The Journal of Phytopharmacology 2023; 12(6):392-398
Online at: www.phytopharmajournal.com

Review Article

ISSN 2320-480X
JPHYTO 2023; 12(6): 392-398
November- December
Received: 24-10-2023
Accepted: 19-12-2023

doi: 10.31254/phyto.2023.12605

Niranjan D
Assistant Professor (Contractual), Animal Husbandry Polytechnic, Konehalli, KVAFSU, Karnataka, India

Shridhar NB
Professor and Head, Department of Veterinary Pharmacology and Toxicology, Veterinary College Shivamogga, KVAFSU, Karnataka, India

Vinuta MH
Senior MVSc Scholar, Department of Veterinary Pharmacology and Toxicology, Veterinary College Shivamogga, KVAFSU, Karnataka, India

Manjunatha SS
Assistant Professor, Department of Veterinary Pathology, Veterinary College Shivamogga, KVAFSU, Karnataka, India

Sunilchandra U
Associate Professor, Department of Veterinary Pharmacology and Toxicology, Veterinary College Shivamogga, KVAFSU, Karnataka, India

Pradeep BS
Assistant Professor and Head, Department of Veterinary Parasitology, Veterinary College, Shivamogga, KVAFSU, Karnataka, India

Manju GU
Assistant Professor and Head, Department of Animal Nutrition, Veterinary College, Gadag, KVAFSU, Karnataka, India

Patel Suresh Revanna
Associate Professor (I/C), Department of Veterinary Medicine, Veterinary College, Shivamogga, KVAFSU, Karnataka, India

Correspondence:
Niranjan D
Assistant professor (Contractual), Animal Husbandry Polytechnic, Konehalli, KVAFSU, Karnataka, India
Email: Niranjan.niranjan.d@gmail.com

Botanical, pharmacological and toxicological properties of *Trema orientalis*: A Review

Niranjan D, Shridhar NB, Vinuta MH, Manjunatha SS, Sunilchandra U, Pradeep BS, Manju GU, Patel Suresh Revanna

ABSTRACT

The plants were the primary source of primitive medicines which used to cure human ailments in past centuries. In modern medicine also many drugs are being discovered from plants. *Trema orientalis* is a tropical small to medium-sized tree also called Indian charcoal tree was native to South Africa, tropical Asia and Australia. It is widely distributed all over the world. It was used traditionally to treat infections and fevers. The leaves are simple, alternating, stipulated with short grey hairs below and serrated edges all around drooping branches. The fruits are tiny, oblong and meaty, when ripened, it turns glossy black. It has one dull-black seed embedded in bright-green flesh. The alkaloids, steroids and flavonoids were found to be abundant in *T. orientalis*, while tannins, saponins, terpenoids, glycosides and carbohydrates were present in moderate quantity. The crude methanolic extract of *T. orientalis* had antibacterial activity against various bacteria. It has also proven analgesic efficacy in acetic acid-induced writhing experiments in lab animals. In certain investigations, the stem bark extract of *T. orientalis* drastically lowered blood glucose in diabetic rats created through streptozotocin. One of the researchers demonstrated dose-dependent reduction in body temperature in rats with pyrexia using ethanolic extract of *T. orientalis*. The methanolic and ethanolic extracts of different parts of *T. orientalis* plant showed antidepressant, anxiolytic, hepatoprotective, anti-inflammatory, anti-cancerous, diuretic activity, anti-oxidant, anti-malarial and anti-ulcer activity. The clinicopathological alterations were induced by treatment of Jamnapari crossbred goats orally with *Trema orientalis* ethanolic leaf extract (ELETO). The gross and histological alterations in major vital organs, as well as the clinical symptoms were considered as indicators of the toxicity in a study. Another investigation revealed that *T. orientalis* was non-toxic and had a sizable haematopoietic effect. Thus further more research is required to extrapolate traditional uses of this plant to use it as medicine along with precaution regarding toxic dose.

Keywords: *T. orientalis*, Medicine, Extract, Traditional.

INTRODUCTION

For centuries together, plants were the primary source of primitive medications used to cure human ailments. In the modern era of medical engineering, plants were given utmost importance in drug development and discovery. During 2000-2006, many drugs approved for human use, have been derived from plant sources [1]. The family Cannabaceae currently consists of 10 genera. It consisted of erected herbaceous plants, woody vines and trees. There are 15 species of the genus Trema, which were found throughout the tropical and subtropical regions of the world [2].

Trema orientalis was a typical pioneer plant used in traditional medicine for the treatment of ailments in tropical regions, mainly in Asia. This species of Trema was often used to cure infections and fevers. The antibacterial and antiviral characters have been utilized to treat variety of respiratory infections. The phytochemical analysis of *T. orientalis* exhibited a variety of chemical constituents in its various plant parts, including tremetol, simiarenol and simiarenone in the leaves, swertianin, scopoletin, numerous fatty acids and glycosides in the stem bark, sterols and fatty acids in the roots [3,4].

