DOI: https://doi.org/10.36094/sc.v89.2024.A_Review_on_the_Pharmacological_Activities.Ray.314

Research Communication

Sci. and Cult. 90 (7–8) : 314-320 (2024)

A Review on the Pharmacological Activities of *Thuja orientalis* L.

***Abstract*: Medicinal plants are the abode of natural compounds that are rich sources of various remedies and provide opportunities for new drug discoveries. One such medicinally valuable species is *Thuja orientalis* L. or *Platycladus orientalis* (L.) Franco, belonging to the gymnospermous family Cupressaceae. The present study is a comprehensive review on its various pharmacological properties, exhibiting antimicrobial effects against a wide range of bacteria and fungi, anti-inflammatory, antioxidant, anticarcinogenic, anthelminthic as well as shows hair-growth promoting effects, collected from the reports of several investigations conducted. This review emphasizes the significance of the species in the spectrum of modern medicine, and the need and scope of further clinical research that will lead to novel drug formulations.**

Keywords: *Thuja orientalis*, pharmacological, antibacterial, anti-inflammatory

Thuja orientalis L. is a synonym of *Platycladus orientalis* (L.) Franco, belonging to the family Cupressaceae of gymnosperms. The species is widely distributed in India, China, Nepal, Korea and Japan. Now, it is recognised as near-threatened (NT) species in the IUCN Red list[1]. It is an evergreen coniferous taxon with a habit of shrub or tree ranging within the height of 12 to more than 20 feet. It showcases a flat spread foliage with scale-like leaves, and with fleshy, ovoid cones. Seeds are ovoid with rudimentary wing-like margin; seedlings are phanerocotylar with two paracotyledons.

***Taxonomic Position*:** Phylum: Tracheophyta

Class: Pinopsida

Order: Pinales

Family: Cupressaceae

Genus: *Platycladus*

Species: *Platycladus orientalis* (L.) Franco (Accepted)/*Thuja orientalis* L. (Synonym)/ *Biota orientalis* (L.) Endl. (Synonym)

The medicinal importance of this plant has been recognised for ages and been widely used in traditional systems of treatments as well as in homeopathy. The utilization of the plant has been found to treat cold, cough, high blood pressure, rheumatism, etc. The crude extracts and essential oils of the plant have been analysed to show that it possesses several antibacterial and antioxidant properties[2]. A very recent finding has been documented for the use of the plant extract as an antinociceptive activity in treating gout-related pain[3]. The seed extracts of the plant have been reported to rescue depressive behaviour in a rat model induced by chronic, unpredicted, mild stress (CUMS)[4]. Recent research has shown the efficacy of solid lipid nanoparticles of *T. orientalis* that possess 5-alpha reductase inhibiting activity for treatment of hairloss and hirsutum[5]. By virtue of its essential oil, the use of *T. orientalis* as an insecticide is also known. It is used in insect-repellent sprays for its unique aroma. It is also grown as an ornamental plant in many regions.

***Chemical Constituents*:** The phytochemicals of *T. orientalis* constitutes flavonoids, terpenoids and fatty acids. Monoterpenoids like á-pinene, carene, limonene, sabinene; sesquiterpenes, alcohols like cedrol, cuparenols, etc are present in various combinations in different parts of the plant. Different carotenes and xanthophylls, which are the two divisions of carotenoids or tetraterpenoids, are major components of the plant's chemical constitution. Some important flavonoid compounds present are amentoflavone, hinokiflavone, quercetin, myricetin, etc. Palmitic acid, stearic acid and linolenic acid are some of the major fatty acids found. The most beneficial chemical compounds of the essential oil from all the plant's parts were á-pinene, carene, limonene, sabinene and cedrol [6,7]. Monoterpenes - á-Thujone and â-thujone, are reported to be present in the essential oil derived from the plant extracts[8]. The phenol and flavonoid quantitative estimation

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of phenol and flavonoid content in the different parts of the plant from different states of India have been done[9]. The significant biological activities of the plant are due to the synergistic potential of these phytochemicals present. The chemical constituents present in the different parts of the plant body is enumerated as follows:

Part of Plant	Chemical Compounds
Leaves	Flavonoids, isopimarane diterpenoids, α-pinene, α-cedrol, 3-carene, limonene, β-phellandrene, caryophyllene
Heartwood	Aromadendrin, taxifolin, widdrene, cedrol, widdrol, thujopsadiene, dehydro -α-curcumene, β-isobiotol and curcumenether
Fruits	Fruit oil: α-pinene, 3-carene, α-cedrol and phellandrene Alpha-cedrol 15-hydroxypinusolidic acid, platydiol,docosyl 3-hydroxyferulate Monoterpene hydrocarbons, sesquiterpene hydrocarbons, α-pinene Rhodoxanthin, amentoflavone, hinokiflavone, quercetin, myricetin, carotene, xanthophylls and ascorbic acid D-Limonene, β-phellandren, β-myrcene Diterpenoids
Seed	Palmitic, stearic; C18 unsaturated acids, C20 unsaturated acids
Pollen	Monolignol derivatives

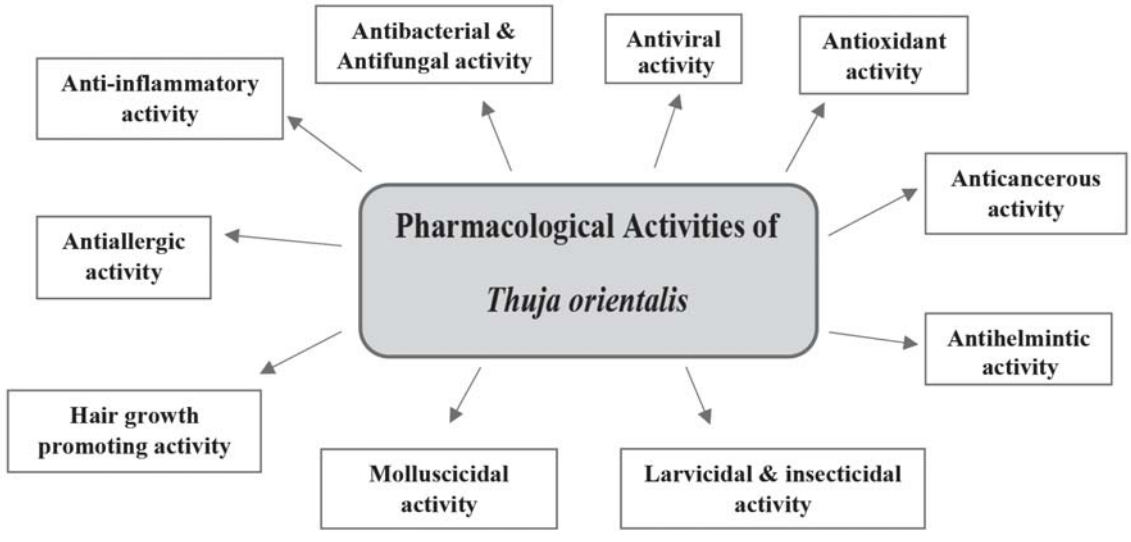
Pharmacological Activities: Several reports from the studies on the pharmacological activities of *T. orientalis* conducted during the past few decades, have been documented. Some of the significant studies have been focussed here, are as follows: -

Antibacterial and Antifungal Activity: The essential oil from seed coats of *T. orientalis* had antimicrobial effect on six bacteria and five fungi species. Out of them, the essential oil was found to show remarkable results of activity against *Salmonella typhi* and *Bacillus subtilis*. As for the antifungal activity, the neat essential oil exhibited significant growth inhibitory effects against *Curvicularia lunata*, *Aspergillus niger* and *A fumigatus*[10]. Similar antibacterial activity against *Agrobacterium tumefaciens* of the petroleum ether extract of the stem of *T. orientalis* was reported.

The ethanolic extract of the fruit of *T. orientalis*, was fractionated with organic solvents to investigate its antimicrobial property. The n-hexane soluble fraction was observed to exhibit the maximum antibacterial activity against gram positive bacteria, *Staphylococcus aureus*, *Bacillus subtilis* and *Streptococcus pneumoniae*, without any mutagenic effect[11].

The antioxidant activity of the leaf extract was demonstrated using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. The crude methanolic extract of the leaves showed considerable inhibitory effects against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Agrobacterium tumefaciens*[12].

The effectiveness of the stem and leaf extracts of *T. orientalis* against pathogenic microorganisms, like *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Alcaligenes faecalis* and *Klebsiella pneumoniae*, was investigated and also



showed fungicidal activity against *Aspergillus flavus* and *A. niger*. It was also conclusively stated that it could be utilised as a natural antimicrobial agent to control infection caused by these pathogens, that have been observed to become antibiotic-resistant[13].

