



***Holoptelea integrifolia* Planch: A potential Ayurvedic medicinal plant**

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Accepted on: 22-05-2013; **Finalized on:** 31-07-2013.

ABSTRACT

Holoptelea integrifolia Planch (Ulmaceae) is an evergreen, scattered, glabrous tree with 30-35 m in height and is commonly known as Chilbil in India. In India, stem bark and leaves of the plant are used in indigenous system of medicines such as Ayurveda, Unani, Siddha for the prevention of variety of diseases such as bitter, astringent, acrid, anti-inflammatory, digestive, carminative, laxative depurative, and diuretic. Literature survey of plant *H. integrifolia* showed the presence of various phyto constituents having pharmacological activities such as antioxidant, adaptogen, hepatoprotective, antiulcer, antibacterial, anti-inflammatory and antitumor activity. Thus, the present review will provide up to date referential information to the researchers working on this particular plant.

Keywords: Analgesic, *Holoptelea integrifolia*, Hypolipidemic, Tamoxifen.

INTRODUCTION

The Indian elm *Holoptelea integrifolia* (Planch) is an ornamental road side tree and can be simplified as ho-loh-tee-uh from Greek holos (whole) and ptelea (elm) in-teg-ree-foh-lee-uh meaning, entirely (undivided). It belongs to family Ulmaceae which comprises 15 genera and 200 species. It is commonly known as Chilbil, Kanju in Hindi, Chirivilva, Poothigam in Sanskrit and Indian Elm tree in English.¹ It is distributed over tropical and temperate region of northern hemisphere.² *H. integrifolia* is considered to be native to Asian –Tropical region including India, Nepal, Srilanka, Cambodia, Laos, Myanmar, Vietnam and China.³ It is an important pollen allergen of India, sensitizes almost 10% of the atopic population in Delhi.⁴ The objective of the present review is to provide an up to date information about this particular plant including areas such as physicochemical properties, phytochemistry, pharmacology. Thus, the review will act as a valuable source of information for researchers regarding its medicinal and commercial values.

Taxonomy of the Plant

Domain	: Eukaryota
Kingdom	: Plantae
Phylum	: Tracheophyta
Class	: Magnoliopsida
Order	: Urticales
Family	: Ulmaceae
Genus	: Holoptelea
Specific epithet	: integrifolia - Planch
Botanical name	: <i>Holoptelea integrifolia</i> (Roxb.) Planch

Various common name⁵

Hindi	: Papri, Chilbil, Kanju, Cilbil, Poothigam, Chirabil
Sanskrit	: Chirivilva, Pootikaranja, Vayasi, Karanji, Chirabilwa
English	: Indian Elm, Jungle cork tree, Monkey Biscuit Tree
Malayalam	: Aavil, Aval
Punjabi	: Rajain, Khulen, Arjan
Telugu	: Nemilnara, Nali, Thapasi, Nemali, Pedanevili
Kannada	: Kaladri, Nilavahi, Rahubija, Rasbija
Tamil	: Aya, Ayil, Kanci, Avil, Pattai
Bengali	: Nata Karanja
Marathi	: Ainasadada, Vavala, Vavli, Papra, Bawal
Oriya	: Dhauranjan, Turuda, Karanja
Gujarati	: Charal, Charel, Kanjo, Chirbil, Chirmil
Konkani	: Vamvlo
Burmese	: Myaukseik, Pyaukseik
Nepali	: Sano pangro
Siddha	: Iya

Botanical description

It is a large deciduous tree with spreading branches and grows up to 30-35 m in height and 3 m girth. Bark is whitish, yellow grey, covered with blisters, peeling in corky, exfoliate with regular intervals. Leaves are simple, alternate, elliptic-ovate, entire glabrous with cordate base, acuminate, nerves 5-8 pairs, 5-13 cm long and 3.2-6.3 cm wide. The bark when cut and the leaves when crushed emit an unpleasant odour. Flowers are polygamous, greenish yellow to brown in short racemes



or fascicles. In male flowers, 8 stamens and in bisexual flowers 5 stamens are present, basally adnate to tepals, ovary is unilocular and stalked, Style very short (2.5-4 mm long); stigmas 2 in number. The flowers appear at the scars of fallen leaves on tree from February to March. Fruits are one seeded samara, light brown, obliquely elliptic or orbicular, winged and stalked, indehiscent, 2.5 - 3.5 cm long 1.5-2.5 cm wide. The fruits are seen during month of April to May. Seeds are small, whitish, kidney shaped, flat samara.⁶

