10.5005/jp-journals-10059-0018

REVIEW ARTICLE

Pharmacological Profile of *Tithonia diversifolia* (Hemsl.) A.Gray: A Comprehensive Review

[1]Lalrinpuia Kawlni, [2]Manajit Bora, [3]Sachchida N Upadhyay, [4]Jayram Hazra

ABSTRACT

Aim: This review aims to provide an up-to-date overview of pharmacological studies of *Tithonia diversifolia* (Hemsl.) A.Gray. Moreover, the focus of this review is the possible exploitation of this species to treat different diseases and to suggest future investigations.

Background: *Tithonia diversifolia* (Hemsl.) A.Gray is an important medicinal plant whose leaf is the major organ used alone or in combination with other plants for the treatment of a wide variety of ailments. This plant has been a subject of research interest because of its various indigenous medicinal uses in many countries.

Results: Different pharmacological studies on *T. deversifolia* show that it possesses antibacterial, antioxidant, anti-inflammatory, antinociception, analgesic, antidiarrheal, antimalarial, antihyperglycemic, and cancer chemopreventive activities due to the presence of different active constituents.

Conclusion: *Tithonia diversifolia* (Hemsl.) A.Gray extracts and their active constituents should be subjected to detailed mechanistic studies to fully understand the mode of action of the active constituents.

Clinical significance: Till date, there is no scientific literature/data regarding clinical trials of this plant except preclinical studies on different laboratory animals.

Keywords: Pharmacological studies, Therapeutic uses, *Tithonia diversifolia*, Traditional medicine.

How to cite this article: Kawlni L, Bora M, Upadhyay SN, Hazra J. Pharmacological Profile of *Tithonia diversifolia* (Hemsl.) A.Gray: A Comprehensive Review. J Drug Res Ayurvedic Sci 2017;2(3):183-187.

Source of support: Nil

Conflict of interest: None

BACKGROUND

Tithonia diversifolia is a species of flowering plant in the Asteraceae family, i.e., commonly known as the tree marigold,[1] Mexican sunflower, Japanese sunflower, or Nitobe chrysanthemum. It is moderately resistant to drought. It is a native shrub to Colombia, Guatemala, Honduras, Mexico, Nicaragua, Panama, the United States, Zanzibar, and exotic in India, Kenya, Philippines. This shrub is an important medicinal plant whose leaf is the major plants part used alone or in combination with other plants for the treatment of a wide variety of ailments, such as stomach pains, indigestion, sore throat, liver diseases, and pain. This is because the leaf is considered to have most of the active constituents.[2] It has been reported to possess antiplasmodial activity[3] and testified to have the presence of sesquiterpene lactones as well as an artemisinin acid analog from *T. diversifolia*.[4,5] It also possesses anti-inflammatory and analgesic properties;[6] have resistance against bile, kidney, urinary and venereal diseases, testicular inflammation, frigidity, sterility, heavy menstruation, rheumatism and arthritis, upper respiratory tract infections ranging from cough to tuberculosis, intestinal worms and schistosomiasis, cancer chemopreventive activity;[7] cytotoxic properties,[8,9] and antimicrobial activity.[10,11] This plant is a weed that grows quickly and has become an option as an affordable alternative to expensive synthetic fertilizers. It has shown to increase plant yields and the soil nutrients of nitrogen, phosphorus, and potassium.[12] *Tithonia diversifolia* has been a subject of research interest because of its various indigenous medicinal uses in many countries.

[1,2]Research Officer (Pharmacology), [3]Assistant Director (Pharmacology), [4]Director (Ayurveda)

[1-4]National Research Institute of Ayurvedic Drug Development Kolkata, West Bengal, India

Corresponding Author: Lalrinpuia Kawlni, Research Officer (Pharmacology), National Research Institute of Ayurvedic Drug Development, Kolkata, West Bengal, India, Phone: +919862961639, e-mail: vetpharmacol@gmail.com