More than forty bio compounds were identified from the essential oil of the fruit extract of *T. orientalis*, grown in Nigeria. Their study established the correlation between the phytoconstituents and pharmacological properties like being antioxidant and antimicrobial. Antibacterial activities were reported against *Streptococcus agalactiae*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Salmonella typhimurium*. These activities were accounted to the virtue of monoterpenoids present in the oil, like 1R-á-pinene, á-pinene, cyclofenchene, (+)-3- carene, etc[14].

The essential oil of *T. orientalis* was reported to have antimicrobial activity against various microorganisms. The antimicrobial activity was assessed, both qualitatively and quantitatively by microdilution method, in which the highest activity of the oil was observed against gram negative bacteria *Vibrio parahaemolyticus* and gram-positive bacteria like *Staphylococcus aureus*, *Bacillus subtilis* and *Streptococcus pyogenes*. It did not show any activity against *Klebsiella pneumonia*, *Proteus vulgaris*, *Salmonella typhimurium* and *Micrococcus luteus*[15]. The antibacterial activity of the methanolic leaf extract of the plant growing in Kumaun Himalayan region was examined, where, *Bacillus subtilis* was seen to be inhibited significantly.

The ethanolic extract of the plant's leaves were observed to be effective in the antifungal property against *Alternaria alternata*, *Colletotrichum falcatum*, *Fusarium oxysporum*, *Pyricularia oryzae*, *Sclerotinia rolfsii*, *Sclerotinia sclerotiorum* and *Tilletia indica*, and the inhibitory activity was significantly effective than the widely used antifungal agent Clotrimazol[16].

The essential oil of *T. orientalis*, analysed from the GC-MS showed ä-3-carene as the main component among a total of 38 compounds. The essential oil exhibited growth inhibitory activity against dermatophytic fungal pathogens like *Trichophyton rubrum, T. tonsurans;* although it did not inhibit growth of *Candida albicans* [17].

The ethanolic extracts of the leaves of *T. orientalis*, *Cannabis sativa* and *Psidium guajava* were assessed for their antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA).A significant synergistic effect with antimicrobial activity was reported with the extract of *T. orientalis* when used combined with *C. sativa* and *P. guajava*; though the individual plant extracts at 50% also showed growth inhibitory results. The inhibitory effects were attributed to the presence of the phenolics like quercetin and gallic acid, and catechin, as found by HPTLC [18].

The silver nanoparticles of the leaves extract of *T. orientalis* were synthesized and these nanoparticles exhibited antimicrobial activity showing growth inhibition against *Bacillus subtilis*, *Staphylococcus aureus*, *Salmonella typhi* and *Escherichia coli* [19].

The methanolic extract of the plant containing terpenoids was found to potentially inhibit or suppress the growth of *Magnaporthe oryzae* that causes the rice blast disease. This antifungal property supports the use of the plant as a crop protectant in the disease [20].

Antioxidant Property: The water extract of leaves of *T. orientalis* exhibited greater reducing power and antioxidative effect than the alcoholic extract, and this could be attributed to the fact that the phenolic compounds are higher in the water extract. The results from the experiment on human red blood cells (RBC) revealed that the plant's extract contains rich antioxidants that has free radical scavenging properties, thereby can protect human cells from oxidative damage [21].

Nine flavonoids were isolated by fractionating methanolic extract of the fruits of *T. orientalis.* Through the conduction of 2,2-diphenyl-1-picrylhydrazyl (DPHH) and 2,22 -azinobis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS) scavenging assay, it was reported that catechin, quercitrin, hypolaetin 7-*O*-â-xylopyranoside, isoquercitrin and myricitrin, showed antioxidant properties with varying degrees. The other flavonoids like cupressuflavone, amentoflavone and robustaflavone exhibited notable human neutrophil elastase (HNE) inhibitory activities [22].

Some of the main components in the essential oil extracts from the different parts of the plant are a-Pinene, ß-pinene, limonene, etc. The extracts of these different parts were observed to present different efficacies of their antioxidant activity with different testing methods.

The effect of the plant extract in human serum and red blood cells (RBC), in terms of its antioxidant and anti-hemolytic potential, was examined by the prooxidant-antioxidant balance (PAB) assay. The study revealed that the water extract of *T. orientalis* showed stronger antioxidant effect in human serum showing its potential of

reducing the free radicals; the extract also inhibited hydrogen peroxide (H_2O_2)-induced RBC hemolysis[23].

The antioxidant properties of the plant extracts from Northern Iran have been observed to be directly proportional to the phenol and flavonoid content [24].

Anti-inflammatory Activity: The anti-inflammatory potential of the plant was also investigated on rat leukocytes and rabbit platelets; *T. orientalis* was reported to inhibit the synthesis of leukotriene B4 and 5-hydroxyeicosatetraenoic acid (5-HETE)[25].

