Review Article

THE WONDERS OF A MEDICINAL TREE: HOLOPTELEA INTEGRIFOLIA (ROXB.) PLANCH

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ABSTRACT

In this busy era of herbal sciences, extensive study is being carried out on numerous plants to find novel drugs among which Holoptelea integrifolia Roxb. (Indian Elm) tree is just one of them. The age old knowledge ethnopharmacological significance, especially the stem, bark and leaves is well recognized in several Siddha, Ayurvedic, Unani literature. The plant parts are extensively used for its astringent, anti-inflammatory, digestive, carminative, laxative, depurative and diuretic properties. This plant is bestowed with a plethora of curative principles, namely antiviral, antimicrobial, anti-fungal, anti-arthritic, antioxidant, wound healing, anti-helminthic, anti-diabetic, anti-diarrheal, anti-tumor, adaptogenic, analgesic, hepatoprotective, larvicidal activities. Phytochemical investigation confirms the presence of signature chemical constituents such as terpenoids, alkaloids, glycosides, carbohydrates, steroids, saponins, tannins, proteins and flavonoids. The recent discovery of antibiotic nature of callus promises of the discovery of callus derived novel antibiotics and unique drugs. The present review sheds light on current research trends in Holoptelea integrifolia with a serious look at its diverse ethnomedical uses as well as its prospect.

Keywords: Holoptelea integrifolia, Ethnomedicinal property, Anti-inflammatory, Antioxidant, Anti-adherent, Anti-biofilm

INTRODUCTION

Plant-derived drugs are used as medicines for treating various diseases for decades. Today we still dependant on “Ayurveda” in about 75% of our medicines. The increasing prevalence of multi-drug resistant strains of the bacteria and the recent appearance of Ebola, Swine Flu, Bird Flu, HIV II and new strains with low susceptibility to antibiotics raise the specter of the untreatable bacterial infections and add urgency to the search for new infection-fighting strategies. Herbal medicines have recently drawn much attention as an alternative source of useful drugs for treating or preventing various diseases. Holoptelea integrifolia is a roadside tree possessing a wide range of biological activities. This medicinal plant is enriched with a variety of phytochemicals, which are widely applicable in curing diverse ailment in human and animals.

The plant species originated from Pacific Island [1]. It is distributed in temperate and tropical areas of northern hemispheres. In India, it is found in the outer Himalayan region up to 2000ft. It is a large deciduous tree with a height up to 30-35m. The bark is gray, exploiting in somewhat corky scales. Leaves alternate, elliptic-ovate, 5-13 cm long, acuminate, entire, sub-coreacious pinnately veined. Flowers are greenish-yellow, usually male or hermaphroditic, monochlamydeous or rarely polygamous and flowering usually takes place in the month of January to February.

Fruits are sub orbicular samara with membranous wings and one small kidney shaped seed, usually seen during the month of April to May [2]. The review is based on the scientific articles published up to February 2016. The content of this review has been adopted from archiving services like Science Direct, Springer, Pubmed, Scopus, Elsevier. We also searched Google Scholar, EMBASE by using following keywords: phytochemicals, ayurvedic, antioxidant, antibacterial, antifungal, anti-arthritic, anti-convulsant, anti-cancer, wound healing.

Phytochemical constituents

The plant has been reported to possess various chemical constituents. Different plant parts like stem bark, heartwood, leaf, seed, pollen, root are the major sources of various medicinally important phytochemicals. Holoptelina A and B [3, 4], 2-amino napthoquinone, friedelin, epifriedelin, β-sitosterol, β-D-glucose, β-amyrin, betulin and betulinic acid are derived from stem bark [5]. 2,3-dihydroxyolean-12-en-28-oic acid, hederagenin are isolated from heart wood [6] while hexacosanol, octacosanol, 1,4-napthalenidione, α-amyrin [7] and a newly invented phytosterol 17-(6-diethylamino) decan-3-yl)-10, 13-dimethyl-12, 13-dihydro-10H-cyclopenta[a] phenanthren-3-ol has been isolated from leaf [8]. Seeds are the major sources of fatty acids like palmitic acid, myristic, stearic, linoleic, linolenic acid and steroids like stigmastanol, α and β-sitosterol, β-amyrin, friedel-1-en-3-one, lupeol, β-sitosterol β-glucose [9]. Histamine, 5-hydroxy tryptamine are derived from pollen grains [5]. 24-ethyl-chol-22-en-3α-ol is derived from roots [10].