RESULTS

Botanical Description

Tithonia diversifolia is a woody herb or succulent shrub, 1.2 to 3 m tall, with opposite leaves (3–5), attenuate base, acute apex, and crenate margin. Leaf size is 5 to 17 × 5 to 12 cm, densely pubescent beneath with palmate venation. Occasionally, upper leaves are unloaded. Flowers are yellow, their ray size is 306 cm × 5 to 18 mm. The flower heads are solitary on a peduncle, 6 to 13 cm long. Each mature stem may bear several flowers at the top of branches. The plant flowers and produces seeds throughout the year. The light-weight seeds can be dispersed by wind, water, and animals.[13]

PHARMACOLOGICAL STUDIES

Antibacterial Activity

The medicinal properties of the aqueous leaves extract of *T. diversifolia* were evaluated *in vitro* by antimicrobial

and antifungal assays and it showed growth inhibitory effects on *Staphylococcus aureus* and *Escherichia coli*, but *Pseudomonas aeruginosa* and *Saccharomyces cerevisiae* were resistant to all the plant extracts and the antibiotic controls. The minimum inhibitory concentrations of the aqueous extract of *T. diversifolia* on *S. aureus* and *E. coli* were both 12.50 mg. The minimum bacterial concentration of the aqueous extract against the test organism ranged from 12.50 to 25.00 mg.[14]

Antioxidant Activity

The evaluation of the antioxidant activity was assessed by the sequestrant ability of extracts on free radical 2,2-diphenyl-1-picrylhidrazila (DPPH). A methanol solution of DPPH at the concentration of 40 mg/mL was prepared where the aqueous and ethanolic crude extracts of *T. diversifolia* were diluted in methanol at the following concentrations (5–2, 5–1, 0–0, 75–0.5, and 0.25 mg/mL). A strong antioxidant activity of both the aqueous ethanol extracts was observed as ethanol dose dependent on the type DPPH with IC_{50} of 2.273 and 0.630 mg/mL respectively, for aqueous crude extract and crude extract ethanol, and it was found that the plant species is a promising source of antioxidant compounds.[15]

Anti-inflammatory Activity

Aqueous leaf extract of *T. diversifolia* at a dose of 400 mg/kg exhibited significant anti-inflammatory activity in carrageenan-induced rat paw edema model. The mean percentage inhibition of paw volume was highest in rats to which indomethacin was administered (85.65%), followed by the rats administered aspirin (68.40%) which was comparable to that of rats given *T. diversifolia* (63.79%). Indomethacin caused the highest inhibition of paw edema, followed by inhibition caused by aspirin and that caused by *T. diversifolia* extract.[16]

Antinociception Activity

Aqueous leaf extract of *T. diversifolia* at a dose of 400 mg/kg exhibited significant antinociceptive activity in mice. The group dosed with morphine had the highest reaction time of 31.81 ± 1.50 s^{-1}, followed by the extract which caused a significant ($p < 0.05$) increase in reaction time of 25.18 ± 0.70 s^{-1} in the hot plate test when compared with the untreated control reaction time of 18.22 ± 0.27 s^{-1} indicating an increase in pain threshold level.[16] The mean number of writhing movements was significantly lower ($p < 0.05$) in mice dosed with 400 mg/kg aqueous leaf extract of *T. diversifolia* (26.17 ± 0.7) culminating in 43.92% inhibition of writhing when compared with the negative control (46.7 ± 1.4), although this was higher than the writhing values in mice that were administered with the standard analgesic agent, paracetamol (23.5 ± 1.3) with percentage inhibition of 49.64%.[16]

Acute Toxicity Test

Oral administration of *T. diversifolia* leaves' aqueous extract to rats up to 10000 mg/kg caused no death in the two phases of the test after 24 hours. The LD_{50} of *T. diversifolia* extract in rats was estimated to be greater than 10000 mg/kg.[17]

Antidiarrheal Activity

The antidiarrheal effect of aqueous extract of *T. diversifolia* leaves (200, 400, and 800 mg/kg doses) was studied using castor-oil-induced-diarrhea model (dropping test), castor-oil-induced enteropooling (secretory test), and gastrointestinal transit test (charcoal transit) in rats. The results showed that *T. diversifolia* leaves' aqueous extract reduced wet fecal output in castor-oil-induced diarrhea but with slightly greater frequencies in comparison with loperamide-treated animals and had less volume of intestinal contents as compared with the negative control (distilled-water-treated animals). It also had a significant ($p < 0.05$) nondose-dependent reduction in speed and distance traveled by charcoal in gastrointestinal tract but slightly higher speed and longer distance than the atropine-treated rats. Aqueous extract was found to have remarkable antidiarrheal effect in castor-oil-induced diarrhea, enteropooling, and gastrointestinal motility models attesting to its utility in a wide range of diarrheal states traditionally.[17]

