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## Biological, chemical and pharmacological aspects of *Madhuca longifolia*

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### ABSTRACT

*Madhuca longifolia* (*M. longifolia*) is also known as Mahua belonging to the family sapotaceae family. *M. longifolia* is used in traditional and folklore system of medicine widely across India, Nepal, and Sri Lanka for its various pharmacological properties as in snake bites and in diabetes. Phytochemicals studies documented the different bioactive constituents, namely, glycosides, flavonoids, terpenes and saponins. The pharmacological studies proved that it possess wide range of biological activities such as antiulcer, antiinflammatory, antioxidant and antidiabetic activities. The toxicity studies reveal its non-toxic effect even at larger doses. Thus *M. longifolia* can be considered as a therapeutic agent for specific diseases. Scientific investigation on various isolated bioactive components and its efficacy on diseases proved the future usefulness of different species of *Madhuca*. This review summarizes the phytochemical, pharmacological, medicinal and non-medicinal uses of *M. longifolia*. Further exploration on *M. longifolia* for its therapeutic potential is however required for depth traditional knowledge.

## 1. Introduction

From ayurvedic era, herbal medicines are considered as the backbone of traditional system of medicine, as they have potent pharmacological effect, and hence are considered to be potential source of new drug development[1]. More than 75% of the population in developing countries still depends on traditional medicines. It has been found from scientific intervention that plant derived compounds show broad spectrum of efficacy and safety with comparatively lesser side effect as compared to synthetic molecules. Thus there is a need to increase screening of plants having medicinal value[2,3].

*Madhuca longifolia* (*M. longifolia*) also termed as mahua or butter nut tree (Mahva, Mohva, Mohua, Erappe, Ippa, Iluppai, Madhukah, Irippa), belong to family sapotaceae[4]. These are medium evergreen deciduous tree, distributed widely across India, Nepal, and Sri Lanka. Various parts of *M. longifolia* is used in traditional and folklore system of medicine, due to its various pharmacological properties[5,6]. Therefore it is also termed as universal panacea of ayurvedic medicine[7]. Different parts of *M. longifolia* has shown efficacy in the treatment of epilepsy,

diabetes, inflammation, bronchitis, ulcer and other diseases[8-10]. *Madhuca* oil extracted from seed is used as biofuel, edible fats and has shown good antioxidant and antimicrobial properties[10-12]. The flowers are well known for its reducing sugar content and have been used as cooling agent, astringent, demulcent and clinical study proves its activity in increasing the sperm count[13,14]. Leaves of *M. longifolia* are used in Cushing's disease and bronchitis and have antioxidant properties[14,15]. The barks have shown remedy for itching, swelling, snake poisoning and diabetes[16,17].

## 2. Botanical description

*M. longifolia* trees are normally 15–16 m high, with clustered leaves at the end of branches. The barks are brownish to yellowish grey in colour. Elliptic flowers are small, cream coloured and are produced in clusters[16,17].

Its taxonomy and nomenclature are as follows: Plant name: *M. longifolia*; Kingdom: Plantae; Phylum: Tracheophyta; Order: Ericales; Family: Sapotaceae; Genus: *Madhuca*; Species: *longifolia*.

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### 3. Traditional uses

In traditional and folklore medicine, *Madhuca* plays an immense role for the prevention and cure of many diseases. Different part shows versatile pharmacological activity. Flowers have been used for bronchitis, demulcent, diuretic, analgesic, as cooling agents and tonic. It is also used for treatment against helminths infestation as well as pharyngitis and also shows aphrodisiac activity. The bark also exhibits various pharmacological properties and is used for bronchitis, diabetes, rheumatism, bleeding, ulcer, tonsillitis, pharyngitis and spongy gums. It has also shown to be good remedy against swelling, snakebite poisoning, itching and fractures. Leaves of *Madhuca* have been used for the treatment of diabetes, Cushing's disease, bronchitis, rheumatism, haemorrhoids, cephalagia, intestinal diseases, and dermatopathy. The leaves are used as hepatoprotectants, for wound healing activity and as antioxidant. Seed fat has emulscent property, are used in hypoglycaemia, rheumatism, headache, in piles as a laxative, in skin disease and also as a galactogogue. *Madhuca* roots have shown its action against inflammation, and as antipyretic. The roots are also used in diarrhea, as antioxidant, and for the treatment of phthisis and scrofula[12,17,18].