Traditional use

Both bark and leaves are bitter, astringent, acid, anti-inflammatory, digestive, carminative, laxative depurative and urinary astringent.⁷ Dried bark is used as an oxytocic for pregnant ladies.⁸ The leaf decoction is taken orally to regulate fat metabolism.⁹ Stem bark and seed paste is used for treating ringworms, eczema and cutaneous affection when applied externally. Stem bark is externally used to treat inflammation of lymph gland, for fever,¹⁰ and scabies and ringworm too. A paste made with the leaves and bark is used to treat leucoderma.¹¹ Ethnomedicinally, the leaves and stem bark of *H. integrifolia* are used by tribal people for cancer treatment.¹² Leaves of plant is used for treating odema, leprosy, and other skin diseases, intestinal disorders, piles, and sprue.¹³⁻¹⁵ Leaf bud mixed with lime juice is applied externally on affected area for treatment of hair loss due to infection and treatment of herpes infection.¹⁶ In Nepal, bark is externally used for reducing rheumatic swellings.¹⁷ The fruit pulp mixed with black salt and is given for the treatment of menstrual disorders.¹⁸ One tablet per day can be given to the patient suffering from jaundice.¹⁹ Stem bark is used as an anti-inflammatory agent for eyes.²⁰ Some Ayurvedic Medicinal Properties of plant includes Rasa: Tikta, Kashaya, Guna: Lakhu, Rooksha, Virya: Ushna, Rogagnata: Kaphapattikavikara Shotha, Agnimandya, Chhardi, Karma: Pittahara, Stambhaka, Shothahara, Deepana, Anulomana, Vipaka: Katu, Doshagnata: Kaphapittashamaka.⁵

Phytochemistry

H. integrifolia plant contains a large number of phytoconstituents such as flavonoids, alkaloids, steroids, tannins, saponins, glycosides.²¹ Holoptelin-A (Figure A), Holoptelin-B (Figure B), friedlin (Figure C), epifriedlin (Figure D), 2-aminonaphthoquinone, β -sitosterol, β -D-glucose, β -amyrin, hederagenin have been isolated from heart wood and bark while hexacosanol (Figure F), octacosanol, β -sitosterol and α -amyrin (Figure E) were isolated from leaves of tree. 1, 4-naphthalenedione has been isolated from leaves and possess antibacterial activity against *Staphylococcus aureus*.²² Two new medicinal pentacyclic triterpenoids, betulinic acid (3β -Hydroxy- lup-20(29)-en-28-oic acid) (Figure G) and betulin (Lup-20(29)-ene- 3β , 28-diol) (Figure H) were isolated from bark of plant. Betulinic acid possesses biological potential such as, inhibitors of HIV -1 entry, HIV- protease or of reverse transcriptase (RT), anti malarial, anti bacterial

(against gram positive), anti inflammatory, anthelmintic (*Caenorhabditis elegans*), antioxidant whereas Betulin had significant anticancer effect on, adenocarcinoma, cervix carcinoma, hepatoma, and breast cancer.²³