The petroleum ether and aqueous extract of the leaves of *T. orientalis* could attenuate writhing and showed promising results, when compared to the drugs pentazocine and paracetamol, exhibiting its analgesic activity.

Anti-inflammatory activity of the aqueous extract of *T. orientalis* in the endothelial cells of human umbilical vein was observed. The treatment of the extract suppressed the expression of adhesion molecules induced by the tumour necrosis factor-á (TNF-á); the production of the reactive oxygen species (ROS) was also reduced considerably[26].

Isoquercitrin, out of the seven compounds isolated was found to be the most significant in mitigating oxidation that induces damage to the cells in *in vitro* condition, as studied for the retinal ganglion cell line (RGC). It was also reported to directly affect the reduction of lipid peroxidation, depleting the levels of glutathione as well as elevating some specific radical species. The oral administration of isoquercitrin was documented to be safe for treating diseases like glaucoma[27].

A high content of polyphenols, flavonoids etc were extracted from the methanolic extract of leaves of *T. orientalis* and the extract also showed antioxidant activities like free radical damage, peroxidation of linoleic acid, in *in vitro* experiments. The utilization of the leaves of this plant is widespread in traditional Chinese medicine system, to treat chronic bronchitis, asthma, excessive cough and mucus formation, etc. This is attributed to the anti-inflammatory potential of the plant.

A labdane diterpene was isolated from the alcoholic extracts of *T. orientalis* and was documented to inhibit production of Nitric oxide (NO) induced by LPS, reduce pro-inflammatory mediators' production and inhibit the inflammatory effects by suppressing the activity of Necrotic factor- êB and ERK phosphorylation. All these features of the compound enforce its choice towards developing an important anti-inflammatory drug ingredient. The anti-inflammatory activities of the plant leaf extract can be effectively used in treating Parkinson's disease, since the extract could protect the dopaminergic neurons against the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity[28].

The anti-inflammatory and analgesic activities of *T. orientalis* were established in an experiment conducted in albino rats using carrageenan-induced inflammatory model, acetic acid-induced writhing test and hot plate methods. The aqueous methanolic extract of the fruit had been observed to exhibit the property.

T. orientalis is proposed to be used as an herbal therapeutic agent for treating various inflammatory diseases. The effect of *T. orientalis* on mice who were subjected to OVA airway challenge due to sensitization to ovalbumin was evaluated. It was observed that the treatment of *T. orientalis* not only attenuated the inflammation of the airway and mucus hypersecretion, but also the expression of the inducible nitric oxide synthase (iNOS) and matrix metalloproteinase (MMP 9) in lung tissue was reduced[29].

Root extract of *T. orientalis* along with that of *Saussurea costus* had been tested to be efficient in treating the chronic skin inflammatory disease - atopic dermatitis. The flavonoid components in *T. orientalis* were acknowledged to have contributed to the effects of regressing the production of reactive oxygen species, nitric oxide, etc[30].

Antiviral Activity: The potentiality of the extract of *T. orientalis* against the influenza infection was reported as it could reduce the cytotoxic effect of the infection, and was gradually more effective at higher concentrations[31].

Anticancer Activity: The oil extract of the aerial parts of the plant from Saudi Arabia and Egypt were assessed and their cytotoxic effect on human cell line were compared. Both the oil extract of the plants sourced from these two different regions showed good results in terms of their cytotoxicity. The plant extract from Saudi Arabia showed the highest effect against the breast carcinoma followed by human colon carcinoma and liver carcinoma cell line, which was attributed to the presence of high percentage of monoterpenes like limonene, bisabolol, ápinene and â-pinene[32].

Successful inhibition of angiogenesis had been reported by the administration of *T. orientalis* extract, as examined in *Danio rerio* (zebrafish) embryo, whose genome has a similarity with that of humans. The study revealed that the plant's extract did not possess any toxic and teratogenic effect, and considerably reduced the growth of the cancerous cell. The plant extract was found to be efficiently supressing the growth of the lung tumour cell when examined on human lung cancer line (A549). Therefore, the treatment of *T. orientalis* leaf extract, both in *in vivo* and *in vitro* conditions, proved to be nontoxic with potential anticancerous attributes[33].

Sorafenib, an oral multi-kinase inhibitor, together with the leaf extract of *Thuja orientalis* L. (*Platycladus orientalis* L.) have shown to inhibit cell growth and induce apoptosis in human cervical cancer cells, by effectively targeting the levels of expression of tumor suppressor TIG3. It also has been observed to reduce the expression of PCNA, a key marker of human cell proliferation and Bcl-2, which is the key marker of inhibition of apoptosis[34].