Antimalarial Activity

Comparison of the effectiveness of Chloroquine with the aqueous and methanolic extracts of *T. diversifolia* showed that Chloroquine was 100% effective in clearing the parasite, while the aqueous and methanolic extracts were 50 and 74% effective in clearing the parasites respectively. Both aqueous and methanolic extracts were more effective when administered before the onset of the infection, probably indicating the time-dependency of the antimalarial effects. Earlier application of the extracts at the onset of the malaria symptoms was more effective in reducing the parasitemia within a few days. The administration of the plant extracts during the malaria episode was also effective with longer period of administration. The LC_{50} of the aqueous extract in mice was 1.2 mL/100 gm body weight (BW), while the maximum tolerated dose was found to be 1.0 mL/gm.[18]

The antimalarial properties of *T. diversifolia* were investigated *in vitro* against three strains of *Plasmodium falciparum*. The ether extract from aerial parts of the plant

demonstrated good antiplasmodial activity (IC_{50} on plasmodium falciparum chloroquine sensitive strain: 0.75 µg/mL). A bioassay-guided fractionation of the extract led to the isolation of the known sesquiterpene lactone tagitinin C as an active component against Plasmodium (IC_{50} on plasmodium falciparum chloroquine sensitive strain: 0.33 µg/mL).[19]

Antihyperglycemic Activity

The antihyperglycemic activity of aqueous leaf extracts of *T. diversifolia* at dose of 500 mg/kg BW was studied by oral glucose tolerance test (OGTT) in normal mice and was administrated daily orally in alloxan-induced diabetic mice for 4 weeks. Hypoglycemic effect of *T. diversifolia* at dose of 500 mg/kg BW showed significantly reduced blood glucose level on OGTT in normal mice ($p < 0.05$). Moreover, the plant-extract-treated alloxan-induced diabetes mice for 30 days significantly decreased blood levels of glucose, total cholesterol, triglyceride, and low-density lipoprotein cholesterol and increased high-density lipoprotein cholesterol.[20]

Cancer Chemopreventive Activity

Activity-guided fractionation of an ethyl acetate extract of the aerial parts of *T. diversifolia*, using an antiproliferation bioassay performed with human colon cancer (Col2) cells, led to the isolation of three new sesquiterpenoids, 2-alpha-hydroxytirotundin, tithofolinolide, and 3-alpha-acetoxydiversifolol, along with eight known sesquiterpene lactones, 3-beta-acetoxy-8-beta-isobutyryloxyreynosin, tagitinin C, 1-beta-2-alpha-epoxytagitinin C, 4-alpha-10-alpha-dihydroxy-3-oxo-8-beta isobutyryloxyguaia-11(13)-en-12,6-alpha-olide, 3-alpha-acetoxy-4alpha-hydroxy-11(13)-eudesmen-12-oic acid methyl ester, 17,20-dihydroxygeranylnerol, tagitinin A, and tirotundin. These isolates were evaluated for their potential as cancer chemopreventive agents by measuring their antiproliferative activity in Col2 cells and induction of cellular differentiation in human promyelocytic leukemia (HL-60) cells. Selected compounds were investigated for their ability to inhibit 7,12-dimethylbenz[a] anthracene-induced preneoplastic lesions in a mouse mammary organ culture assay. Among these isolates, tagitinin C and 1-beta-2-alpha-epoxytagitinin C showed significant antiproliferative activity, tithofolinolide, 3-beta-acetoxy-8-beta-isobutyryloxyreynosin, and 4-alpha,10-alpha-dihydroxy-3-oxo-8beta-isobutyryloxyguaia-11(13)-en-12,6-alpha-olide induced HL-60 cellular differentiation, and 43-beta-acetoxy-8-beta-isobutyryloxyreynosin significantly inhibited (63.0% at 10 µg/mL) lesion formation in the mouse mammary organ culture assay.[7]