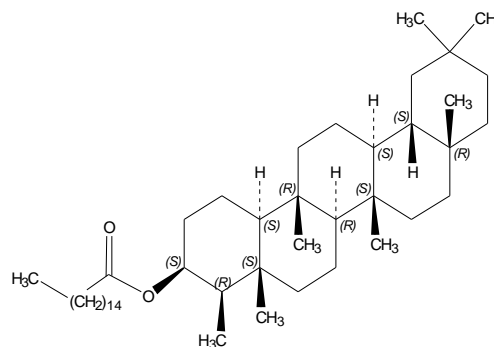


Figure A: Holoptelin-A

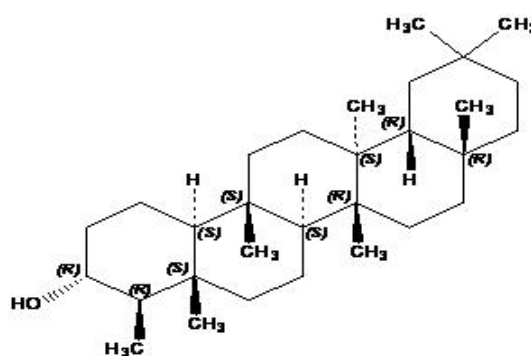


Figure B: Holoptelin-B

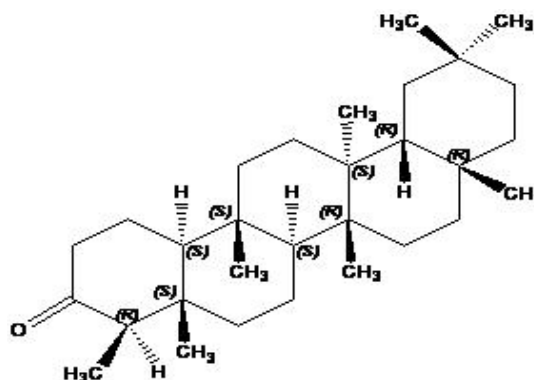


Figure C: Friedlin

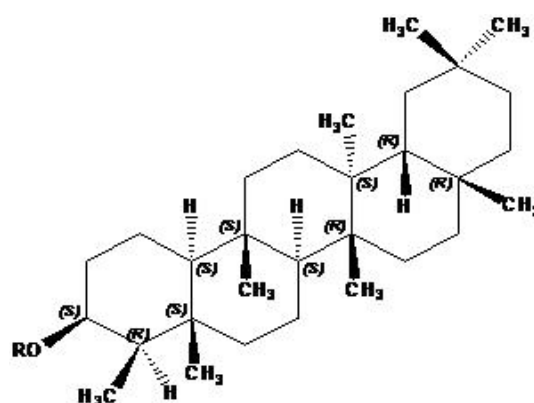


Figure D: Epifriedlin

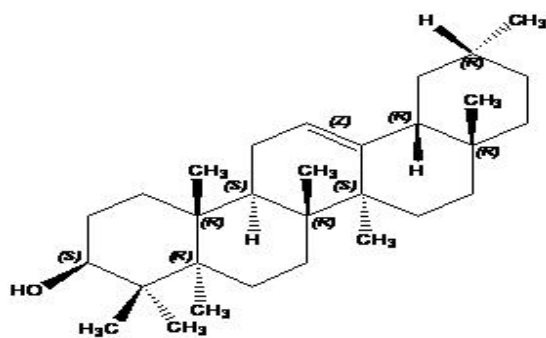
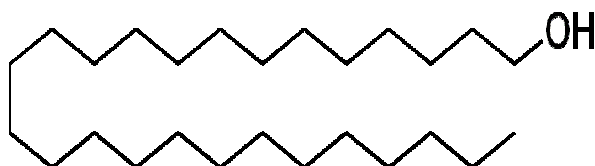
Figure E: β -amyrin

Figure F: n-hexacosanol

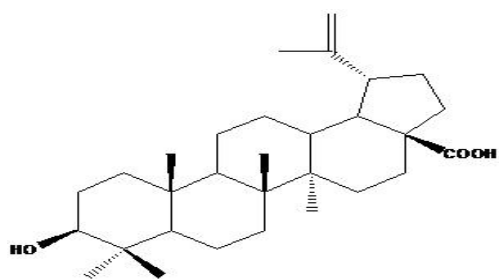


Figure G: Betulinic Acid

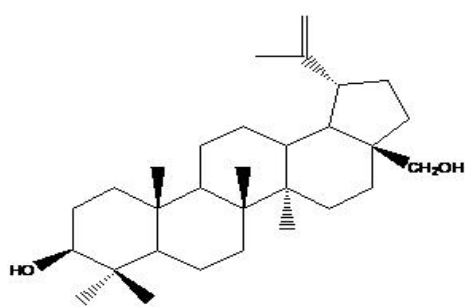


Figure H: Betulin

Figure 1: Phytoconstituents isolated from *Holoptelea integrifolia*.