Trema orientalis

The generic name was originated from the Greek word, "Trema" meaning hole or puncture or pitted seeds. The species name was originated from the Latin word "orientalis" meaning eastern. The plant was commonly called by several names such as pigeon wood, hop out, nettle tree, Indian nettle tree, Indian charcoal tree and gunpowder tree. The plant has been found throughout the Indian sub-continent and used as local herbal medicine [5]

Taxonomical position of *T. orientalis* [6]

Kingdom	:	Plantae
Sub kingdom	:	Viridiplantae
Super division	:	Embryophyta
Division	:	Tracheophyta
Subdivision	:	Spermatophytina
Class	:	Magnoliopsida
Super Order	:	Rosanae
Order	:	Rosales
Family	:	Cannabaceae
Genus	:	Trema Lour.
Species	:	*Trema orientalis* (L.) Blume-Oriental Trema

Vernacular names

Table 1: Vernacular names of *Trema orientalis* plant [7].

Language	Common name
English	Gun powder tree, Indian charcoal tree, Indian nettle, Oriental nettle, Pigeon wood, Poison peach and Popti
Kannada	ಗೊಕುರ್ (Gorku), ಕರುಹಾಲೆ (Karuhaale)
Hindi	जियो (Gio), जीवन (Jivan)
Sanskrit	जीवनी (Jivani), jivanti
Bengali	Chikan and jiban
Telugu	Kondajonna, Kakamushti and Moralai
Marathi	Ghol, Kapshi and Khargol
Tamil	Ambaratthi and Taeliaamaram
Malayalam	Ratthi
Malay	Menarong, mengkirai and randagong
Chinese	Yi se shanhuang ma
Indonesia	Kuray and lenggung
Japanese	Urajiroenoki

Origin and Distribution

T. orientalis was found in low land humid tropics. It was one of the earliest trees to grow in barren lands, riverbanks devastated by floods and in nutrient deprived soils. It was sensitive to forest fire [7]. The Indian charcoal tree (*Trema orientale* Linn.) was native to South Africa, tropical Asia and Australia and was widely distributed all over the world [5].

In India, *T. orientalis* is distributed across Andhra Pradesh, Karnataka, Kerala, Maharashtra and Odisha states. In Karnataka, it is commonly seen in Bengaluru, Chikkamagaluru, Davanagere, Dharwad, Shivamogga and Uttara kannada districts. It had been one of the initial species of plants to thrive on riverbanks shattered by floodwaters, inhabiting a wide variety of soils from dense clay to fine sand [8].

Morphology

T. orientalis was either a bush or an average to medium sized tree, depending on the climate and region in which it flourished. In forests, it reached heights of up to 18 m, whereas in savannahs, it could reach only up to 1.5 m. The thin branchlets have white and silky hairs covering them. Grey or brown bark which was soft but had parallel longitudinal lines and corky patches. It could endure prolonged droughts because of its large tap root system [5].

Simple, alternating, stipulated with short grey hairs below and serrated edges all around drooping branches. The leaves were 14 cm long, papery, scratchy to touch and above portion was dull in appearance. The leaf blade of the plant was unequal-sided at the base, leathery, delicate, obliquely oval, crenate-serrulate and alternately chartaceous rough above, but softly covered beneath with typical white pubescent as per the findings of [9]. The apex was edged acutely and basally three veined. Secondary veins were 4 to 6 in number on either side of midvein. The surface was entirely covered by hairs which were 6–10 mm long, hairy and slender petiole. The leaf was green in colour, tasted a little bit bitter and smell was unremarkable. [9], also reported that microscopically, lamina and part of the midrib would be visible in transverse section of leaf. The dorsiventral type lamina was distinguished into palisade and spongy parenchyma. Both the upper and lower epidermis exhibited the presence of glandular trichomes and a unicellular multiseriate coating. The single layer of upper epidermis was polygonal and covered with cuticle. Palisade cells were present in two to three layers up to the midrib and contained rosette-shaped calcium oxalate crystals.

Small, unisexual, green or greenwashed-white coloured flowers were arranged in dense clusters. The inflorescence was composed of male flowers along with few female flowers [7].

Fruit was tiny, oblong and meaty. When ripened, it turns glossy black and was 4-6 mm in size. It has one dull-black seed embedded in bright-green flesh. *T. orientalis* blooms from February to April in India and flowers were unisexual. Although, varying with the location, in most parts of India, the ripening of the fruit was between December and May. The birds had consumed the fruit and dispersed the seeds [7].

PHYTOCHEMICAL CONSTITUENTS

As per the findings of [10], alkaloids, steroids and flavonoids were found to be abundant in *T. orientalis*, while tannins, saponins, terpenoids, glycosides and carbohydrates were present in moderate quantity. Resins and protein were detected in minute amount, with the exception of oil and reducing sugar, which were not detected. The terpenoids, saponins, bound sugars, tannins, cardiac glycoside, flavonoids, and free anthraquinones were found in the stem bark extract [11]. As per [12], the ethanol, ethyl acetate and hexane extract of *T. orientalis* seeds subjected to phytochemical screening for major bioactive compounds revealed the presence of tannins, saponins, terpenoids, alkaloids, balsam, volatile oil and cardiac glycosides. The ethanolic extract of the leafy stem of the *T. orientalis* revealed the presence of flavonoids, lignans, essential oils, tannin, saponins and cardiac glycosides [13].