Ethnomedicinal uses

The plant parts are harvested by tribal people for their curative properties. A list of ancient ayurvedic uses of plants parts has been given below:

Fig. 1: A twig of Holoptela integrifolia showing significant different plant parts. Courtesy: http://www.ibin.gov.in/ibin/components/com_ibin/species_htm/Holoptela%20integrifolia3/Holoptela%20integrifolia.htm

#Taxonomic Details
Biological activity

Advantageous or adverse effects of any drug on living substances are known as its biological activity. Biological activity of a drug determines its uses in medicinal application. Activity is generally dose depended. *Holoptelea integrifolia* also possesses such biologically active compounds that lead this tree as a very popular ethnomedicinal plant since 'Ayurvedic' era. Incessant efforts of scientists and researchers, from decades, are able to reveal various biological activities as well as active principles of this plant. Such findings are based upon its ethnomedicinal properties which create a connection between ancient Ayurveda and modern medical science and technology.

**Anti inflammatory activity**

Inflammation is an immuno-vascular response against detrimental stimuli. Anti-inflammatory is the property of a substance which reduces inflammation or swelling. Aqueous (@ 500 mg/kg) [28], ethanolic (@ 250, 500 mg/kg) [29] and methanolic (@ 100, 500 mg/kg) [30] leaf extract of *H. integrifolia* showed a significant inhibition of paw oedema formation in carrageenan-induced paw oedema test. It suggests the usefulness of the leaves of this tree in treating acute and chronic inflammations. It is recently reported that methanic extract of fruit also possesses anti-inflammatory activity [31].

**Antibacterial activity**

An antibacterial is a substance that destroys bacteria or inhibits their growth. The chloroform extract of stem bark [32] and leaves [33] of *H. integrifolia* was found to be highly effective against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, and Citobacter freundii, Micrococcus luteus, P. aeruginosa P. fluorescense respectively at diverge range of concentration. The diethyl ether extract (4 µg/ml) of leaves has showed a significant inhibition of paw oedema formation in carrageenan-induced paw oedema test. It suggests the usefulness of the leaves of this tree in treating acute and chronic inflammations. It is recently reported that methanic extract of fruit also possesses anti-inflammatory activity [31].

**Antiviral activity**

Antiviral substance either destroys a virus or represses its ability to replicate. Betulonic acid and betulin, isolated from the stem bark of *Holoptelea integrifolia* are responsible for antiviral properties against Herpes simplex type1, influenza FPV/Rostock and ECHO 6 viruses. Betulonic acid exerts potential inhibition on HIV-1 entry and HIV-protease or of reverse transcriptase activity [36].

**Antifungal activity**

An antifungal drug refers to the chemical agent that is lethal to fungi or suppresses their reproduction or growth; effective against fungal infection. *Holoptelea integrifolia* has a broad anti-fungal effect [37]. Methanolic extract (MIC-152.2-1250 µg/ml) [37], petroleum ether extract (MIC-200 ppm) [38], ethylaceate leaf extract (MIC-39-625