BIOLOGICAL ACTIVITY

Antibacterial effect

The *in vitro* antibacterial activity of aqueous extract of *H. integrifolia* (leaves) was studied by employing the agar well diffusion method. The test was performed against various bacteria *Streptococcus pyogenes*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella typhi*. At different concentration of the aqueous extract of leaf of plant, zone of inhibition was observed against all resistant bacterial strains.²⁴

The degree of inactivation of β -lactame activity by the inhibitor 1, 4 Naphthalene dion isolated from the plant *H. integrifolia* was determined taking amoxicillin as substrate against resistant strain of *Staphylococcus aureus* in the microiodimetric assay. The mechanism

involved in β -lactame resistance in *Staphylococcus aureus* is due to production of an enzyme β lactamase which altered or hydrolyse the amide bond of the beta lactamase ring. As a result the antibiotics can no longer inhibit bacterial cell wall synthesis. Modeling and molecular studies indicated that compound 1,4 Naphthalene have significant activity to inhibit the β -lactame activity due to fit in to active site and thus locking β -lactamase. Hence the compound showed synergistic effect for the development of effective β - lactamase inhibitor that can be used against β - lactamase resistant microbial strains or *Staphylococcus aureus*. The β -lactame activity of *Staphylococcus aureus* was maximum in case of diethyl ether extract followed by hexane, acetone and water extract.^{25,26}

Various extract such as chloroform, petroleum ether, methanol and aqueous of stem bark of

H. integrifolia at different concentration were screened for their antibacterial activity using disc diffusion method against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa*. The susceptibility of the microorganism to the extract of these plants was compared with selected antibiotics ampicillin. The chloroform extract of *H. integrifolia* was found to be very effective against all the test microorganism used. Petroleum ether extract was only effective against *E. coli* and *B. subtilis*: methanol extract was effective against *E.coli* aqueous extract against *S. aureus*, *B. subtilis*, *E. coli* and *P. aruginosa*.²⁷

The chloroform extract of leaves of plant showed potential antibacterial activity by disc diffusion method against four bacterial strains *Citrobacter freundii*, *Micrococcus luteus*, *Pseudomonas aeruginosa* and *Pseudomonas fluorescence* where zone of inhibition was compared with the standard drug Cephotaxime. The maximum activity of chloroform extract against all tested organism *Citrobacter freundii* compared to other bacterial strains.²⁸

Anti-inflammatory activity

Ethanol extract of leaves of *H. integrifolia* (EHL) also showed significant anti-inflammatory effects in various animal models. EHL was given orally to rats at a dose 250 and 500 mg/kg per oral to study its effect on inflammatory reaction (carrageenan induced granuloma models). The study revealed that the ethanol extract of *H. integrifolia* showed significant anti-inflammatory activity in various tested animal model.²⁹

The effect of Petroleum ether, methanol extract (100-200 mg/kg p.o.) was given to observe percentage inhibition of paw oedema which were comparable with Diclofenac sodium as standard anti-inflammatory drug. The methanolic extract at dose 100 and 200 mg/kg significantly reduced oedema formation induced by carrageenan while petroleum ether shows non significantly anti-inflammatory activity at both dose (100 and 200 mg/kg).³⁰