[14], reported the presence of tetradecanal, hexadecanoic acid, farnesylacetone, heptacosane and linalool components in the leaf oil of *T. orientalis*. The octacosanoic acid, 1-octacosanyl acetate, simiarenone, simiarenol, episimiarenol and a new triterpene alcohol

called trematol were found in the stem bark in addition to the presence of methylswertianin and decussatin glycosides. In the study conducted by Kuo *et al.* [15], chemical analysis has been done to identify and isolate triterpenoids, sterols, fatty acids and flavonoid glycosides in the trunk and roots of *T. orientalis* included, (+)-catechin, (+)-epicatechin, (+)-syringaresinol, and trans-4-hydroxy-cinnamic acid, (-)-ampelopsin F and N-(trans-p-coumaroyl) tyramine. The chemical analysis carried out by [16,17] on dichloromethane and ethyl acetate extracts from the trunk and root barks of *T. orientalis* isolated sixteen different substances. The spectrum data was used to evaluate methylswertianin, glycosides of decussatin, sweroside, scopoletin, (-) epicatechin, lupeol, p-hydroxybenzoic acid and 3,4-dihydroxybenzoic acid.

TRADITIONAL USES

T. orientalis herb was used for therapeutic purposes in various parts of Africa. The Zulus of South Africa consumed the young leaves as spinach and made traditional medicines from the roots and stem bark. The fruit, leaves, bark, stem, twig and seeds of the above species were commonly employed in conventional medicine [18]. *T. orientalis* Linn. was used as a part of the traditional medicine in many countries because of its widespread and numerous intriguing pharmacological properties. The bark of the plant was applied as a poultice for sore muscles and the bark, roots and leaves have been prescribed for the relief of haematuria, asthma, diarrhoea and epilepsy [19,20].

Decoctions of the stem bark were employed as vermifuges and anti-diarrhoeal agents. Fever and toothaches were treated with an infusion of the stems and twigs. A decoction of *T. orientalis* stem bark and leaves were used to treat malaria, as well as to treat aching joints and muscles and venereal diseases. For the relief of toothaches, both the stem bark and leaf decoctions were used in form of gargle, inhalation and vapour bath [10,21,22,] reported that the bark had been used to manufacture cough syrups, while the leaves were used to heal coughs and sore throats. Both of them were also used in treating bronchitis, gonorrhoea, malaria, yellow fever, toothaches and helminthiasis.

As per [7], the plant was known to have anti plasmodial activities, along with that the bark infusion was used to treat poisoning and the leaves were used as general antidote to different types of poisonings. Tribal people used leaf decoction for deworming and to treat diarrhoea.

As per [5] *T. orientalis* leaves, *Bidens pilosa* leaves, *Citrus aurantifolia* leaves and unripened pineapple peels were mixed and boiled. The resulting decoction was used to treat jaundice. Bronchitis, pneumonia and pleurisy were treated using the *T. orientalis* leaves macerated in lemon juice. Cough remedies were also made from the combination of leaves and lemon juice. In some regions of Central Africa, Madagascar and West Africa, the leaves of *T. orientalis* plants were used to prepare decoction to treat ascariasis and taeniasis. Children who had bronchitis, pneumonia and pleurisy were treated with infusions made from the fruits and flowers [23]. Roots were used to treat trauma, haemostasis, haematuria, enterorrhagia and gastrorrhagia [24].

PHARMACOLOGICAL PROPERTIES

Antibacterial activity

[25], reported that the crude methanolic extract of *T. orientalis* had antibacterial activity against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Plesiomonas shigelloides*, *Shigella dysenteriae* and *Vibrio cholerae*, while the aqueous extract of plant had similar effects on *S. aureus* and *Staphylococcus epidermidis*. The outcome of antibacterial activity was determined by the diameter of the zone of inhibition (in mm). Both the methanol and aqueous extracts had demonstrated antibacterial efficacy against gram-positive and gram-negative microorganisms when contrasted with a gentamicin standard. Compared to methanol extract aqueous extract exhibited greater antibacterial activity. *T. orientalis* stem bark extract was prepared from five different solvents like n-hexane, chloroform, ethyl acetate, methanol and water. The antibacterial activity of these extracts was measured in form of minimum inhibitory concentration by agar well diffusion assay technique. The aqueous extract exhibited the zone of inhibition of 9 mm for *S. aureus*, 10 mm for *Klebsiella pneumoniae* and 13 mm for both bacteria at 200 mg/ml. According to [11], the chloroform extract proved effective against all the microorganisms tested with zones of inhibition for *Pseudomonas flourescens* ranging from 15 mm to 30 mm, for *S. aureus* from 16 mm to 35 mm, for *Proteus mirabilis* from 12 mm to 25 mm and for *K. pneumoniae* from 12 mm to 24 mm. The methanolic extract of *T. orientalis* exhibited effective antibacterial activity against *E. coli.*

Analgesic activity

[25], investigated the analgesic efficacy of methanolic and the aqueous extract of *T. orientalis* with the help of mice's writhing experiment produced by acetic acid. The extract of methanol reduced the amount of writhing caused by acetic acid in mice by 16.67% and 30.01%, respectively, at doses of 250 mg/kg and 500 mg/kg body weight (b.w). However, the acetic acid-induced writhing inhibition in mice was inhibited by the aqueous extract at doses of 250 mg/kg and 500 mg/kg by 38.34% and 56.67% respectively. When diclofenac sodium was administered as the standard drug at a dose of 25 mg/kg b.w, the inhibition was 48.34%.