### Table 1: Ethnomedicinal profile of Holoptelea integrifolia

<table>
<thead>
<tr>
<th>Part used</th>
<th>Mode of application</th>
<th>Disease</th>
<th>Tribe/Area</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Juice of boiled bark</td>
<td>Common fever, Herpes simplex</td>
<td>Sub-himalayan tract up to 1000m</td>
<td>[12]</td>
</tr>
<tr>
<td></td>
<td>Pounded and tied over the knee joint</td>
<td>infection,</td>
<td>Thara, Bhoxa village up to 1000m</td>
<td>[13]</td>
</tr>
<tr>
<td></td>
<td>Cut and tied on the arm</td>
<td>Weakness, Inflammation of lymph glands, ringworm, scabies, Chronic wound</td>
<td>Singh Nagar, Dehairadun</td>
<td>[14]</td>
</tr>
<tr>
<td></td>
<td>Bark is pounded with root of <em>Capparis zeylanica</em></td>
<td>Rheumatism</td>
<td>Blil, Pavar, Vanjari, Tadavi, of Jalgaon</td>
<td>[15]</td>
</tr>
<tr>
<td></td>
<td><em>Dichrostachys cinerea</em> and mixed with black pepper juice</td>
<td>Eczema</td>
<td>Bayar, Bind, Charo, Kol.</td>
<td>[16]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Joint Pain</td>
<td>Musahar, Gond</td>
<td>[17]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malaria</td>
<td>Koya</td>
<td>[18]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Facial Paralysis</td>
<td>Koya</td>
<td>[19]</td>
</tr>
<tr>
<td>Leaf</td>
<td>Peel</td>
<td>Leucoderma</td>
<td>Thara, Bhoxa village of Udham</td>
<td>[20]</td>
</tr>
<tr>
<td></td>
<td>And decoction is made with root of <em>Plumbago zeylanica</em>, fruit of <em>Carica papaya</em></td>
<td>Inflammation</td>
<td>Singh Nagar, Dehairadun</td>
<td>[21]</td>
</tr>
<tr>
<td></td>
<td>Boiled in water and given water bath</td>
<td>Wound cleaner</td>
<td>Gond</td>
<td>[22]</td>
</tr>
<tr>
<td></td>
<td>Young leaf cut and tied on backbone</td>
<td>Tumor, Alopica</td>
<td>Koya</td>
<td>[23]</td>
</tr>
<tr>
<td></td>
<td>Decoction of leaf</td>
<td>Termination of pregnancy</td>
<td>Koya</td>
<td>[24]</td>
</tr>
<tr>
<td></td>
<td>Juice</td>
<td>Lepryosis, Inflammation, Skin</td>
<td>Bayar, Bind, Charo, Kol.</td>
<td>[25]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>disease, Scorpion sting</td>
<td>Musahar, Gond</td>
<td>[26]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ricketts</td>
<td>Naughar</td>
<td>[27]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ringworm, Eczema, Cutaneous disease</td>
<td>Sub Himalayan tract up to 1000mt, Kol</td>
<td>[28]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uncontrolled bleeding</td>
<td>Koya</td>
<td>[29]</td>
</tr>
<tr>
<td>Fruit</td>
<td>Dried</td>
<td>Nasal drop</td>
<td>Sub Himalayan forest of northeastern U. P</td>
<td>[30]</td>
</tr>
<tr>
<td></td>
<td>Seeds are externally applied in the form of poultice on injured part</td>
<td>Polyurea and other urinary problems</td>
<td>Sub Himalayan tract</td>
<td>[31]</td>
</tr>
<tr>
<td></td>
<td>Seeds are crushed in water and given thrice a day</td>
<td>Brain tonic and general debility</td>
<td>Sub Himalayan tract</td>
<td>[32]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uncontrolled bleeding and Quick healing</td>
<td>Bayar, Bind, Charo, Kol, Musahar, Gond</td>
<td>[33]</td>
</tr>
</tbody>
</table>
The hexane and ethyl acetate extract of bark had significant cytotoxic activity against breast cancer formation [46]. Another experiment showed that the methanolic extract of leaves at doses of 250 and 500 mg/kg showed significant antidiabetic activity [50]. Recently, it has been revealed that 5% aqueous extract (at 300 mg/kg), petroleum ether extract (at 100, 200 mg/kg) of stem bark also exert antidiabetic effect on blood glucose level, body weight and lipid profile at dose dependent manner [51].

