*
Flavonoid	Sodium hydroxide (10 %), HCl (5 %)	+
Tannins	$FeCl_3$ (1 %)	+
Alkaloids	Hydrochloric acid, Dragendroff's reagent	-
Triterpenes	Acetic anhydride ; Sulphuric acid	-
Coumarins	Sodium hydroxide (10 %) ; H_20; heating	-
Saponins	Distilled water follow vigorous agitation	+
Essential oils	Sulphuric vanillin	+
Lignanes	Sulphuric vanillin	+
Anthocyanines	Sulphuric vanillin	-
Naphtoquinones	KOH-MeOH (10 %)	-
Anthracenes derivatives	KOH-EtOH (10 %)	-
Cardiac glycosides	Sulphuric acid (10 %)	+

Figure 2: Antibacterial activity of methanol and aqueous extract of leaves of Trema orientalis

Name of bacteria	Diameter zone of inhibition in mm		
	Gentamycin (30 µg/well)	Methanol extract (500 µg/well)	Aqueous extract (500 µg/well)
Gram positive bacteria			
Staphylococcus aureus	23	9	11
Staphylococcus epidermidis	21	9	11
Staphylococcus saprophyticus	32	-	13
Streptococcus pyogenes	21	-	10
Gram negative bacteria			
Plesiomonas shigelloides	24	8	9
Shigella dysenteriae	24	9	10
Vibrio cholerae	28	9	9
Salmonella typh	31	-	-
Shigella flexneri	21	-	10
Shigella boydii	23	-	-
Shigella sonnei	24	-	9
Pseudomonas aeruginosa	27	-	10

'-' No inhibition