Antidiarrhoeal activity

Ethanol extract of leaves of *H. integrifolia* showed antidiarrhoeal activity induced by oral administered of castor oil (0.5 ml) and magnesium sulfate (2 mg/kg) on swiss albino mice. Oral administration of ethanolic extract at dose 250 and 500 mg/kg exhibited reduction in total number of diarrhoeic faeces in a dose dependent manner compared with loperamide at the dose of 3 mg/kg orally. The extracts also exhibited significant role in reduction of the intestinal transit in charcoal meal test when compared to atropine sulphate (5 mg/kg). The ethanol extract of leaves of *H. integrifolia* showed a significant potential of antidiarrhoeal activity and is traditionally used in herbal medicine.³¹

Adaptogenic effect

The ethanolic extract of stem bark of *H. integrifolia* demonstrated a dose dependent adaptogenic activity by using forced swimming endurance test and chronic cold restraint stress models. The extract given at dose of 250 and 500 mg/kg showed the dose dependent adaptogenic activity, which is relatively closer to the activity of 100 mg/kg of *Withania somnifera*. These effects were due to the presence of tannins, saponins, alkaloids, flavonoids, in the stem bark of *Holoptelea integrifolia*.³²

Antioxidant activity

The methanolic extract of both leaves (MLE) and stem bark (MSBE) of *H. integrifolia* were evaluated for antioxidant activity against 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging activity by HPLC method³³, and total phenolic content was also estimated. Antioxidant potential on the crude extract of *H. integrifolia* has been evaluated using two different methods i.e. ferric thiocyanate and thiobarbituric acid method. Ethanol extract showed significant antioxidant potential by inhibiting the oxidation of linoleic acid in both FTC and TBA methods, when compared with standard drug vitamin E, at specific concentration.³⁴

Anthelmintic activity

The effect of benzene, chloroform, methanol and aqueous extract of the stem bark of *H. integrifolia* has been evaluated for anthelmintic activity in adult *Pheretima posthuma* (earthworm) worm. Piperazine citrate was used as standard reference drug. Both methanol and aqueous extract showed dose dependent anthelmintic activity, which was comparable with reference drug piperazine citrate at dose of 40 and 60 mg/ml.³⁵

In another study, anthelmintic activity of two different extracts (methanolic and aqueous extracts) of stem bark of *H. integrifolia* against adult *Pheretima posthuma* were evaluated. Piperazine citrate was used as standard drug (10m/ml). The aqueous and ethanolic extract showed significant helminthic activity at 10, 25, 50, 100 mg/ml concentration which are comparable with standard drug piperazine citrate.³⁶

Antitumor effect

The ethanolic extract of leaves of *H. integrifolia* was investigated for its antitumor activity against Dalton's ascetic lymphoma (DAL) in swiss albino mice. DAL cell were injected intraperitoneally (110 cell) to each mice. The animals were treated orally with 250 and 500 mg/kg body weight of ethanolic extract of *H. integrifolia* leaves for 14 consecutive days. A significant increase in the life span and non-viable cell count in peritoneal exudated in EHI treated group were observed in dose dependent fashion when compared with DAL treated groups. These observations suggested that EHI possess antitumor effect against Dalton's ascetic lymphoma (DAL).³⁷

Anticancer effect

Breast cancer prevention property and anti-oxidant status of ethanolic extract of *H. integrifolia*, against 7,12-dimethyl benz(a)anthracene (DMBA)- induced breast carcinoma in Female Sprague-Dawley rats were evaluated in this study. Body weight of animals, tumor burden, tumor multiplicity, tumor volume of breast and antioxidants like CAT, SOD, GSH and GPx levels were also measured. Tamoxifen used as the standard drug. The extract given orally at doses of 250 and 500 mg/kg p.o. showed significant (P < 0.05, 0.01) dose-dependent % inhibition of breast cancer formation.³⁸

Wound healing effect

The methanolic extract of leaves and stem bark of *H. integrifolia* were studied for the wound healing potential in Wistar Albino rats. The wound healing activity was studied using two wound models, excision wound model and incision wound model. The results from excision model showed more than 90% wound healing in treated groups by 14 days of post surgery, whereas only 62.99% healing was observed in the control group. In incision model, higher breaking strengths and higher hydroxyl proline content in treated groups suggested higher collagen redeposition than the control group. Finally histopathology studies conformed 'wound healing properties of *H. integrifolia*.³⁹

