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A mini review on chemistry and biology of *Holoptelea integrifolia* Roxb. Planch (Ulmaceae)

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ABSTRACT

Holoptelea integrifolia Roxb. (Indian Elm) is a very useful and popular traditional medicinal plant in India. During the last three decades, apart from the chemistry of plant compounds, considerable progress regarding the biological activity and medicinal applications of Indian Elm has been achieved. Ethno-medically, the leaves and stem bark of this plant have been used by tribes as antiviral, antioxidant, antimicrobial, abortifacient preparations and in the management of cancer. Recent studies on plant show that it has potential to fight against tumor and obesity as well. Phytochemical investigation shows the presence of chemical constituents such as terpenoids, alkaloids, glycosides, carbohydrates, sterols, saponins, tannins, proteins and flavanoids. The isolated principles such as β -amyirin, β -sitosterol, holoptelin-A, holoptelin-B, hederagenin, hexacosanol, β -D-glucose, friedelin, epifriedelin, 2-amino naphthoquinone, 1,4-naphthalenedione, are considered as responsible for various activities. This review highlights the traditional uses, reported biological/pharmacological activities, isolated compounds and therapeutic applications of *Holoptelea integrifolia* which might be helpful for scientists and researchers to find out new chemical entities responsible for its claimed traditional uses.

1. Introduction

Medicinal plants are part and parcel of human society to combat diseases, from the dawn of civilization[1]. *Holoptelea integrifolia* is well known roadside tree having a wide spectrum of biological activities. The name of plant can be simplified as ho-loh-TEE-lee-uh from the Greek holos (whole) and ptelea (elm) in-teg-ree-FOH-lee-uh or in-teg-rih-FOH-lee-uh meaning, leaves entire (undivided). *Holoptelea integrifolia* (Roxb.) Planch is also known as *Ulmus integrifolia* Roxb. belonging to family Ulmaceae. It is commonly known as Indian Elm tree in English; Papri, Chilbil, Kanju in Hindi and Chirivilva, Poothigam in Sanskrit. Indian elm is a medium sized to large glabrous deciduous tree, with whitish or yellowish grey bark exfoliating in irregular flakes and with an offensive smell when freshly cut[2]. The family Ulmaceae, having 15 genera and about 200 species is distributed over tropical and temperate regions of northern

hemisphere[3]. The native distribution of the plant can be seen in Asia-Tropical region including India, Nepal, Sri Lanka, Indo-China, Cambodia, Laos, Myanmar, Vietnam, Burma and China[4]. Various parts of the tree have been found to be useful in the treatment of bronchitis and obesity[5]. The tree has been reported to possess ovipositor deterrent and protease inhibitor activities[6]. Traditionally, the bark and leaves are used as bitter, astringent, anthelmintic and helps in treatment of inflammation, acid gastritis, dyspepsia, colic, intestinal worms, vomiting, edema, piles, wound healing, leprosy, diabetes, hemorrhoids, dysmenorrhoea, diarrhoea, rheumatism, polyuria, helminthiasis, tuberculosis, fistula, flatulence, vitiligo, filariasis, and skin diseases. In Nepal, bark and leaves are applied externally on the white patches in leucoderma[7]. Many chemical constituents such as terpenoids, sterols, saponins, tannins, proteins, carbohydrates and alkaloids have been reported in this plant[8, 9].

2. Common names

Various common names of *Holoptelea integrifolia* are mentioned below:

Sanskrit: Chirivilva, Pootikaranja, Udakirya, Hasthivaruni,

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Markati, Vayasi, Karanji,

Karabhanji, Chirabilwa, Puthikaranja, Puutika

Hindi: Papri, Chilbil, Kanju, Cilbil, Banchilla, Bawal, Poothigam, Dhamna, Begana, Chirabil

English: Indian Elm, Jungle cork tree, Monkey Biscuit Tree, Indian Beech tree

Malayalam: Aavil, Njettaval, Aval

Punjabi: Rajain, Khulen, Arjan Telugu: Nemilnara, Nali, Thapasi, Nemali, Pedanevili