Antihyperglycemic activity

As per the study of [26], a mechanism distinct from that of sulfonylurea agents allowed stem bark extract from *T. orientalis* to substantially decrease blood glucose levels in diabetic rats developed from streptozotocin (STZ). Both the healthy and STZ-induced diabetic rats were used to test the ability of the aqueous stem bark extract of *Trema orientalis* on blood sugar levels. In rats with normal blood sugar levels, blood glucose levels were not reduced by just one oral dose of *T. orientalis* aqueous extract. In comparison to the untreated diabetic group, the *T. orientalis* extract (300 mg/kg) exhibited considerable hypoglycemic activity in STZ-induced diabetic rats, with a peak performance of 29.67% at 5 hours after treatment with a 75 mg/kg dose. While glibenclamide significantly reduced blood sugar in normoglycemic rats, it had no effect in STZ-diabetic rats. In rats with STZ induced diabetes, by deploying an oral glucose tolerance test, the capability of *T. orientalis* to cause hypoglycemia was determined. The aqueous extract of *T. orientalis* and the reference drug, glibenclamide (10 mg/kg), considerably reduced the blood glucose levels in the diabetic rats in comparison to the diabetic controls. Blood glucose levels were significantly lower for one week and continued to be lower after repeated administration of *T. orientalis* extract for two weeks.

Anti pyretic activity

[27], reported that the ethanolic extract of leaves of *T. orientalis* demonstrated a dose-dependent reduction in body temperature in rats

with pyrexia being induced by injecting 10 ml/kg b.w of 20% brewer's yeast suspension in saline solution by subcutaneous route. The rectal temperature was recorded at 30, 60, 90, 120, 150 and 300 min after yeast injection. After 18 hours of yeast injection, the experimental rats were administered with the standard (paracetamol @ 100 mg/kg) and plant extract in respective groups. In comparison with the control group and standard group, rats of all three extract treated groups exhibited a dose-dependent reduction in body temperature.

Hypolipidemic activity

As per the study of [28], EETO (Ethanolic extract of *Trema orientalis*) showed a significant atherogenic index and protection against hyperlipidaemia in fructose-induced rat model. The EETO demonstrated a significant ($p<0.05$) hypolipidemic effect by decreasing the serum levels of cholesterol, triglyceride, LDL and VLDL and an increase in HDL levels, in comparison to the standard drug simvastatin. The enzyme activity that catalyses the conversion of HMG to mevalonate was measured by the ratio of HMG-CoA to mevalonate. These biochemical findings, which were equivalent to the common hypolipidemic medicine simvastatin, were later verified by histological analysis of sections of liver.

Hepatoprotective activity

[29], demonstrated the hepatoprotective effect of methanolic extract of *T. orientalis* (METO) leaf in cadmium (Cd) induced hepatotoxicity in rats. The continuous Cd dosing caused the failure of hepatocytes to absorb bilirubin and impaired bilirubin excretion, which lead to rise in total and conjugated bilirubin concentrations in blood resulting in liver dysfunction. There was increase in serum alanine transaminase (ALT) activity after Cd treatment which was considered as marker enzyme for liver damage caused by chemicals, but the METO administration diminished the activity of serum ALT. The capacity of METO to block this action was an indication that it has the ability to repair cellular membrane damage. The METO appeared to be hepatoprotective and chemo preventive as evidenced by reduced loss of hepatic excretory and synthetic functions. There was hepatocyte congestion after Cd administration, METO protected liver against severe damages due to Cd such as diffused hydropic degeneration, cell necrosis, kupffer cell proliferation and hepatic venule congestion. Another indication of the hepatoprotective activity of METO was the decrease in structural damage of liver due to the presence of bioactive chemicals with known therapeutic properties.

Antidepressant and anxiolytic Activities

The antidepressant and anxiolytic properties of ethanolic extract of *T. orientalis* leaves (EETO) was evaluated in mice by [30], with doses at 200 mg and 400 mg/kg body weight. Hole board models and elevated plus mazes (EPM) were used to assess the anxiolytic activity. The time of immobility was taken into account when assessing the forced swimming and tail suspension experiments as predictive animal models of antidepressant action. Additionally, the EETO had shortened the immobility period in the forced swimming test and the tail suspension test, other two animal models of antidepressant action. The EETO considerably increased the duration of time spent in open arms in the EPM test compared to control and they also significantly increased the frequency of head pokes in the hole board test compared to control. The overall findings of the study suggested that an EETO had considerable antidepressant and anxiolytic properties.