**Antidiarrheal activity**

Diarrhea is the condition of abnormal liquid bowel movements each day, leading to dehydration. The most common cause is an intestinal infection due to a virus, bacteria, or parasite. The ethanolic leaf extract of *H. integrifolia* at doses of 250, 500 mg/kg showed significant (P<0.01 in both cases) antidiarrheal activity in experimental diarrhea induced by castor oil (0.5 ml) and magnesium sulphate (2 mg/kg) in mice. The extract also reduces the intestinal transit (P<0.01) in charcoal meal test in mice [52].

**Wound healing activity**

Wound healing is a complex tissue repairing mechanism of damage skin or tissue after trauma. The methanolic extracts of both stem bark and leaves at a concentration of 50 mg/550 mm^2 of wound area were found to possess wound healing potential on albino rats in incision and excision wound model (>90% wound healing recorded) [37].

**Adaptogenic activity**

Adaptogens are a new class of metabolic regulators which increases the assists any organism to adapt to its environmental factors. The ethanolic extract of stem bark of *H. integrifolia* revealed adaptogenic activity at doses of 250 and 500 mg/kg on albino Wister rats. This effect is due to the presence of tannins, saponins, alkaloids, flavonoids, in the stem bark [53].

**Analgesic activity**

An analgesic or painkiller refers to any drug used to relieve pain. Ethanol extract of *H. integrifolia* leaf at a dose of 500 mg/kg per oral exhibits significant (P<0.05) analgesic activity while ethyl acetate extract showed moderate activity. Aqueous and n-butanol extract of the plant showed mild analgesic effects. The maximum effect was shown at 150 min, after consuming the drug [54].

**Hypolipidemic activity**

Hypolipidemic agents are lipid-lowering drugs, used in treating hyperlipidemia. The methanolic extract of leaf and bark of *H. integrifolia* exert hypolipidemic effect by markedly lowering body weight, serum lipid, HMGR activity and apo-B as well as increasing high-density lipoprotein-cholesterol and apo-A1 concentration. The focal analysis indicates the ability of the extract to prevent intestinal fat absorption. Extract possesses a compound 3-[7-ethoxy-4-methyl-2-oxo-2H-chromen-3-yl] propionate (Cl) which might have inhibited HMGR activity, thus blocked intestinal fat absorption [55].

**Hepatoprotective activity**

Hepatotoxicity implies chemical mediated liver damage. Hepatoprotection is the ability to prevent damages to the liver. Methanolic leaf extract of *H. integrifolia* exert hypolipidemic effect by markedly lowering body weight, serum lipid, and induced hepatotoxicity on rats altered the levels of serum marker enzymes Alanine Transaminase (ALT), Aspartate Transaminase (AST), Alkaline Phosphatase (ALP) and Total Bilirubin (TB). These observations were supported by histopathological changes such as steatosis (fatty change, fatty degeneration or adipose degeneration), inflammatory infiltrations and perivenular fibrosis [56].

**Antiemetic activity**

An antiemetic is a drug that prevents vomiting and nausea. Ethanol extract of *H. integrifolia* at doses of 250, 500 mg/kg shows the promising effect on cisplatin-induced nausea on rat [57].

**Larvicidal activity**

A larvicide is an insecticide that kills the larval stage of an insect. Acetone extract of leaves of *H. integrifolia* at various concentrations,
revealed the effect on larval mortality of *Culex vishnui* after 24, 48, 72h exposures. The study showed the significantly higher mortality rate (P<0.05) of all larval instars at 0.5% concentration. The highest mortality was observed at 400 ppm concentration and 72h exposure of acetone extract [58].