Kannada: Kaladri, Nilavahi, Rahubija, Thavasai, Rasbija

Tamil: Aya, Ayil, Kanci, Vellaya, Avil, Pattai

Bengali: Nata Karanja

Marathi: Ainasadada, Vavala, Vavli, Papra, Bawal

Oriya: Dhauranjan, Turuda, Karanja

Gujarati: Charal, Charel, Kanjo, Waola, Chirbil, Chirmil

Konkani: Vamvlo

Burmese: Myaukseik, Pyaukseik

Nepali: Sano pangro

Siddha: Iya

3. Plant morphology

H. integrifolia is a large deciduous tree that grows up to 15 to 25 meters in height. Its bark is whitish yellowish grey, ash-grey, brown-violet in color and exfoliates with regular intervals and with offensive smell when cut. Leaves are simple alternate, elliptic, usually distichous, acuminate and the base is rounded or cordate. Leaf margin is entire glabrous (often serrate on seedlings and shoots), 3 to 5 inches long, and 1.25 to 2.5 inches wide. The leaf blade is pinnately veined with 3 to 7 veins on each side, ascending and uniting below the margin^[10]. Flowers are greenish yellow, usually male or hermaphrodite, monochlamydeous, or rarely polygamous and flowering usually takes place in month of January to February. Sepals are concave, obovate, about 3 to 4 inches long and puberulous on back. Embryo stands erect, curved, or involute and cotyledons are flat, curved, or flexed. Ovary is compressed, pubescent and the stalk lengthens as the fruit ripens. Fruits are sub orbicular samara with membranous wings, and usually seen during month of April to May. Shape of fruit is 2 cm in diameter and 0.6 to 1 inch broad and notched at the top. The stalk is 0.2 to 0.5 inch long and lobes incurved with persistent stigmas^[11–13]. Thickness of fresh bark is about 9 to 27 mm whereas dried bark is 7 to 11 mm thick and the external surface is hard due to longitudinal fissures and irregular rectangular rhitydome^[14].

4. Taxonomy

Domain: Eukaryota

Kingdom: Plantae

Phylum: Tracheophyta

Class: Magnoliopsida

Order: Urticales

Family: Ulmaceae

Genus: *Holoptelea*

Specific epithet: *integrifolia* – Planch.

Botanical name: *Holoptelea integrifolia* (Roxb.) Planch

5. Chemical Constituents

The tree has been reported to contain various chemical constituents like terpenoids, sterols, saponins, tannins, proteins, carbohydrates, flavanoids and alkaloids^[43]. 1, 4-naphthalenedione has been isolated from leaves whereas Holoptelin-A and B have been isolated from stem bark. Friedelin, epifriedelinol, β -D-glucose, 2-aminnaphthaquinone are reported in stem bark. Hexacosanol, octacosanol, β -amyrin, β -sitosterol are some other isolated from leaves which might be responsible for various activities shown by the tree^[15]. Various constituents reported in various parts of the plant have been shown in Figure 1.

6. Biological activities of plant

6.1. Anti-inflammatory activity

The ethanolic extract of leaves of *H. integrifolia* showed significant percentage inhibition of paw edema as compared to standard drug, Indomethacin (10 mg/kg per oral). The ethanolic extracts were given in doses of 250 and 500 mg/kg per oral which were comparable with reference drug^[15]. In the same manner, the aqueous extract of leaves at dose 250 and 500 mg/kg per oral was given to observe percent inhibition of paw edema which were comparable with Indomethacin (10mg/kg per oral) used as a reference drug. The extract showed a significant dose dependent inhibition of edema formation^[18]. It suggests the usefulness of leaves of tree in acute and chronic inflammatory conditions.

6.2. Anthelmintic activity

The methanolic and aqueous extracts of stem bark of *H. integrifolia*, were found to possess significant anthelmintic activity in comparison to the standard drug (Piperazine Citrate) against adult earth worm *Pheretima posthuma*. The methanol extract at various concentrations showed shortest time of paralysis and death^[19]. In the same manner various concentrations (10, 25, 50 and 100 mg/ml) of ethanolic and aqueous extract of bark were tested against worms (*Eisenia foetida*), compared to standard Piperazine Citrate (10 mg/ml). The extracts not only demonstrated paralysis, but also caused death of worms especially at higher concentrations^[20]. The results showed that constituents of bark could be a potent anthelmintic agent for next generation.