Anti-inflammatory activity

In the study of [20], the methanolic extract of leaves of *T. orientalis* (METO) had shown a considerable inhibitory effect on the oedema formation from the first hour to the fifth hour in Wistar rats at 200 and 400 mg/kg doses respectively. The control group were administered with vehicle (1% w/v Tween 80 in water) at a dose of 10 ml/kg b.w. The test groups were administered with METO, whereas the positive control group received aspirin at a dose of 150 mg/kg. One hour before injecting 0.1 ml of newly made carrageenan suspension (1% w/v) into left hind paw of each rat, the medications were given orally. Following the injection of carrageenin, the paw volume was measured at every hour for five hours using a plethysmometer. The METO had shown a considerable inhibitory effect on the oedema formation from the first hour to the fifth hour. The third hour had the highest levels of inhibition, with 24.59% ($p <0.001$) and 40.98% ($p <0.001$) at the dose rate of 200 and 400 mg/kg, respectively. These results were comparable to aspirin (positive control) which exhibited an inhibition of 51.23%.

Anticancerous activity

As per the study of [31], Swiss albino mice were used to test the *in vivo* anticancer activity of methanolic extract of *T. orientalis* leaves (METO) against Ehrlich ascites carcinoma (EAC). By using the MTT assay (3-4,5-dimethyl-2-thiazolyl-2,5-diphenyl-2H-tetrazolium bromide), the cytotoxic activity of METO was assessed *in vitro*. By utilising trypan blue dye to count the EAC cells on a haemocytometer, it was possible to assess the growth inhibitory activity and morphological changes. Through the use of DAPI (4′,6-diamidino-2-phenylindole) labelling, the apoptotic cells were determined. The haematological and biochemical characteristics of the experimental mice were also calculated. The viable tumour cell count, morphological alterations and nuclear damages of the EAC cells were noticed following treatment with the METO. The maximum safe dose of METO was determined to be 800 mg/kg b.w and the LD_{50} was 3120.650 mg/kg body weight. When compared to control mice, the oral administration of the METO at 400 mg/kg body weight resulted in a 59% inhibition of tumour cell growth. Important apoptotic characteristics were additionally evident, including chromatin condensation, nuclear fragmentation, membrane blebbing and agglomeration of the apoptotic bodies when stained with DAPI under a fluorescent microscope. The altered haematological parameters were brought back to normal levels in dose dependent manner by the METO. With an IC_{50} value of 29.952 ± 1.816 µg/ml against the EAC cell, the METO demonstrated a strengthening cytotoxic impact. Thus, METO proved to be a natural anti-cancer substance with the ability to induce apoptosis and being cytotoxic to carcinoma cells.

Diuretic activity

[20], investigated the diuretic activity of methanolic extract of aerial parts of *T. orientalis* leaves (METO) in mice which were fasted for 24 hours before the experiment. A dose of 10 ml/kg body weight of vehicle (1% w/v Tween 80 in water) was given orally to the control group. Urea solution was given to group II at 500 mg/kg dosage. Furosemide, a common diuretic, was administered to group III at a dose of 0.5 mg/kg. Groups IV and V, the test groups were administered with METO at doses of 200 and 400 mg/kg respectively. The METO impact on mice urination was monitored for 5 hours and the results showed that the extract has a pronounced diuretic effect on the test animals. This was equivalent to the effects of the diuretic urea and the common medication furosemide. Na^+/K^+ excretion ratio was

1.48 and 1.45 at doses of 200 and 400 mg/kg, respectively and for electrolyte loss that was comparable to that of furosemide.

Antioxidant activity

An antiradical activity of 69.73% (scavenging activity of the stable 1,1-diphenyl-2-picryl hydrazyl (DPPH) free radical) was reported by [32], using a methanol soluble fraction isolated from *T. orientalis* leaves. This value was practically identical to that of 1 mM ascorbic acid. The iron chelating activity of *T. orientalis* leaves was 40.74% when extracted in methanol, which means the activity was just approximately 50% that of an EDTA ligand. Overall, *T. orientalis* leaves (methanol extract) had good iron chelating and antiradical actions as well as flavonoid content. The iron chelating ability of the extract made it clear that it has potential as a herbal iron chelator.

Antimalarial activity

[33], shown that aqueous extracts of T. orientalis leaves and bark had anti-plasmodial effect in vivo in a mice model. *Plasmodium berghei* was injected intraperitoneally to Swiss Albino mice weighing around 23-27 g. Based on the toxicity signs and mortality, the lethal dose for mice was predicted to be greater than 5000 mg/kg. Aqueous crude leaf and bark extracts were administered at doses of 400, 800 and 1600 mg/kg, with chloroquine being the positive control. The packed cell volume, parasitaemia and parasite inhibition were calculated. At 400, 800 and 1600 mg/kg, the leaf extract inhibited the protozoa by 51.55, 62.78 and 76.08 %, whereas the bark extract inhibited protozoa by 44.3, 65.82 and 74.23 %, respectively. At 400, 800 and 1600 mg/kg, the percentage parasitaemia of the leaf extract reduced by 45.0, 70.3 and 74.7 %, but the percentage parasitaemia of the bark extract decreased by 37.4, 53 and 52.0 %, respectively. PCV was 48.85, 49.88 and 50.99 % in mice treated with 400, 800 and 1600 mg/kg leaf extract, while it was 49.38, 48.88 and 51.94 % in mice treated with bark extract, respectively. The results supported the folkloric use of the plant by illustrating its potential anti plasmodial action against *Plasmodium berghei*.

