IJPSR (2022), Volume 13, Issue 6 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 17 September 2021; received in revised form, 25 October 2021; accepted, 09 November 2021; published 01 June 2022

PHYTOCHEMISTRY AND PHARMACOLOGICAL ACTIVITIES OF *THEVETIA PERUVIANA*: A REVIEW

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Keywords:

Thevetia peruviana, Cardiac glycoside, Phytoconstituents, Traditional use, Pharmacological activities

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ABSTRACT: In any nation's public health care system, plants play an essential role in therapeutic treatment. The plant *Thevetia peruviana* is an evergreen ornamental dicotyledonous shrub belonging to the family Apocynaceae. *Thevetia peruviana* is widely distributed in Central and South America and Asian countries, especially in India and Srilanka. Alkaloids, flavonoids, steroids, terpenoids, tannins, saponins, cardiac glycosides, and other secondary metabolites are found in *Thevetia peruviana*. All parts of these plants are toxic and contain a variety of cardiac glycosides, including neriifolin, thevetin A, thevetin B, and oleandrin. The leaves of the plant are used as a cardiotonic and diuretic and are also reported to possess medicinal value in traditional systems of medicine. Several studies reported pharmacological activity in various plant parts, including seeds, flowers, bark, fruits and leaves. The purpose of this review is to provide the complete data, including morphology, cultivation and propagation, distribution, phytochemistry, traditional uses & pharmacological activities.

INTRODUCTION: *Thevetia peruviana*, commonly known as yellow oleander in English and Peeli Kaner in Hindi, is widespread throughout the India. The plant is mostly used as an ornamental in gardens, road dividers along the sides of roads. It does not require any maintenance and can easily survive in extreme conditions [1]. It requires minimum water when it is in its growing stage. It began flowering after one & a half years. It blooms three times a year. Fruit contains 2-4 flat gray seeds, yield about half a liter of oil from 1 kg of dry kernel [2]. It grows to about 10-18 feet high, with spirally arranged, linear leaves about 13 to 15 cm in length [3].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(6).2274-82

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(6).2274-82

Thevetia peruviana contains a milky sap, latex, that consists of a compound called Thevetin. Thevetin is used as a heart stimulant, but its natural form is extremely poisonous. Thevetin is a cardenolide called Thevetin A and Thevetin B (Cerebroside); others include Neriifolin, Thevetoxin Peruvoside, and Ruvoside [4]. The seeds are more poisonous in their natural form than other parts of plants [2]. Since its active compounds were found in various parts of the plant (contents of cardiac glycosides in leaf 0.07 %, fruit 0.045 %, seed (kernel) 4.8 %, milk 0.036 %), ingestion of seeds or other parts of the plant may cause intoxication [5].

Alkaloids, glycosides, saponins, flavonoids, fixed oils and fats, tannins, and phenolic compounds are other phytoconstituents found in yellow oleander [6]. The plant or its parts can be used to treat various human ailments, including diabetes, liver toxicity, fungal infection, microbial infection, inflammation, pyrexia and pain relief [7].

The plant shows effective medicinal properties and is reported to have anti-HIV, anti-inflammatory, anti-spermatogenic, anti-termite, antifungal, anti-oxidant, antimicrobial, antidiarrhoeal, antimicrobial, and cytotoxic activities *etc.* [8].

TABLE 1: TAXONOMY [9, 10]

S. no.	Taxonomy	
1	Kingdom	Plantae
2	Subkingdom/ Subkingdom	Tracheobionta /Spermatophytes
3	Division	Magnoliophyta
4	Class	Magnoliopsida
5	Subclass	Asteridae
6	Order	Gentianales
7	Family	Apocynaceae
8	Genus	Thevetia
9	Species	Peruviana

Synonyms: *Cascabela thevetia, Cerbera thevetia, Thevetia neriifolia* [10].

TABLE 2: VERNACULAR NAME [11, 12]

S. no.	Vernacular Name	
1	Common name	Be-still Tree, Suicide Tree, Lucky nut
2	English	yellow oleander,
3	Hindi	Peeli Kaner, Kulkephul
4	Sanskrit	Ashvaghna, Divyapusha and Haripriya
5	Tamil	Manjal Arali
6	Bengali	Kolke, Kolkaphul
7	Marathi	Bitti Manipuri: Utonglei
8	Others	Manjaaralie, Shatakunda, Pachaganeru, Ponnarali, Ashvamaraka

Morphology:

Height: *Thevetia peruviana* is an evergreen shrub or small tree usually about 3-8m tall, with a diffusely branched and dense crown.