6.3. Antibacterial activity

The chloroform extract of stem bark of *H. integrifolia* was found to be very effective against microorganisms like *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa* at concentrations of 50, 30, 25 and 100 μ g/ml respectively. The antibacterial activity of extract was studied by employing Disc diffusion method where zone of inhibition was compared with standard drug, Ampicillin^[21]. The diethyl ether extract of leaves has shown maximum activity against β -lactam resistant strains of *Staphylococcus aureus* and an active principle responsible for the activity was found. This anti-bacterial principle (1, 4-naphthalenedione) has been isolated from leaves of *H. integrifolia*. Structural similarity of isolated compound (1, 4-naphthalenedione) with functional group of β -lactamase resistant antibiotic indicated

that it acts as inhibitor to β -lactamase[22]. Isolated compound showed synergistic effect with amoxicillin by inhibiting enzymatic activity of β -lactamase. Modeling and molecular studies indicated that compound can fit into active site of β -lactamase. The result suggests that this compound can serve as potential lead compound for development of effective β -lactamase inhibitor[23,29].

6.4. Antidiarrhoeal effect

The ethanolic extract of leaves of *H. integrifolia* was studied for its antidiarrhoeal properties in experimental diarrhoea, induced by Castor oil and Magnesium sulphate in mice. At the doses of 250 and 500 mg/kg per oral, the ethanolic extract showed significant and dose-dependent antidiarrhoeal activity. The extracts also significantly reduced the intestinal transit in charcoal meal test when compared to Atropine sulphate (5 mg/kg). The results showed that the ethanolic extract of leaves of Indian Elm have a significant antidiarrhoeal activity and supports its traditional uses in herbal medicine[24].

6.5. Antitumor activity

The root of Indian Elm is being used as an important constituent for traditionally used herbal formulations for curing tumors[42]. The antitumor activity of ethanolic extract of leaves of *H. integrifolia* was evaluated against Dalton's ascetic lymphoma (DAL) in Swiss albino mice. The evaluated

parameters were tumor volume, tumor cell count, viable tumor cell count mean survival time and increase in life span to access antitumor activity. The extract given in concentrations of 250 & 500 mg/kg showed increase in life span of DAL treated mice and restored hematological parameters as compared with DAL bearing mice in dose dependent manner. The extract restored the mean survival time and decreased tumor volume count in treated mice. It suggests that leaves of Indian Elm possess potent anticancer activity and increases life span[25].

6.6. Adaptogenic effect

The adaptogenic activities of ethanolic extracts of *H. integrifolia* were studied using forced swimming endurance test and chronic cold restraint stress models. It was concluded that both 250mg/kg and 500mg/kg doses of ethanolic extract of stem bark showed dose dependent adaptogenic activity. This activity was compared with and found closer to the activity of 100mg/kg of *Withania somnifera*. These effects may be due to the presence of tannins, saponins, alkaloids, phenolics, flavanoids in the extract of Indian Elm bark as flavanoids, tannins and phenolics are mainly responsible for the adaptogenic activity[26].

6.7. Anti-diabetic effect

Methanol and petroleum ether extracts of leaves of *H. integrifolia* shows significant anti-diabetic effect. Diabetes was