Antiulcer activity

As per the study of [27], 95% ethanol was used to develop the ulcer in six sets of male Wistar albino rats. Each group contained six rats and all groups were fasted for 24 hours but allowed to drink water. Based on their groupings and weights, different doses of test substances were administered orally to all the rats. Pantoprazole at 20 mg/kg, p.o was the standard used, while the test groups I, II and III received ethanolic extracts of *T. orientalis* leaves at doses of 100, 200, and 300 mg/kg after 24 hours. When compared to the control and the reference drug pantoprazole, all three groups with test doses of the ethanolic extract of *T. orientalis* revealed a dose-dependent reduction in Ulcer Index. Also, the *per cent* protection from ulcer for the doses 100 mg/kg, 200 mg/kg and 300 mg/kg were 96.80, 98.64 and 99.02 respectively. The presence of flavonoids, tannins and triterpenoids in *T. orientalis* were attributed for the cytoprotective and antiulcerogenic activity. It was hypothesized that these active substances could prevent the damaging effects of reactive oxidants on the gastrointestinal lumen by promoting mucus, bicarbonate and prostaglandin secretion.

TOXICOLOGICAL PROPERTIES

Toxicity studies

As per the study of [34], the clinicopathological alterations were induced by the oral administration of ethanolic leaf extract of *Trema orientalis* (ELETO) in Jamnapari crossbred goats. The gross and histological alterations in major vital organs, as well as the clinical symptoms were considered as indicators of the toxicity. In a perfectly randomized design, four groups of five goats each were created from a total of twenty goats weighing between 15-20 kg. Group IV acted as the control group while test groups I, II, and III received doses of ELETO of 0.5, 1 and 2 g/kg b.wt, p.o./day for a total of 14 days. The appetite was reduced in groups II and III. Group III goats exhibited lacrimation, rectal tenesmus and a considerable loss in body weight as compared to the control group. There were gall bladder engorgement, congestive icteric liver, hepatocellular degeneration, vacuolation, necrosis and renal congestion, which revealed that the ELETO was hepatotoxic and nephrotoxic in goats at repeated oral doses equal to or greater than 2 g/kg b.wt, while there was no detectable toxicity at lower dosages.

As per the investigation conducted by [35], it was shown that more than 2000 mg/kg of *T. orientalis* methanolic extract was the approximate acute lethal dose (LD_{50}) for male Wistar albino rats. No deaths occurred in the first group of three male rats given 2000 mg/kg of *T. orientalis* methanolic extracts during acute oral toxicity testing in rats. The wellness measures showed no toxicity over the course of 14-day monitoring period. The second group of male rats that received the extract at a dose of 2000 mg/kg also revealed similar observations. Rats were fed *T. orientalis* orally at doses of 400 mg/kg/b.w. for the sub-acute toxicity research, which showed significant alterations in animal behaviour as well as significant decrease in body weight, from day 1 to day 28.

As per the study carried out by [36] acute toxicity was studied using twenty-four mice split into six groups by administration of methanolic extract of *T. orientalis* stem bark extract. A single oral dose of 500 mg/kg, 1500 mg/kg, 2200 mg/kg, 5000 mg/kg and 7500 mg/kg/body weight were administered to each group, while distilled water was given to the control group. Over the course of 24 hours, the mice were monitored for any signs of acute poisoning. Since there were no toxicity symptoms and just one death per group at a response/death rate of 25%, the LD_{50} of the extract was calculated as more than 7500 mg/kg, based on the probit analysis method.

The haematopoietic impact was tested in 25 albino rats, which were divided into five groups and given daily doses of 0.0625 g/kg, 0.125 g/kg, 0.25 g/kg and 0.5 g/kg body wight of the methanol extract, respectively, for 28 days. Acute toxicity testing revealed a 25% response at a limit dose of 7500 mg/kg, while the haematopoietic effect resulted in a significant increase in the PCV, Hb, RBC, and lymphocyte count ($p = 0.05$) in comparison to the control and a significant decrease in the WBC, eosinophils, neutrophils and platelet counts ($p < 0.05$). It was estimated that LD_{50} would be higher than 2000 mg/kg. This investigation demonstrated that this herb was non-toxic and had a sizable haematopoietic effect. As a result, it supported the traditional use of plant as a haematinic.

All the haematological parameters were found to be affected by *T. orientalis* methanol extract, with PCV, Hb, RBC and lymphocyte levels increased, while neutrophil, eosinophil, WBC and platelet levels significantly reduced. The extract dose of 0.0625 g/kg generally appeared to have the greatest impact compared to other administered doses.