Leaves: Leaves are dark green, alternate, simple with reticulate venation, spirally arranged, and about 13-15cm in length.

Flowers: are in small clusters at the tip of twigs, bright yellow and funnel-shaped with spirally twisted, with five petal lobes.

Fruits: The fruits are somewhat globular, slightly fleshy, and have a diameter of 4-5 cm. They are green in colour and turn black on ripening.. Each fruit contains a nut, which is longitudinally and transversely divided. Milky juice is contained in all parts of plants [10, 13].

Stem: Stem is green, turning silver/gray as it ages.

Seeds: Four seeds in the fruit and seeds are endospermic [14].

Habitat: Roadside areas, gardens, waste areas, waterways, open woodlands, pastures, and arid regions and in areas where drought conditions are dominant [1].


FIG. 1 AND 2: FLOWER OF *THEVETIA PERUVIANA*

FIG. 3: *THEVETIA PERUVIANA* TREE

FIG. 4: FRUIT OF *THEVETIA PERUVIANA*

FIG. 5: LEAVES OF *THEVETIA PERUVIANA*

Cultivation and Propagation: *Thevetia peruviana* is cultivated as an ornamental plant and planted as a large flowering shrub or small ornamental tree standards in gardens and parks in temperate climates.

It is a container plant placed inside a greenhouse or used as a house plant in frost-prone areas during the winter season. It can grow in a variety of soils and is drought tolerant.

Exposure: Part, full, or reflected sun; revels in heat.

Water: ample is best.

Soil: Improved garden soil with good drainage

Maintenance: Low, periodic pruning and litter cleanup; training when young to the tree if desired.

Form: Shrub or tree.

Season: Evergreen.

Soil: Will tolerate most kinds of soil as long as they are well-drained and are situated in full sun in a sheltered area.

Useful as a landscaping plant in warmer climates as it does not need much maintenance. Seeds are propagated in the spring or early summer when the spring has been turned off from hardwood cutting.

In spring condition, a glass containing 10% bleach 90% warm water, and a clean seed coat are taken for 2-3 min after wash seed and soaked in warm water for 24 h. For both, use seed cutting compost that contains perlite [15].

Distribution: This plant is found in tropical America, especially Mexico, Brazil, and West Indies [16], Australia, China [17], and South Asian countries, especially in India and Sri Lanka [4], grown throughout the tropical and subtropical regions.

Chemical Constituents: Alkaloids, flavonoids, steroids, terpenoids, tannins, saponins, cardiac glycosides, and other secondary metabolites are found in *Thevetia peruviana*.

Phytoconstituents isolated from the various parts of *Thevetia peruviana* are discussed as follows:

Leaves: Cardiac glycosides, sterols, iridoid glucosides, pentacyclic triterpenes and a cardenolide were identified in leaf extracts. The compounds neolupenyl acetate, 11-oxours-12-en-28-oic acid, lupeol acetate, oleanolic acid, ursolic acid, stigmast-5-en-7- one, and β-sitosterol all are known from fresh uncrushed leaves.

Kaempferol and quercetin flavonol glycosides have been isolated from the leaves. Leaves also contain polyhydroxy-dino monoterpenoids and their apiosyl glucosides [10, 17].

Bark: Four cardenolide glycosides have been identified in the bark extract: neriifolin, thevefolin, peruvoside, and (20S) – 18, 20-epoxy digitoxigenin α-L-thevetoside [17.]

Root: Root extract showed the presence of iridoids, theveside, theviridoside, and two new glucosides theviridoside identified by Chinese researchers, namely 10-O-β- D-Glucopyranosyl theviridoside and 3-O-β-D-Glucopyranosyl theviridoside [17].

Fruit Pericarp and Flowers: Epiperuviol acetate, hesperetin-7-glucoside, α-and β-amyrin, kaempferol and quercetin. Quercetin-7-o-galactoside was also found in the flowers [14, 17, 18].

Seeds: Seed kernels are very rich in cardioactive glycosides, triosides, *i.e*., the aglycone of these glycosides consists of three sugar units. The major constitutional glycoside is Thevetin.

Thevetin is a mixture of two triosides, namely Thevetin A and Thevetin B (cereberoside). Seed kernel also contains neriifolin, acetyl neriifolin, thevefolin, theveneriin, and peruvoside, which are monoside in nature.