Anti-helminthic Activity: The leaf extract of *T. orientalis* was reported in 2005 to exhibit anthelminthic activity against the nematode *Haemonchus contortus*, which is pathogenic for ruminants[35]. The anthelminthic activity shown by the ethanolic leaf extracts of the plant against Indian earthworms, *Pheretima posthuma*, was analysed and was attributed to be due to the action of the polyphenolic compounds, that leads to the paralysis and death of the worms.

Hair Growth-promoting Activity: The overactivation of 5 Ca-reductase has been seen to be causing male gender-related conditions like pattern baldness, alopecia, hirsutism, etc among many others. Strong 5 Ca-reductase inhibitors were extracted from *T. orientalis* that was patented to be used therapeutically in treatments of these androgenic disorders.

The hair growth promoting effects of hot water extract of *T. orientalis* were studied. In 2016, a series of experiments in mice regarding this property of the plant were presented.The sesquiterpineol, cedrol, was observed to significantly promote hair growth in the experimental mice model that were in the telogen phase of hair growth. Cedrol was observed to be effective in increasing hair weight and hair follicle length. Cedrol increases the flow of blood around the hair bulbs and upgrade the oxygen and nutrient delivery to the hair follicle cells[36].

Antiallergic Activity: Antiallergic activity of the diterpene, lambertianic acid that is derived from the leaf extract of *T. orientalis* was examined on bone-marrow derived mast cells in mouse. Lambertianic acid could effectively inhibit the production of allergy mediators like prostaglandin (PGD_2), interleukin-6 (IL-6), etc[37].

Larvicidal and Insecticidal Activity: The essential oil of the leaf extract of the plant was shown to possess significant larvicidal property against two very important species of mosquito, *Aedes aegypti* and *Culex pipiens*[38]. The essential oils exhibited similar larvicidal properties against *Anopheles stephensi* also. In the study, it was concluded that the plant extract by virtue of its essential oil component could be utilized as a natural larvicidal agent for vector management in several diseases.

T. orientalis was also found to be effective in the larvicidal activity against *Spodoptera littoralis* that causes serious damage to many economically important crops, in the temperate regions of Asia and Middle East countries[39].

The essential oil of the plant was examined on terms of its efficiency as a repellent for *Tetranychus urticae*, a spider mite. The results revealed that various concentrations had repellent effects on the adult mites, as well as the mites could be even killed at a concentration of 1000 µl/ litre[40].

Molluscicidal Activity: Thujone was identified to be the potent molluscicide component, from the ethanolic fruit extract of *T. orientalis.* The leaf extract had been found to show concentration-dependent inhibitory activity against the mollusc, *Lymnaea acuminata*[41]. It was further examined that thujone could inhibit the acetylcholinesterase, acid and alkaline phosphatase activities in the nervous tissue of the snail, which serves as the intermediatory host for the liver fluke causing fascioliasis.

Future Prospects in Research: The evidences provided till now establishes the prospect of this novel medicinal plant as an alternative to chemical drugs in treatments of many chronic diseases. The utilization of the plant extract as an antimicrobial agent can be further studied, since the antibiotic resistance of microbes is a prevalent concern in many cases. The anticancerous potential of the plant requires more clinical trials. The study on the human lung cancer line with the plant extract can bring better protocols in the field of cancer treatment with reduced side-effects.

Conclusion: *Thuja orientalis* is one of the most significant gymnosperms with a number of vital phytochemicals. From the literature and documentation, it can be asserted that the cumulative action of the bio compounds in affecting the physiological parameters establishes the taxa's value in the medicinal world. Traditional as well as homeopathic medicine have recognised certain aspects of the plant's medicinal potentiality. In the oriental world, it is regarded as a valuable resource of natural remedies. The scientific reports and analysis, so far, has proved that further investigation is needed for rendering information about more phytoconstituents of this species. Moreover, the study on clinical efficacy of the plant's metabolites would certainly accentuate the utilization of the plant in the field of modern medicine as well. A sustainable utilization of this important plant along with its proper monitoring and conservation in wild is also absolutely essential in the coming years. With a plethora of therapeutic novelties, *Thuja orientalis* can be hailed as one of the most promising taxa of plant kingdom that attracts further critical scientific focus for future medicinal endeavours. ❐

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Received: 26 June, 2023

Revised: 09 April, 2024

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