CONCLUSION

Trema orientalis was a typical pioneer plant used in traditional medicine for the treatment of ailments in tropical regions. The plant has been found throughout the Indian sub-continent and used as local herbal medicine. *T. orientalis* was a shrub or small to medium-sized tree, height varying with the region and climatic conditions. It has simple serrated leaves, greenwashed-white coloured flowers and tiny, oblong and meaty fruits. The stem bark extract contained terpenoids, saponins, bound sugars, tannins, cardiac glycoside, flavonoids and free anthraquinones. *T. orientalis* herb was used for therapeutic purposes in various parts of Africa. In traditional medicine the fruit, leaves, bark, stem, twig and seeds of this plant were utilized extensively. Various studies have demonstrated pharmacological properties of *T. orientalis* such as antibacterial, antioxidant, antidepressant, anxiolytic, hepatoprotective, anti-inflammatory, anti-cancerous, diuretic activity etc. Many studies showed it was non-toxic and had a sizable haematopoietic effect, also LD_{50} was estimated to be more than 7500 mg/kg. So, it can be concluded that this further more research is required to extrapolate traditional uses of this plant to use it as medicine along with precaution regarding toxic dose.

Conflict of Interest

None declared.

Financial Support

None declared.

ORCID ID

Niranjan.D: https://orcid.org/0009-0005-1332-9918
N B Shridhar: https://orcid.org/0000-0001-6671-1006
Pradeep.B.S: https://orcid.org/0009-0008-3319-0206

REFERENCES

1. Saklani A, Kutty SK. Plant-derived compounds in clinical trials. Drug discovery today. 2008 Feb 1;13(3-4):161-71.
2. St-Laurent L, Baum BR, Akpagana K, Arnason JT. A numerical taxonomic study of Trema (Ulmaceae) from Togo, West Africa. Systematic Botany. 2000 Jul;25(3):399-413.
3. Jin D, Dai K, Xie Z, Chen J. Secondary metabolites profiled in cannabis inflorescences, leaves, stem barks, and roots for medicinal purposes. Scientific Reports. 2020 Feb 24;10(1):3309.
4. Parvez A, Azad MA, Islam MZ, Munna MM, Shaheen SM, Rahman MM, Azad AK. A phytochemical and pharmacological review on Trema orientalis: a potential medicinal plant. Pharmacology Online. 2019 Dec 30; 3:103-119.
5. Adinortey MB, Galyuon IK, Asamoah NO. Trema orientalis Linn. Blume: A potential for prospecting for drugs for various uses. Pharmacognosy reviews. 2013 Jan;7(13):67.
6. Integrated Taxonomic Information System (ITIS) on-line database. 2011. https://www.itis.gov.in, CC0 TSN 897053. https://doi.org/10.5066/F7 KH0KBK.
7. Orwa C, Mutua A, Kindt R, Jamnadass R, Simons A. Agroforestree Database: a tree reference and selection guide. Version 4. Agroforestree Database: a tree reference and selection guide. Version 4. 2009.
8. Sankara Rao, K., Raja Swamy, K., Deepak Kumar., Arun Singh, R. and Gopalakrishna Bhat, K. 2019. Flora of Peninsular India. http://peninsula.ces.iisc. ac.in/plants. php?name=Trema orientalis.
9. Panchal HS, Master SM, Saluja AK, Patel MR. Pharmacognostic and phytochemical evaluation of Trema orientalis leaf. International Journal of Pharmacy and Pharmaceutical Sciences. 2015;7(5):317-319.
10. Bhat RB, Etejere EO, Oladipo VT. Ethnobotanical studies from central Nigeria. Economic Botany. 1990 Sep; 44:382-90.
11. Ajayi GO, Idoko A, Usman A. Phytochemical analysis and antibacterial activity of Trema orientalis (Ulmaceae) stem bark extracts on respiratory tract bacteria. Tropical Journal of Natural Product Research. 2018;2(12):512-516.
12. Osanaiye A, Catherine B, Rukayyah A. Phytochemical analysis, anti–microbial screening and antioxidant activity of the seed of Trema orientalis, Acad. J. Sci. 2014;3(1):211-217.
13. Adjileye RA, Amoussa AM, Lagnika L. Trema orientalis L. and Dialium guineense Wild. used to manage hypertension in Bénin: phytochemical study and antioxidant activity. J Med Plants Stud. 2019;7(3):43-48.
14. Tchamo DN, Dijoux-Franca MG, Mariotte AM, Tsamo E, Daskiewicz JB, Bayet C, Barron D, Conseil G, Di Pietro A. Prenylated xanthones as potential P-glycoprotein modulators. Bioorganic & medicinal chemistry letters. 2000 Jun 19;10(12):1343-1345.
15. Kuo WL, Huang YL, Wang ST, Ni CL, Shien BJ, Chen CC. Chemical constituents of Trema orientalis. J. Chin. Med. 2007 Jun 1;18(1):27-36.
16. Ogunkoya, L., Olubajo, O.O. and Sondha, D.S., 1973. Simiarenone from Trema orientalis. Phytochemistry, 12(3), pp.732-733.
17. Ogunkoya L, Olubajo OO, Sondha DS. A new triterpenoid alcohol from Trema orientalis. Phytochemistry. 1977 Jan 1;16(10):1606-1608.
18. Iwu, M. M. 1993. Pharmacognostical Profile of Trema guineensis. In: African medicinal plants, Edt. Iwu, M.M. Edn 2nd., CRC Press, Maryland. pp.109-110.
19. Kirtikar KR, Basu BD. Indian medicinal plants. Basu, Bhuwaneśwari Âśrama; 1918.
20. Uddin SN, Yesmin MN, Pramanik MK, Akond MA. Anti-inflammatory, antinociceptive and diuretic activities of Trema orientalis Linn. Advances in Traditional Medicine. 2009;9(4):320-325.
21. Rasoanaivo P, Petitjean A, Ratsimamanga-Urverg S, Rakoto-Ratsimamanga A. Medicinal plants used to treat malaria in Madagascar. Journal of Ethnopharmacology. 1992 Sep 1;37(2):117-27.
22. Rulangaranga, Z. K. 1990. Conservation of medicinal and aromatic plants in Tanzania proceedings of a workshop on priority species for tree planting and afforestation in Tanzania. Morogoro, Tanzania. May, pp.14-18.
23. Watt JM, Breyer-Brandwijk MG. The Medicinal and Poisonous Plants of Southern and Eastern Africa being an Account of their Medicinal and other Uses, Chemical Composition, Pharmacological Effects and Toxicology in Man and Animal. The Medicinal and Poisonous Plants of Southern and Eastern Africa being an Account of their Medicinal and other Uses, Chemical Composition, Pharmacological Effects and Toxicology in Man and Animal. 1962(Edn 2).
24. Hines DA, Eckman K. Indigenous multipurpose trees of Tanzania: uses and economic benefits for people. Ottawa, ON, Canada: Cultural Survival Canada; 1993.