Fatty oils constitute more than 62% of the seed kernel. The seed also contains small quantities of theveside, viridoside, and perusitin. Apigenin-5-methyl ether has been isolated from seed shells [10, 19].

Traditional use: Amenorrhoea, malarial fever, jaundice, haemorrhoids, constipation, headaches, skin diseases and other traditional uses of *Thevetia peruviana.* The active compounds can be found in various parts of *Thevetia peruviana* and have a wide range of therapeutic effects [10, 14, 20, 21].

TABLE 3: TRADITIONAL USES OF VARIOUS PARTS OF THEVETIA PERUVIANA

Plant Parts	Traditional use
Leaves	Emetic and purgative, jaundice, fever, eye drops and nose drops to cure colds, violent headaches. Flavonol glycoside from leaves has an inhibitory effect against HIV-1 Reverse Transcriptase and HIV1 Integrase
Seeds	Seeds are poisonous, abortifacient, and alterative. Emetic, haemorrhoids, skin problems, laxative, used as purgative in dropsy and rheumatism
Bark	Malarial fever, snake bites, purgative, emetic, sores, amenorrhoea, cathartic, febrifuge, useful in different kinds of intermittent fevers
Roots	Snakebites, roots are made into plaster and applied to tumors.
Fruits	Ointments and liniments

Pharmacological Activities:

Antimicrobial Activity: The antimicrobial activity of *Thevetia peruviana* leaves extract with 95% alcohol as organic solvent was analyzed against ten medically important pathogenic microbes. The extract was found to be effective against *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, but only at higher doses, *Proteus Vulgaris* were susceptible. The extract also showed moderate antimicrobial activity against *Staphylococcus aureus*, *Candida albicans*, *Aspergillus niger*, *Mucor*, *Rhizopus*, and *Penicillium species* [22]. Seed kernel extracts were evaluated for antimicrobial activity against human skin pathogenic microorganisms. Antimicrobial efficacy against Pseudomonas aeruginosa, *Nocardia asteroids*, and *Candida albicans* strains were effective for ethyl acetate than chloroform and methanol fractions, but lower concentrations of chloroform fractions showed higher sensitivity against *C. albicans* [23].

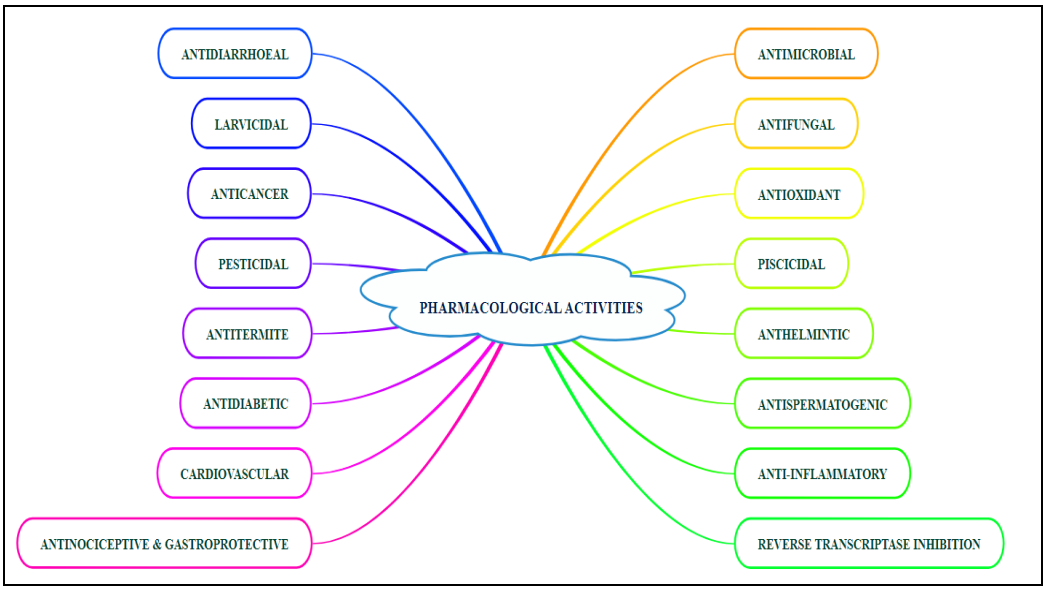

FIG. 6: PHARMACOLOGICAL ACTIVITIES OF *THEVETIA PERUVIANA*

Antifungal Activity: The antifungal activity of crude extracts and some of the corresponding fractions obtained from seeds of *Thevetia peruviana* was studied. Extracts obtained either with n-hexane or dichloromethane were fractionated by column chromatography or further analyzed by thin-layer chromatography. All seed extracts and fractions were tested for inhibition of the fungus *Cladosporium cucumerinum* for the evaluation of photoactive inhibitory effects. Antifungal light-dependent activity was observed for some of the fractions and both crude extracts. The most photoactive fraction was analyzed by capillary gas chromatography with mass spectrometry in order to identify its constituents. Pulegone was identified to be a major component of the terpene fraction, and it appears to be involved in the observed phototoxicity against the tested fungus [24].