### 4. Chemical constituents

The flowers mostly contain vitamin A and vitamin C[19,20]. Many phytoconstituents have been found in bark, which may be responsible for various activities[21,22]. It constitutes of oleanic

acids,  $\alpha$ -spinasterol,  $\alpha$ -amyrin acetate, erythrodiol monocaprylate betulinic acid,  $\alpha$ -terpeniol, and sesquiterene alcohol[23,24]. Fruits of *Madhuca* chemically consists of quercetin, dihydroquercetin,  $\beta$ -sitosterol, as well as  $\alpha$  and  $\beta$  amyrin acetates[25,26]. Main constituents of *M. longifolia* seeds are some amino acids like glycine, alanine, cysteine, leucine, and isoleucine. It also consists of arachidic, oleic, linoleic, myristic, palmitic and stearic acids[27-29]. Quercetin, Misaponin A and B are also found in seeds. Several bioactive constituents have been isolated and identified in the leaves of *Madhuca* like sitosterol, quercetin, 3-O-Lrhamnoside, stigmasterol, *n*-hexacosanol, *n*-octacosanol, carotene, myricitin, erthrodiol,  $\beta$  D glucoside,  $\beta$  sitosterol, 3  $\beta$  caproxyolcan 12 en 28-ol, 3 galactoside, 3-O-arabinoside, and xanthophylls[26].

### 5. Scientific proven uses of *Madhuca* species

Several scientist substantiated the traditional observation, through various experimental procedures. The bark and leaves are the frequently used parts. The ease of availability of leaves and bark helps in extensive use in traditional system of medicine. The presence of different phytoconstituents like alkaloids, terpenoids, saponins, and flavonoids is proposed to be responsible for various pharmacological actions. Scientific evaluations and study authenticates the ethnomedicinal and novel pharmacological effects. Different pharmacological findings obtained from various parts of *M. longifolia* have been tabulated in Table 1.

**Table 1**

Pharmacological studies of various plant parts.

Plant parts	Pharmacological activity	Extract	Dose	Experimental model	References
Bark	Anti-ulcer	Ethanollic extract	400 mg/kg	<i>in vivo</i>	[29]
	Anti-diabetic	Ethanollic extract; Methanollic extract	100–200 mg/kg; 75 mg/kg	<i>in vivo</i>	[16,30]
	Wound healing	Ethanollic extract	5% w/w	<i>in vivo</i>	[31]
	Hepatoprotective	Methanollic extract	200–400 mg/kg	<i>in vivo</i>	[32,33]
	Antioxidant	Ethanollic extract	100–300 mg/kg	<i>in vitro</i>	[27,28]
	Anti-inflammatory	Ethanollic extract	Data not available	<i>in vivo</i>	[34]
	Antimicrobial	Acetone, chloroform, ethanollic extracts	50–100 $\mu$ g/mL	Bacteria ( <i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i> , <i>Escherichia coli</i> ), fungi ( <i>Aspergillus oryzae</i> )	[7,17]
Flower	Analgesic	Alcoholic extract	64 mg/kg	<i>in vivo</i>	[35]
	Hepatoprotective	Methanollic extract	100–200 mg/kg	<i>in vivo</i>	[11]
	Anti-ulcer	Ethanollic extracts	100–300 mg/kg	<i>in vivo</i>	[36]
Leaves	Wound healing	Ethanollic extract	5% w/w	<i>in vivo</i>	[31]
	Cytotoxic	acetone, ethanollic extracts	200 $\mu$ g/mL	Ascites carcinoma cell lines	[37]
	Anxiolytic	Hydro alcoholic	100 mg/kg	<i>in vivo</i>	[38]
	Anti-hyperglycaemic	Hydroethanollic extract	300 mg/kg	<i>in vivo</i>	[39]
	Antioxidant	Ethanollic extract	500 mg/kg	<i>in vitro</i>	[14,29]
	Nephro and hepatoprotective	Ethanollic extract	500–750 mg/kg	<i>in vivo</i>	[40]
	Antimicrobial	Acetone, chloroform, ethanollic extracts	50–100 $\mu$ g/mL	Bacteria ( <i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i> , <i>Escherichia coli</i> ), fungi ( <i>Aspergillus oryzae</i> )	[7,8]
	Anti-helminthic	Methanollic extract	60 mg/mL	Earthworms	[41]
	Anti-ulcer activity	Aqueous extract	100–400 mg/kg	<i>in vivo</i>	[36]
	Neuropharmacological	Methanollic extract	50 mg/kg	<i>in vivo</i>	[38,42]
Seed	Anti-inflammatory	Ethanollic extract	10 mg/kg	<i>in vivo</i>	[43]
	Anti-fertility	Crude	10 mg/kg	<i>in vivo</i>	[44,45]
	Anticancer	Ethanollic extract; Methanollic extract	10 $\mu$ g/mL	HeLa cell lines	[7,8]
	Antioxidant	Methanollic extract	100–500 mg/kg	<i>in vitro</i>	[18]
	Alleviate pain	Oil	32 mg/kg	<i>in vivo</i>	[43]