25. Uddin SN. Antioxidant and antibacterial activities of Trema orientalis Linn: an indigenous medicinal plant of Indian subcontinent. Advances in Traditional Medicine. 2008;8(4):395-9.
26. Dimo T, Ngueguim FT, Kamtchouing P, Dongo E, Tan PV. Glucose lowering efficacy of the aqueous stem bark extract of Trema orientalis (Linn) Blume in normal and streptozotocin diabetic rats. Die Pharmazie-An International Journal of Pharmaceutical Sciences. 2006 Mar 1;61(3):233-6.
27. Kanase VG, Singh JY. Evaluation of antipyretic and antiulcer activity of ethanolic extract of leaves of Trema orientalis L. In albino wistar rats. Asia J. Pharmaceut. Clin. Res. 2019;12(12):149-54.
28. Pramod C, Ratheesh M, Jose SP, Jose S. Evaluation of hypolipidemic activity of ethanolic extract of Trema orientalis L. Blume leaves. Journal of Pharmacognosy and Phytochemistry. 2020;9(4): 904-11.
29. Olajide JE, Sanni M, Achimugu OJ, Suleiman MS, Jegede ER, Sheneni VD. Effect of methanol extract of Trema orientalis leaf on some biochemical and histopathological indices of wistar albino rats with cadmium-induced-hepatotoxicity. Scientific African. 2020 Nov 1;10:e00568.
30. Arman MS, Kabir MS, Afroze S, Alam MF, Haque MA, Islam T, Al Ragib A, Rahman MT, Akter-Uz-Zaman KM, Rahman MM. In vivo antidepressant and anxiolytic activities of ethanol extract of Trema orientalis leaves in mice.
31. Kabir M, Al-Noman A, Dash BK, Hasan M, Akhter S, Rahman M. Trema orientalis (Linn.) leaves promotes anticancer activity in Ehrlich ascites carcinoma (EAC) in Swiss albino mice. Journal of basic and clinical physiology and pharmacology. 2019 Nov 19;31(2):20190121.
32. Angasa E, Ningsih S, Manaf S, Murni SA, Umbara F. Iron chelating and antiradical activity of kayu manik leaves (Trema orientalis). Indonesian Journal of Chemistry. 2011 Nov 3;11(2):196-9.
33. Oyebola OE, Morenikeji OA, Ademola IO. In-vivo antimalarial activity of aqueous leaf and bark extracts of Trema orientalis against Plasmodium berghei in mice. Journal of Parasitic Diseases. 2017 Jun; 41: 398-404.
34. Saleh A, Usman A, Ibrahim NB, Abalaka SE, Sani NA, Mohammed A, Zainal-Ariffin SA. Clinicopathological Effects of Oral Administration of Ethanol Leaf Extract of Charcoal–Tree (Trema orientalis Linn Blume) in Jamnapari Crossbred Goats. Nigerian Veterinary Journal. 2020;41(3):223-33.
35. Hemalatha T, Mary DA, Ganthi AS. Acute and sub-acute toxicity study of Trema orientalis (L.) Bl. methanol extract in rats. Journal of Drug Delivery and Therapeutics. 2019 Feb 15;9(1-s):307-11.
36. Kasim LS, Badejo MV, Daodu JO, Ayanuga JK, Olaitan OJ. Haematopoietic and safety study of methanolic extract of the bark of Trema orientalis (L.) Blume Fam. Ulmaceae. Nigerian Journal of Pharmaceutical and Applied Science Research. 2015;4(3):42-8.

HOW TO CITE THIS ARTICLE
Niranjan D, Shridhar NB, Vinuta MH, Manjunatha SS, Sunilchandra U, Pradeep BS, Manju GU, Revanna PS. Botanical, pharmacological and toxicological properties of *Trema orientalis*: A Review. J Phytopharmacol 2023; 12(6):392-398. doi: 10.31254/phyto.2023.12605