Antioxidant Activity: DPPH free radical scavenging test was used to evaluate the antioxidant properties of three morph forms of *Thevetia peruviana*, Juss fruit wall extracts.

As organic solvents, petroleum ether, chloroform, ethyl acetate, and methanol were used. At a 1.2 mg/ml concentration, DPPH free radical scavenging activity for the ethyl acetate fraction was 50% inhibited [25].

Piscicidal Activity: Thevetia peruviana leaf and bark extracts were used as a potent source of piscicidal activity in a range of solvents. *Thevetia peruviana* leaf and bark extracts were administered to the freshwater fish *Catla catla* (Hamilton) for 24 hours to evaluate piscicidal activity in the laboratory and cemented pond conditions. In conditions, this plant's acetone leaf and bark extract were more effective than other solvent extracts. Exposure of sub-lethal doses (40% and 80% of LC_{50}) of acetone leaf and bark extract of this plant over 24 h caused significant ($p<0.05$) alterations in total protein, free amino acids, DNA & RNA, protease and acid and alkaline phosphatase activity, in muscle, liver and gonadal tissues of the experimental fish in laboratory conditions [26].

Anti-spermatogenic Activity: The aim of this study was to *evaluate the antifertility potential of Thevetia* peruviana in male albino rats by phytochemical evaluations. Phytochemical studies showed that the plant contains many active compounds, including α-amyrin acetate, lupeol acetate, α-amyrin, β-amyrin, lupeol, and thevetigenin. Oral administration of *T. peruviana* stem bark methanol extract to male rats at a dose of 100 mg/rat/day did not cause any significant reduction in body weight, while the weight of reproductive organs reduced significantly. The total protein and sialic acid content of the testes, epididymides, seminal vesicle, and ventral prostate, as well as the glycogen content of the testes, all decreased significantly; however, cholesterol significantly increased. *T. peruviana* stem bark methanol extract also caused a decline in spermatogenic elements, *i.e.*, preleptotene and pachytene spermatocytes, secondary spermatocytes, round spermatids, and mature Leydig cells. Leydig cell nuclear diameter, seminiferous tubular diameter, and sertoli area were significantly reduced at this dose level [27].

Anti-inflammatory Activity: Neriifolin, acetyl neriifolin, and thevetin glucosides are present in the seeds of *Thevetia peruviana*.

Phytochemical tests were performed on the fresh flowers of *Thevetia peruviana*. The flowers contain quercetin, kaempferol and quercetin-7-o-galactoside, according to studies. The structure of the isolated compound was characterized by UV, 1H NMR, and 13C NMR spectra. The anti-inflammatory character of the isolated compound was tested by in vitro method, and the results of the study revealed that the isolated compound showed a biphasic property [28].

Larvicidal Activity: Wahedi *et al.*, (2020) studied the larvicidal efficacy of the ethanol and aqueous extracts of leaves of *Thevetia peruviana* against the larvae of the malaria vector Anopheles mosquitoes. Bioassay was carried out on 2nd and 3rd instar larval stages of Anopheles mosquitoes. The toxicity effect of the treatment was measured in terms of mortality, which was observed for 72 hours at a 24 hours interval. Data collected was subjected to analysis of variance (ANOVA) to determine the larvicidal efficacy of *T. peruviana*.

The means were separated using the Least Significant Difference, while the log/probit-regression analysis was used to determine the lethal concentrations of the treatments at 50% and 95% *i.e.* LC_{50} and LC95, respectively. The treatment extracts at 200 and 400 mg/ml significantly recorded higher mortality of Anopheles mosquitoes' larvae compared with the control (acetone) experiment.