DISCUSSION

An extensive and systematic review of the extant literature was carried out, and electronic search on worldwide accepted scientific databases (Science Direct, PubMed, and Google Scholar) was performed to compile the relevant information. All abstracts and full-text articles were examined. The most relevant articles were selected for screening and inclusion in this review. *Tithonia diversifolia* has been reported to possess a number of medicinal properties being used traditionally and has been commonly used for diverse medicinal purpose in many countries of the world. From the above review results, it has been observed that *T. diversifolia* has various therapeutic actions, such as anti-inflammatory, analgesic, antinociception, antimalarial, antibacterial, antitumor, antidiabetic, antidiarrheal, and antihelminthic activity.

CONCLUSION

The plant extracts and their active constituents should be subjected to more detailed mechanistic studies, *in vivo* investigations in various animal models, and hence, further studies has to be taken up to identify and isolate new compounds or particular compounds for the development of new drugs including pharmacokinetic and bioavailability studies to fully understand the mode of action of the different active constituents and also to prove and scientifically validate for its different therapeutic actions, such as anti-inflammatory, analgesic, antinociception, antimalarial, antibacterial, antitumor, antidiabetic and antidiarrheal activity.

Clinical Significance

Till date, there is no scientific literature/data regarding clinical trials of this plant except preclinical studies on different laboratory animals.

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हिन्दी सारांश

टिथोनिया डाइवर्सिफोलिया (हैमसल.) ए.ग्रे का औषधीय प्रोफाइलः एक व्यापक समीक्षा

[1]लाल्रणपुयिया कवल्नी, [2]मांजीत बोरा, [3]साचिदा एन उपाध्याय, [4]जयराम हजरा

लक्ष्यः इस समीक्षा का उद्देश्य टिथोनिया डायवर्सिफोलिया के औषधीय अध्ययनों के वर्तमान स्थिति प्रदान करना है। इसके अलावा, इस समीक्षा का फोकस इस बीमारी के इलाज के लिए और भविष्य की जांच करने के लिए इस प्रजाति का संभावित दोहन लक्षय है।

पृष्ठभूमिः टिथोनिया डाइवर्सिफोलिया एक महत्वपूर्ण औषधीय पौधा जिसका पत्ता प्रमुख बीमारियों की एक विस्तृत विविधता के उपचार के लिए अन्य पौधों के साथ अकेले या संयोजन में उपयोग किया है। कई देशों में इसके विभिन्न स्वदेशी औषधीय उपयोगों की वजह से यह अनुसंधान का विषय रहा है।

परिणामः टिथोनिया डाइवर्सिफोलिया पर विभिन्न औषधीय अध्ययनों से पता चलता है कि यह इस संयंत्र में विभिन्न सक्रिय घटक की उपस्थिति के कारण जीवाणुरोधी, एंटीऑक्सिडेंट, एंटी–इनफ्लेमेटरी, एंटीनोसिसेप्शनें, एनाल्जेसिक, एंटीडीआरहील, मलेरिया रोधी, एंटीहाइपरग्लिसेमिक और कैंसर केमोप्रेवेंतिव क्रियाएँ होती है।

निष्कर्षः टिथोनिया डाइवर्सिफोलिया अर्क और उनके सक्रिय घटक पूरी तरह से सक्रिय घटकों की कार्रवाई की विधा को समझने के लिए और अधिक विस्तार यंत्रवत अध्ययनों के अधीन किया जाना चाहिए।

नैदानिक महत्वः आज तक, विभिन्न वैज्ञानिक प्रयोगशाला जानवरों पर पूर्वकाल संबंधी अध्ययनों को छोड़कर इस संयंत्र के नैदानिक परीक्षणों के बारे में कोई वैज्ञानिक डाटा नहीं है।

शब्द कुँजीः टिथोनिया डाइवर्सिफोलिया, एंटीऑक्सिडेंट, नोसिसप्तिओं, केमोप्रेवेंतिव।