Antiulcer effect

The methanolic extract of *H. integrifolia* shows the antiulcer activity against gastric ulcer induced by pyloric ligation model in rats. The methanolic extracts at 500 mg/kg of plant per oral doses significantly reduced the ulcer index, volume of gastric juice, free acidity, total acidity with respect to control omeprazole.⁴⁰

Analgesic effect

Various extracts from leaves of *H. integrifolia* has shown significant analgesic action in mice by tail flick method. Diclofenac sodium (50 mg/kg) was used as standard. At dose of 500 mg/kg per oral ethanol extract was found to possess significant analgesic activity while ethyl acetate extract showed moderate activity while, n-butanol and aqueous extract of the plant showed mild analgesic effects.⁴¹



Absence of hypolipidemic effect

The study investigates the influence of the aqueous extract of leaves of *H. integrifolia* on the lipid profile in normal and Tyloxapol induced hyperlipidemic rats. Aqueous extract of leaves of *H. integrifolia* (250 and 500 mg/kg) and fenofibrate, a reference standard (65 mg/kg) were orally administered for seven days and lipid profile was tested by estimating the plasma levels of total cholesterol, triglycerides, HDL-c, LDL-c, VLDL-c, and corresponding atherogenic index and LDL-c/HDL-c ratio. The results showed that the aqueous extract of *H. integrifolia* did not have any significant lipid lowering effect.

Hepatoprotective effect

Methanolic extract of the leaves of *H. integrifolia* exhibited significant hepatoprotective activity against carbon tetra chloride induced hepatotoxicity in male Wistar rats at dose of 500 mg/kg per oral. Oral administration of ethanolic extract decreased the elevated levels of alanine transaminase (ALT), alkaline phosphate (ALP), aspartate transaminase (AST) and total bilirubin during the hepatotoxicity, when compared with standard drug sylimarin 100 mg/kg p.o.⁴³

Anti diabetic effect

Anti-diabetic activity on ethanolic and petroleum ether extract of the leaves of *H. integrifolia* has been evaluated against alloxan induced diabetes in male Wistar rat which was comparable with standard drug Glibenclamide.⁴⁴

Mosquito larvicidal potentiality

H. integrifolia leaf extract has been screened against Japanese Encephalitis Vector, *Culex vishuni* Group. Larva immortality of *Culex vishuni* group was observed after 24 h, 48 h and 72 h of exposure with five concentrations (0.1%, 0.2%, 0.3%, 0.4% and 0.5%) of crude extract and four concentrations (100 ppm, 200 ppm, 300 ppm and 400 ppm) of acetone extract of leaf of *H. integrifolia*. Respective lethal concentrations were evaluated by log-probit analysis (at 95% confidence level). Effects of acetone extract of *H. integrifolia* leaves were investigated against non-target predatory fishes and insect larvae. During this present study, the mortality rates of all larval instars at 0.5% concentration were significantly higher than at 0.1%-0.4% concentrations of crude leaf extract. Highest mortality was found at 400 ppm concentration of acetone extract. Larvicidal activity may be due to presence of tannin, saponin, steroid and phenol as bioactive secondary metabolites.⁴⁵

SUMMARY AND CONCLUSION

The present review has justified the role of *Holoptelea integrifolia* as an important medicinal plant used in several indigenous system of medicine and has also found beneficial in the treatment of various diseases such as cancer, diabetes, fever, helminthes infection, diarrhoea, pain reliever, inflammation ailments including rheumatism, liver diseases etc. An analysis of literature

shows that the plant contains different phyto constituents which are responsible for various biological activities. Thus from the study, it is clear that the presence of phytochemical and pharmacological activities may act as a potential tool in development of effective herbal formulation for treatment of various diseases that will serve the society.

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Source of Support: Nil, Conflict of Interest: None.