The regression coefficient (R2) further revealed the superiority of ethanol extract (0.882 ppm) over aqueous extract (0.055 ppm). This was further evident in the LC50 (9.193 ppm, 2.42E+13 ppm) and LC95 (17.545 ppm, 1037.079 ppm) for ethanol and aqueous extracts respectively. Therefore, this study further confirms the efficacy of the use of biopesticides as larvicidal in controlling insect pests, especially Anopheles larvae [29]. Sathish *et al.*, (2015) reported that the larvicidal efficacy of methanol leaf extract of *Thevetia peruviana* was tested against the aquatic stages of *Aedes aegypti*. The mortality, $LC_{50,}$ and LC90 values were noticed against I, II, III, IV instar larvae and pupae of *A. aegypti* after 24 h. The secondary metabolites of *T. peruviana,* which are responsible for larvicidal and pupicidal bioassay, were qualitatively and quantitatively estimated.

In addition, eight phytochemical compounds were noticed by gas-chromatography mass spectrometry [30].

Anticancer Activity: Ramos-Silva *et al.,* (2017) studied that the T. peruviana methanolic extract exhibited cytotoxic activity on four human cancer cell lines: prostate, breast, colorectal, and lung, with values of IC50 1.91 ± 0.76, 5.78 ± 2.12, 6.30 ± 4.45 and 12.04 ± 3.43 µg/ml, respectively. The methanol extract of *T. peruviana* fruit inhibits cell proliferation, has a time-dependent cytotoxic activity, and induces apoptosis of human cancer cell lines, but has minimal or less pronounced effects on normal cells. The fruit extract displayed anticancer properties mainly through mechanisms that included membrane permeability, motility, and DNA fragmentation. Maximum cytotoxic activity was observed in a fraction that contained one flavonoid and cardiac glycosides.

Chemical analyses of the active fractions are currently in progress to better evaluate their biological significance. Additionally, further "in vivo" research is essential to show the full potential for the use of *T. peruviana* fruit extract in cancer therapy. These findings show the importance of *T. peruviana* fruit as a source of bioactive compounds with anticancer potential [31].

Antidiarrhoeal Activity: The ethanol extract of yellow oleander leaves significantly reduced castor oil-induced diarrhoea in albino rats. The control group responded to castor oil-induced diarrhoea in albino rats, while 66.7% of the ethanol extract-treated group and 75% of loperamide (positive control) group responded to the relevant treatment. The mean latent period of ethanol extract-treated group (2.4 ± 1.66) and of the positive control (1.8 ± 1.11) decreased diarrhoea significantly ($p<0.01$) compared to the control group [32].

Pesticidal Activity: The leaves of *Thevetia peruviana* were extracted in aqueous and used to treat *Holotrichia Serrata* (Fab.) adults in this study. After 48 hours of bioassay, the tested aqueous leaf extract effectively produced 50% mortality of *Holotrichia Serrata* (Fab.), and their toxicity was 0.025 %. The leaf extract of Thevetia peruviana showed insecticidal effect against three strains of *T. castaneum* (CR1, CTC12, and FSS2) and their toxicity was in order; ethyl acetate> acetone> methanol> petroleum spirit [33].

Anti-termite Activity: *Thevetia peruviana* seed oil was used to make a surface coating with antifungal, antibacterial and anti-termite properties. The paint exhibited inhibitory activity against *E. coli, S. aureus, Bacillus substalis,* and *Candida albicans* in a concentration-dependent manner. The repellent action of paint against subterranean termites was significant. These results concluded that the *Thevetia Peruviana* based oil plant was substantially protected wood from subterranean termite attack [34].

Antidiabetic Activity: Streptozotocin (STZ) and nicotinamide induced type 2 diabetic male rat models were studied to evaluate antidiabetic activity *in-vivo*. When the effects of the standard drug metformin hydrochloride, 10 mg/kg body weight treated group, and negative control group was compared, it was found that the bark extract of *Cascabela thevtia* L. was able to reduce blood glucose levels and normalize serum biochemical profiles, including lipid content in the test groups. The group treated with 200mg/kg body weight shows a significant effect at $p<0.01$. By comparing different biochemical parameters and histo-architecture of the different test groups of animals, it was found that group V treated with 200 mg/kg body weight showed a significant effect. ><0.01 by using one-way analysis of variance followed by Dunnet comparison all *vs.* control method. Further isolation of the compounds can lead to finding out the exact compound responsible for the activity, but furthermore, studies like molecular level and clinical level studies are required to establish its importance as a potent medicinal plant [35].