### 5.1. Antioxidant activity

Many scientific works prove that free radicals including active nitrogen species and reactive oxygen species are the primary cause in initiation of cellular damage resulting pathological changes and many diseases. Studies of Roy *et al.* and Agrawal *et al.* had shown that the ethanolic extract of bark of *Madhuca* exhibits significant antioxidant potential[27,28]. The extract also averts the lipid peroxidation. Palani *et al.* studied the *in-vitro* free radical scavenging capacity of leaves and subsequently the *in-vivo* antioxidant assessment was carried out by glutathione and lipid peroxidation method is done for *in-vivo* assessment[40].

### 5.2. Anti-inflammatory activity

Inflammation is a complex response of a body to the external stimuli. Formation of inflammatory leukocytes in this process leads to the excess generation of free radicals which alters the cellular function and damages the organs by initiating and promoting the various diseases[46]. Several scientific studies on the ethanolic extract of *Madhuca* bark and seeds had proven anti-inflammatory activity. The crude ethanolic extract, saponin mixture and methanolic bark extract of *M. longifolia* extract has shown significant effect on inflammation induced by carrageenan as followed by the study of Agrawal *et al.* and Gaikwad *et al.* and there was size reduction in paw odema[34,43].

Similar research was carried out and has shown that the crude alkaloid extract of *Madhuca* species also exhibits potent anti-inflammatory activity. On the other hand, ethanolic extract and saponin mixture at dose of 10–15 mg/kg markedly reduces the rat paw oedema induced by formaldehyde, carrageenan and cotton pellet granuloma. However, a dose-dependent activity was found only on the carrageenan induced model[47]. The proposed mechanism of action was that constituents of *Madhuca* inhibit the prostaglandin synthesis as well as its mediators in synthesis. It may also act by reducing the intercellular cell adhesion molecule-1 expression which is induced by tumor necrosis factor  $\alpha$  [47].

### 5.3. Analgesic activity

The drugs used to prevent algesia are termed to be analgesic. Studies suggest that analgesic activity of *Madhuca* is mediated by central or peripheral mechanism. Experimental works of Chandra have demonstrated the analgesic activity of *Madhuca*[35]. Study of Chandra states that the alcoholic extract of flowers has good analgesic activity against hot plate and tail flick method showing central analgesic activity in dose-dependent manner[35]. The dose of 4–64 mg/kg showed a marked increase in analgesic efficacy on all nociceptive methods. The methanolic extract at dose of 50–200 mg/kg i.p markedly reduces acetic acid induced pain in a dose-dependent manner showing that the extract possessed peripheral analgesic activity[47]. Madlongoside, an isolated compound obtained from the *Madhuca* bark, showed a significant central analgesic activity when assessed by hot plate method.

### 5.4. Antipyretic activity

Elevation of body temperature from normal is termed as pyrexia. *Madhuca* also exhibits febrifuge action. Methanolic extract of aerial

part showed significant dose-dependent inhibition on temperature elevation when evaluated by Brewer's yeast induced pyrexia model[47].

### 5.5. Anti-ulcer activity

Peptic ulcer is chronic inflammatory condition referring to the sores and ulcer in the lining of stomach and duodenum[29]. Experimental works of Kalaivani and Jegadeesan had shown that ethanolic extract of bark possess significant antiulcer action[36]. Study of Mohod and Bodhankar had proven the antiulcer activity of aqueous extract of leaves. The crude ethanolic extract of seeds of *Madhuca* showed significant protective effect in pylorus ligation induced gastric ulcer model with a marked decrease in ulcer index as compared to vehicle[48]. This action may be due to its activity through prostaglandin.