**CNS depressant activity**

CNS depression refers to physiological depression of the central nervous system owing to decreased breathing rate, heart rate, and loss of consciousness leading to coma or death. Methanolic leaf extract of *H. integrifolia* at a daily dose of 250 mg/kg revealed the Central Nervous System (CNS) depressant activity in Swiss albino mice by reducing exploratory behavior pattern and muscle relaxation of those animals in head dip test and traction test respectively [59].

**Anti arthritic activity**

Rheumatoid arthritis is an autoimmune disease, affecting the synovial joints and leads to joint destruction. The anti-arthritic activity of petroleum ether and methanolic leaf extract of *H. integrifolia* was evaluated by measuring paw volume displacement, radiographic analysis and secondary lesions changes as a mark of antarthritic activity in Complete Freund’s Adjuvant (CFA) model of rat. Petroleum ether extract at doses of 100, 300 mg/kg was found to be more effective than methanolic extract [60].

**Anticonvulsant activity**

Anticonvulsants are the group of drugs that retard the rapid and excessive neurological disorder during seizures. The petroleum ether extract (at doses of 100, 300 mg/kg) and methanolic extract (300 mg/kg) of leaf delayed onset of convulsion and also prolonged the onset of tonic convulsion in mice. The result supports the ethnomedicinal application of the plant as an anticonvulsant agent [61].

**Antiadherence and antibiofilm activity**

Bacterial biofilm is a bacterial cell community, enclosed by the polymeric matrix and adherent to an inert or living surface. Thereby protects growth and allows survival in a hostile environment. Aqueous, methanol extracts both at a concentration of 15-30 mg/ml and acetone leaf extract at 15 mg/ml of this tree exert promising anti-adherent and anti-biofilm activity against *Staphylococcus aureus* biofilm formation [62].

**Novel area of research**

*Holoptelea integrifolia* shows a new dimension on controlling over metabolic syndrome by ameliorating a number of biomarker molecules associated with diseased state. According to Adult Treatment Panel III of the National Cholesterol Education Program in 2001 five criteria viz. abdominal obesity, impaired fasting glucose, high triglycerides (TG), low HLD-cholesterol (HLD-C) concentration and increased blood pressure had been included in metabolic syndrome. Metabolic Syndrome is diagnosed if any three of these criteria are found in an individual. 60% methanolic leaf extract of *Holoptelea integrifolia* exert up and down regulation of biomarker proteins in 3T3-L1 adipocytes in a dose dependent manner. Several phytochemicals like trigonelline, myo-inositol, piperidine-2-carboxylic acid, uracil, adenine, frideline and α-amyrine have been isolated and characterized from different plant parts. These phytochemicals are assumed to be the active principles responsible for such regulation and can be used alone or optionally combined with nutraceutical, pharmaceutical or dietetically acceptable carrier molecules for preventing diseases associated with metabolic syndrome [63].

**CONCLUSION**

Recent research findings of the forest trees of Indian subcontinent indicate that few of these species (*Shorea robusta*, *Buchanania lanzan*, *Terminalia arjuna*, *Azadirachta indica*, *Saraca asoca*, *Santalum album*, *Terminalia chebula*) really hold promise to become rich source rare phytomedicines. *Holoptelea integrifolia* is such a tree with a plethora of biologically active compounds which need to be isolated and clinically correlated for their unknown medicinal properties. In this review, we have tried to portray an updated account of *Holoptelea integrifolia* with emphasis on its phytomedicines and their clinical studies. As of now, thorough and critical research is being conducted globally to discover novel drugs from unexplored plants, especially from the tropics and sub-tropics. With the recurrence of virulent pathogens and their new aggressive mutants, such unique drugs could be the answer to dreadful diseases like malaria, Ebola, flues, AIDS and cancer.

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**CONFLICT OF INTERESTS**

The authors declare that there is no conflict of interest regarding this publication.

**REFERENCES**


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