Anthelmintic Activity: Anthelmintic activity of yellow oleander bark extract was determined by observing Paralysis and Death time of Earthworm (*Pheretima posthuma*). The higher concentration of extract produced a paralytic effect much earlier and the time to death. The methanolic extract of *Thevetia peruviana* showed anthelmintic activity in a dose-dependent manner. Aqueous extract demonstrated paralysis, as well as death of worms in a much more time even in a higher concentration of 50 mg/ml paralysis and death time, was 42.67±0.72 minutes and 57.67±0.72 min as

compared to albendazole, especially at a lower concentration of 20 mg/ml paralysis and death time was 17.67±0.54 min and 48±0.47 min. As a result, the methanolic extract of *Thevetia peruviana* bark, that is traditionally used by tribals to treat intestinal worm infections, showed moderate anthelmintic activity [36].

Flavanone and Flavanol Glycosides/Reverse Transcriptase Inhibition: Flavanone and flavonol glycosides from the leaves of Thevetia peruviana and their HIV-1 reverse transcriptase and HIV-1 integrase inhibitory activities: Two new flavanone glycosides and a new flavonol glycoside were isolated from the leaves of *T. peruviana* and were investigated for their inhibitory effects against HIV-1 reverse transcriptase and HIV-1 integrase [37].

Cardiovascular: *Thevetia peruviana* produces a milky sap that contains Thevetin, a compound that is used as a heart stimulant but is extremely poisonous in its natural form, as are all parts of the plant, especially the seed. Thevetin A and B (cerebroside) are cardenolides, whereas Peruvoside, nerrifolin, thevetoxin and ruvoside are others [38]. The toxic glycosides present in *Thevetia peruviana*, which are concentrated in the roots and seeds and exhibit digoxin-like effects, act by inhibiting the Na^+K^+ATPase enzyme in the cardiovascular system [39]. The increased intracellular sodium concentration and the increased serum potassium concentration produce a negative chronotropic and positive inotropic effect. The resulting toxic syndrome resembles digitalis poisoning with marked hyperkalemia, conduction abnormalities, and ventricular arrhythmias. The cardiac glycosides peruvoside from yellow oleander are used medicinally for the treatment of cardiac insufficiency. Thevetin is pharmacologically a most active constituent, especially on the heart. Thevetoxin closely resembles Thevetin in pharmacological action but is less toxic [14].

Antinociceptive and Gastroprotective Activity: Kumar *et al.,* (2015) studied the antinociceptive and the gastroprotective effects of orally administered or inhaled Thevetia peruviana Pers. K. (Schum) (Oleander) volatile oil and its principal constituents linalool and 1, 8-cineole were evaluated in mice. Either when orally administered (100µl/kg) or inhaled for 60 min. *Thevetia peruviana* volatile oil significantly reduced the acetic acid-writhing response in a naloxone-sensitive manner. In the hot plate test, the analgesic activity observed after oil inhalation was inhibited by naloxone and atropine sulphate pre-treatment suggesting the involvement of opioidergic as well as cholinergic pathways. Regardless of the administration route and the experimental model used both linalool and 1, 8-cineole did not produce a significant analgesic response. Oral or inhalatory treatment with analgesic doses of volatile oil did not affect mice spontaneous locomotors activity. Concerning the gastric effects, Oleander oil, linalool, and 1, 8-cineole oral administration protected against acute ethanol-induced gastric ulcers but did not prevent indomethacin-induced lesions indicating any interference with arachidonic acid metabolic cascade. In conclusion, besides this gastroprotection, Oleander oil reveals an interesting analgesic activity mainly relevant after inhalation, at doses devoid of sedative side effects, suggesting the interest for potential application of this oil in aromatherapy [40].

CONCLUSION: In recent years, Plants and herbal drugs obtained from natural resources are again gaining importance throughout the world in maintaining the healthcare conditions of individuals. The plant or individual parts of the plant, such as leaves, bark, seeds, and fruit, are used for different disorders in human beings. As discussed in the present paper, the plant possesses many secondary metabolites, especially glycosides, and various pharmacological activities. Despite various claims of medicinal uses on *Thevetia peruviana*, there is a need for some attempts to scientifically confirm it's more potential in the healing of other diseases.

ACKNOWLEDGEMENT: The authors are thankful to Principal, G.H.G Khalsa College of pharmacy, Gurusar Sadhar, (Ludhiana), and the management for providing us all the facilities.

CONFLICTS OF INTERESTS: The authors declared no conflicts of interest.

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How to cite this article:
Sharma T, Kaur J and Singh G: Phytochemistry and pharmacological activities of *Thevetia peruviana*: a review. Int J Pharm Sci & Res 2022; 13(6): 2274-82. doi: 10.13040/IJPSR.0975-8232.13(6).2274-82.