### 5.6. Immunosuppression

A wide range of immunosuppressive drugs have now been adopted to control unwanted immune responses, particularly those giving autoimmune disease and transplant rejection[49]. The immunosuppressant activity of *M. longifolia* was also explored. Administration of methanolic extract of *M. longifolia* to murines was found to decrease the total WBC count and spleen leukocyte count significantly indicating that the extract could suppress the non-specific immune system. Moreover there was a decrement in the relative spleen weight and thymus weight which supports these findings[50,51].

### 5.7. Anti-hyperglycaemic activity

Diabetes mellitus is a metabolic disorder which is most prevailing problem and is increasing rapidly worldwide[52]. Investigation of Dahake *et al* and Seshgiri *et al.* showed the efficacy of a methanolic extract of *Madhuca* bark on hyperglycemia[16,53]. Bark extract of *M. longifolia* has shown significant antidiabetic activity in rats indicating its potential role in diabetes treatment and management. The antidiabetic activity may be due to its effect on glucose utilization[16]. Prashanth *et al.* proved the dose-dependent anti-hyperglycaemic activity of ethanolic extract of bark at dose 100–200 mg/kg against streptozotocin-induced diabetes in rats[30]. A study by Ghosh *et al.* showed that the hydroethanolic extract of *Madhuca* leaves had significant anti-hyperglycaemic activity against alloxan-induced diabetic rats[39]. The methanolic and ethanolic extracts of *Madhuca* seeds also exhibited the antidiabetic activity as studied by Seshgiri *et al*[53]. The authors postulated that these effects of phytoconstituents may be due to the altering of glucose utilization and insulin level. The *in-vitro* studies showed that extracts also effects the rat intestinal enzymes[54].

### 5.8. Neuropharmacological activity

Anticonvulsant effect of *Madhuca* has also been investigated. It is observed that at a dose of 400 mg/kg there is prolongation the onset of a seizure and also decrease in the seizure duration. It suggests that it may possess an active constituent entity having anticonvulsant nature which may help in the treatment or management of absence seizures. The *in-vivo* study proves the anti-convulsant potential of

*Madhuca* and thus supports its traditional use as an anti-epileptic agent[38,42].

### 5.9. *Madhuca* as anti-neoplastic

Chemoprevention is prominence effect of natural or pharmacological agents on reversing, blocking or delaying the onset of cancer with least adverse effect serving in the reduction of cancer related mortality[55]. Few scientific investigations also showed the chemopreventive action of *Madhuca* on human cancer cell lines[56]. The *M. longifolia* has also shown the cytotoxic potential against the carcinoma cell. *In-vitro* cytotoxic assay of *Madhuca* against the Ehrlichascites, carcinoma cell lines proves its anticancer potential. The crude acetone and ethanolic extract of stem and leaves are used for *in-vitro* study at different dose and showed cytotoxic effect at dose 200 µg/mL. The ethanolic extract showed better potency as compared to acetone extract[37].

### 5.10. Antihelminthic activity

The antihelminthic activity of *Madhuca* was evaluated by incubating *Ascardiagalli* with the alcoholic leaf extract. An investigation by Akhil *et al.* showed that methanolic extracts of *M. longifolia* at a dose of 60 mg/mL showed significant anthelmintic activities when compared to standard drug (Piperazine)[41]. The proposed mechanism by scientist is that it inhibits the glucose uptake and lactic acid content and decreases the glycogen content. Loss of motility was also observed, which may be due to inhibition of energy metabolism or ATP production[57].

### 5.11. Hepatoprotective and nephroprotective activity

Hepatoprotective effects of the ethanolic extract of *M. longifolia* bark was studied based on *D*-galactosamine induced liver hepatitis. The hepatoprotective effect of *M. longifolia* has been shown in earlier studies. The rise in serum glutamic-oxaloacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, and bilirubin levels induced by *D*-galactosamine administration was significantly reduced[32]. Its hepatoprotective activity might be due to its effect against cellular leakage and loss of functional integrity of the cell membrane in hepatocytes[27,32,33].

### 5.12. Wound healing

Investigation of Sharma *et al.* deduced the notable wound healing property of *Madhuca* as compared to standard betadine[31]. This activity may be due to the presence of constituents responsible for the promotion of wound healing. In this study, ether-benzene-95% crude ethanolic extract of leaves and bark of *M. longifolia* showed a marked reduction in wound healing time with respect to control in excision wound model. There was a significant increase in the rate of wound closure and epithelisation rate[31].