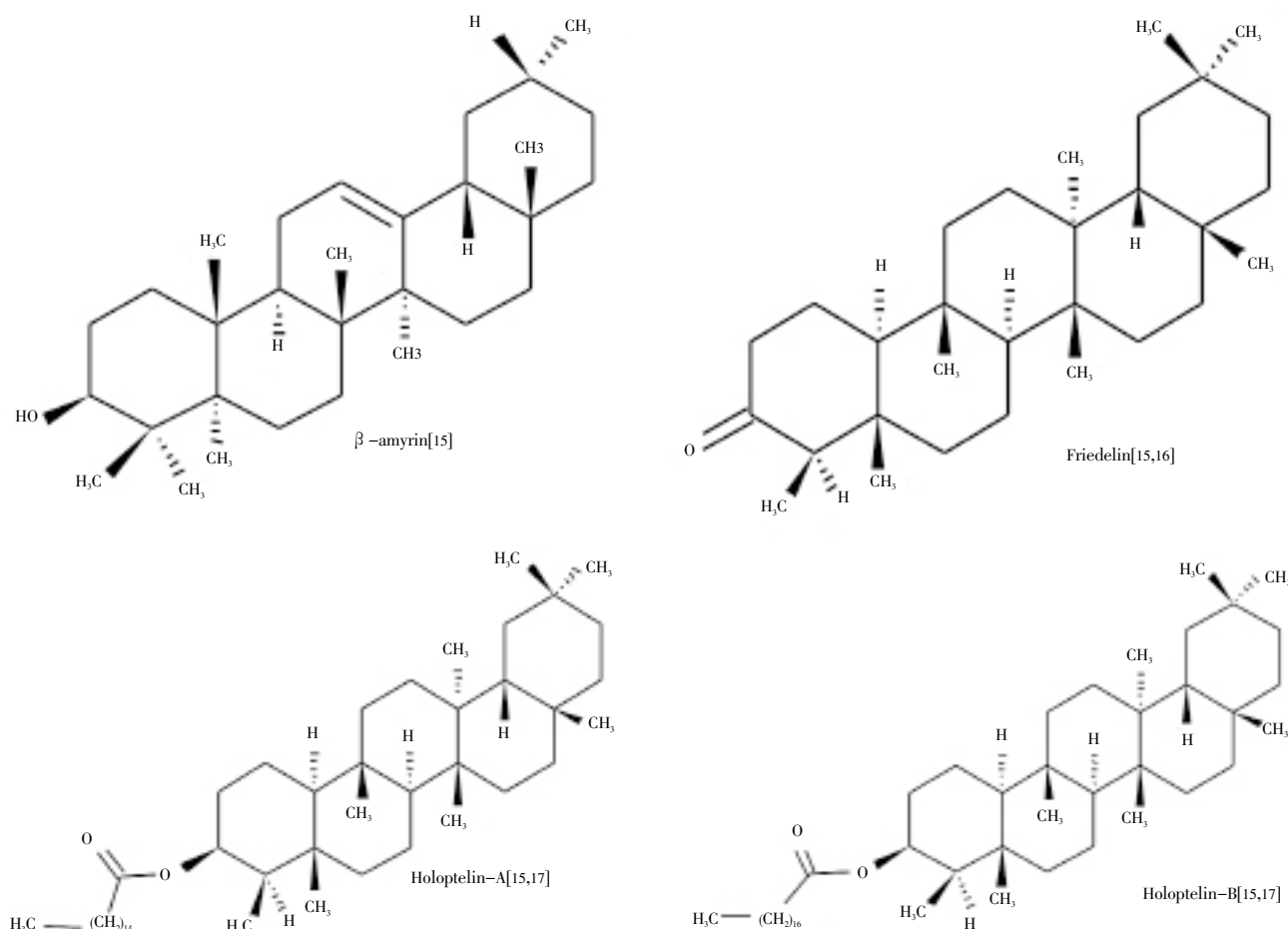


Figure 1. Chemical constituents of *H. integrifolia*.

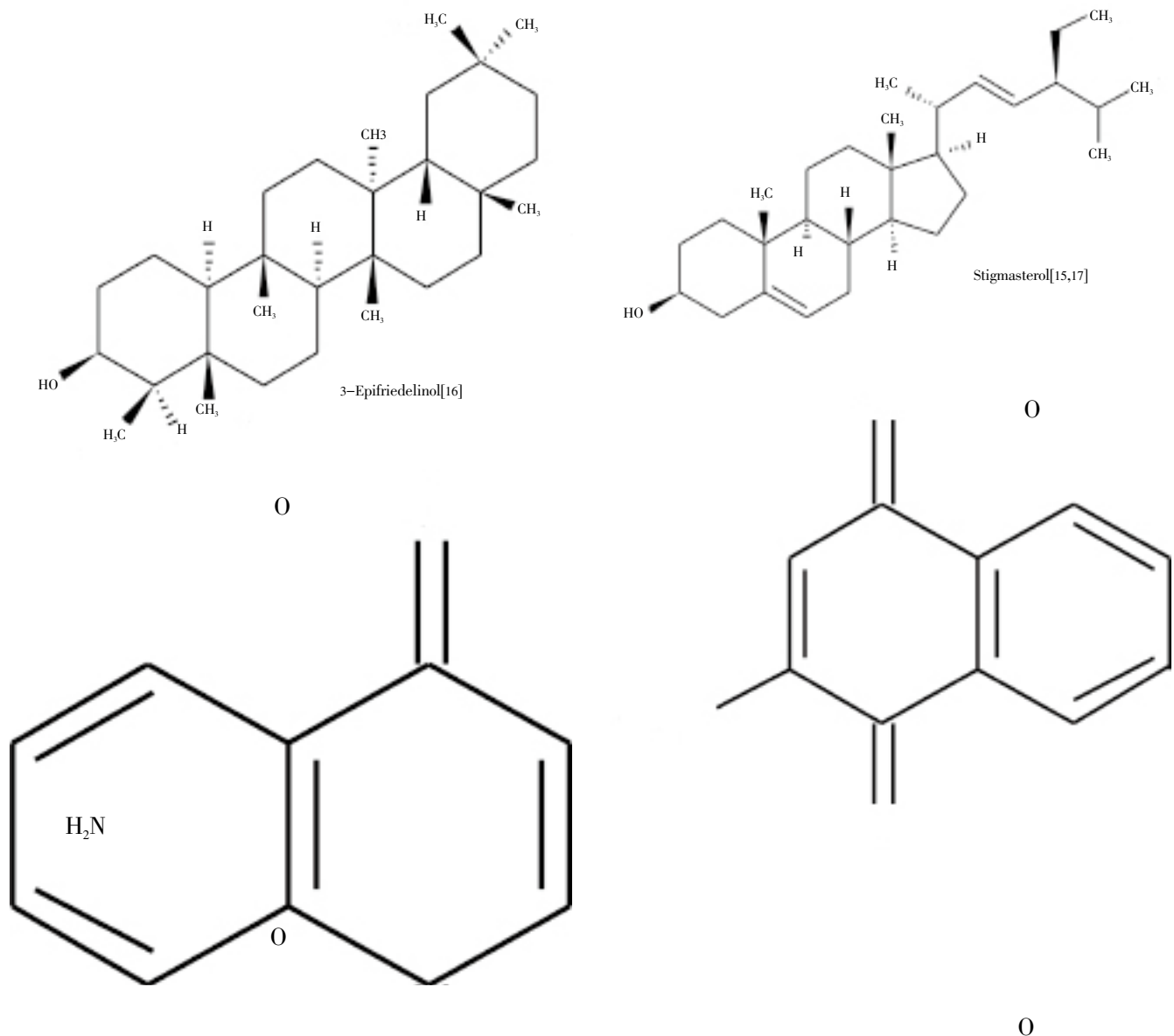


Figure 1. Chemical constituents of *H. integrifolia*.

induced by Alloxan and standard drug used for comparison with extracts was Glibenclamide. Petroleum ether extracts at the concentrations, 100 & 200 mg/kg whereas methanolic extract at concentration of 200 mg/kg showed significantly positive anti-diabetic activity[27].

6.8. Antioxidant activity

Ethanollic crude extract of stem bark of *H. integrifolia* traditionally used in Indian system of medicine was screened for its antioxidant activity using α -tocopherol as standard antioxidant. The free radical scavenging potential of the extract was evaluated by two different antioxidant methods; ferric thiocyanate method and thiobarbituric acid method. The ethanol extract was found to exhibit good antioxidant property, which is comparable to standard vitamin E, at a specific concentration[28,29].

6.9. Wound healing potentials

The Methanolic extracts of both stem bark and leaves of *H.*

integrifolia were found to possess wound healing potentials. In excision wound model, more than 90% wound healing was recorded in treated groups by 14 days of post surgery, where as only 62.99% was observed in the control group. In incision model, higher breaking strengths and higher hydroxyproline content in treated groups suggested higher collagen re-deposition than the control group. Finally, histopathology studies confirmed wound–healing activity of Indian Elm[29].