### 5.13. Anti-fertility activity

The crude seeds extract possess antifertility action when administration to male albino rats due to presence of bioactive entity. On administration of *Madhuca* seed extract to male albino rats,

marked changes were observed proving its effectiveness. It caused weight decrease of testis, epididymis, seminal vesicle, vasa deferens and ventral prostate which may be due to low plasma level of testosterone. Studies showed that decrease in weight of accessory sex organs was also observed indicating the atrophy of glandular tissue and also reduction in secretory cells thus reflecting the decrease level of testosterone. Thus the seeds of *Madhuca* has antifertility potentials in male albino rats[44,45].

## 6. Toxicity

Toxicity is an important parameter that needs to be evaluated in order to minimize the risk aspect associated with any herbal product. Sometimes plants are used directly or along with the formulated drugs which make it mandatory to access the toxic behaviour of plants. On parenteral administration, saponins are extremely toxic with respect to oral route[58]. The median lethal dose LD<sub>50</sub> dose of saponin extracted from *Madhuca* was found to be 1 000 mg/kg in mice on oral administration. The ethanolic leaves extract of *M. longifolia* were administered at a dose of 175 mg/kg for 14 d to male Wistar rats and morphological and histopathological changes were observed. There were no toxicity effect on liver and kidney upto dose of 2 000 mg/kg. The nontoxic effect of methanolic extract of *M. longifolia* bark has also been reported. It was found that bark extract were safe upto the dose level of 2 000 mg/kg[58,59]. However excess dose of mahua oil may lead to antifertility effect as reported by European Food Safety Association. Itsuggest that it causes testicular atrophy and degenerative changes in rats; whereas, no mutagenic or genetic toxicity has been reported in literature till date[60].

## 7. Non-medical and commercial uses

*M. longifolia* leaves are also proved as a useful adsorbent. Studies showed that *M. longifolia* leaves along with polyaniline adsorbs cadmium and lead from water thus, it can be used for purification. Some studies also reveals the anticorrosive nature of its leaves. It protects the mild steel in 1 mol/L HCl solution from the corrosion[61,62].

Leaves of *M. longifolia* are fed on moth *Antracea paphia*, which produces Tassar silk, a wild silk used commercially[63]. Flowers are used for distilled liquor preparations[64]. Seeds kernel yields mahua oil which is utilized for cooking and fuel purposes[65].

## 8. *M. longifolia* in preclinical and clinical studies

An open clinical trial was performed on 40 subjects with oligospermia to study the efficacy and safety of Chandrakanthi chooram. Chandrakanthi chooram is a formulation consisting of 25 ingredients including flowers of *M. longifolia*. The primary outcome of this study was sperm count, its morphology and its motility[66]. Clinical studies and surveys on *M. longifolia* has also been performed for its anti-venom activity, dyslipidemia in Santhal tribes. The study suggest that regular consumption of *Madhuca* drink by Santhal tribes improves their blood sugar and lipid profile[67]. Different parts of *M. longifolia* have been tested preclinically for many pharmacological activities like hepatoprotective, anti-epileptic, antimicrobial,

analgesic, and anti-diabetic[6,8].

Kutajarista is one of the ayurvedic marketed products containing *M. longifolia* which is used for the treatment of amoebiasis and bacterial dysentery, amoebic dysentery, and blood diarrhea[68]. Preclinical study of kutajarista was performed in male Sprague Dawley rats and the dose of 40 mL/kg was administered. From the experiment, it was deduced that it cannot be administered for chronic period at higher dose as it will alter the biochemical profile[69].

## 9. Conclusions

According to scientists, medicines obtained from medicinal plants are best alternative to combat the diseases, as they have immense potential to treat the diseases with least side effect and with high safety and efficacy. They are the strongest contender as alternative treatment and for the adjuvant therapy. *M. longifolia* is one of most versatile plants which has been used for medicinal as well as to household purposes. All parts of plants had been used in the prevention and treatment of diseases like diabetes and inflammation. Different extracts have been found possessing pharmacological activity. Therefore, it is also termed as “Universal panacea in ayurvedic medicine or Paradise tree for tribals”.

In this review, phytochemistry and pharmacological aspects of *Madhuca* has been highlighted. Further exhaustive work is required, because the literature shows limited research in several areas to understand and reveal the mode of its pharmacological activities. In addition, isolation, purification and identification of new entities from *Madhuca* species are required as it may help further to establish the application of isolated compound in treatment of various acute and chronic diseases and provide more assurance in application of isolated compounds.

## Conflict of interest statement

We declare that we have no conflict of interest.

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