7. Medicinal use of various parts of *Holoptelea integrifolia*

The decoction of the bark of this tree is externally used in rheumatism[30]. Oral application of the bark is used to treat intestinal tumors[31]. Dried bark is useful as an oxytocic in pregnant ladies[32]. Decoction of the leaves is orally given to regulate fat metabolism. Leaves along with garlic are externally used to treat ringworm eczema and cutaneous diseases[33]. Paste of the stem bark is externally applied to treat the inflammation of lymph glands. Stem bark paste is externally

applied on the forehead of the patient suffering from common fever^[34]. Moreover, paste of the stem bark is externally applied in cases of ringworm and scabies. Stem bark acts as an anti-inflammatory agent specifically for eyes^[35]. In Nepal, bark is externally used to relieve rheumatic swellings. Bark and leaf paste of plant are applied externally on the white patches^[36]. Bark & leaves are bitter, astringent, acrid, anti-inflammatory, digestive, carminative, laxative, depurative, and urinary astringent. Useful parts are leaves that act as antioxidant, antidiarrhoeal, antimicrobial and anti-inflammatory agent and grinded leaves are used for alopecia and wounds. It pacifies vitiated kapha, hemorrhoids, skin diseases, dyspepsia, fever, postnatal cares, flatulence, colic and vomiting^[37].

8. Safety evaluation

H. integrifolia is an important pollen allergen of India and sensitizes almost 10% of the atopic population in Delhi. Out of 44 atopic Indian patients skin prick tested with its extract, 34% were found to be sensitized. All the patients sensitized to *H. integrifolia* also showed varying degrees of skin positivity to *P. judaica* pollen extract. ELISA and ELISA inhibition studies suggested strong cross-reactivity between *H. integrifolia* and *P. judaica* pollen. Par.j 1, the major allergen of *P. judaica*, was absent in *H. integrifolia* pollen. It concludes that *H. integrifolia* and *P. judaica* pollens share cross-reactive as well as unique epitopes^[38]. The pollen obtained from Indian Elm has got 8 allergenic proteins and 15 protein bands, which were detected by using *P. juliflora* hypersensitive pooled patient's sera when shared IgE binding bands were recognized in its extracts^[39]. A comparison between antigens and pollens collected from different sources has been also done which supports the statement that the tree comprises of allergenic principles^[40].

9. Use of plant in Herbal remedies

In ancient times, the tree was known for its important medicinal values. The decoction of sprouts for disorder of spleen and fever was prescribed by Charaka. Sushruta used it externally as a tearing agent for inducing bursting wounds, and internally for poisoning, fevers, jaundice, urinary disorders, migraine and internal abscesses. Decoction of fruit was used as emetic and for leprosy whereas oilseed was used as laxative. Puutika (*Holoptelea integrifolia*) has also been prescribed alongwith Chitraka (*Plumbago zeylencia*) and Shunti (*Zingiber officinale*) for the treatment of piles. It is also an important ingredient of Kaaranjadi churna (*Bhaavaprakasha*) which is taken with buttermilk for bleeding piles^[41]. The bark of tree is used as an important and necessary constituent of a polyherbal ayurvedic drug – Indukantha Ghritha as an adjuvant to cancer chemotherapy via immunomodulation The formulation is used as adjuvant to a chemotherapeutic drug, cyclophosphamide. The polyherbal formulation is effective in better reduction of the tumor and reversing the adverse effects of Cyclophosphamide. It is multipotent inducer of immune responses acting by way of stimulating leucopoiesis, and activating the non-specific and specific immune mechanisms of the host^[42].

10. Conclusion

Holoptelea integrifolia, the versatile medicinal plant is the unique source of various types of compounds having diverse chemical structure. A very little work has been done on the biological activity and plausible medicinal applications of these compounds and hence extensive investigation is needed to exploit their therapeutic utilities to combat diseases. A drug-development programme should be undertaken to develop modern drugs with the compounds isolated from *H. integrifolia*. Although crude extracts from various parts of the plant have medicinal applications from time immemorial, modern formulations can be developed after extensive investigation of its bioactivity, mechanism of action, pharmacotherapeutics, and toxicity with the help of proper standardization and clinical trials. The global scenario is now changing towards the use of nontoxic plant products having traditional medicinal use; development of modern drugs from the centuries-old knowledge on this tree should be emphasized for the control of various diseases. In fact, time has come to make good use of through modern approaches of drug development. A significant amount of research has already been carried out during the past few decades in exploring the chemistry of different parts of the plant, which generates enough encouragement among the scientists in exploring more information about this medicinal plant. An extensive research and development work should be undertaken on *H. integrifolia* and its products for their better economic and therapeutic utilization. Therefore this review might be helpful for scientists and researchers to find out new chemical entities responsible for its claimed traditional activities.

Conflict of interest statement

We declare that we have no conflict of interest.

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