ABSTRACT

Indian plants have been the predominant source of medicines throughout the vast majority of human history. For centuries, indigenous Indian cultures have used herbal medicine traditionally to treat a myriad of maladies. One of the most versatile and infrequent concerning its phytochemistry and pharmacology is Morinda pubescens (M. pubescens) plant discovered by J. E. Smith. Interest in this plant has been renewed in recent years, first from its identification as a chemopreventive agent for wound healing cancers and subsequently from reports that it has phytochemicals contributing to antimicrobial, antioxidant, hepatoprotective and plant growth stimulatory effects. Although skepticism concerning its standardization, a growing body of in vivo evidence indicates that M. pubescens plant has protective effects in rodent models of stress and disease. In this comprehensive review, the ethnomedicinal reports on the M. pubescens plant demystified with both in vitro and in vivo shreds of evidence which would be further tempting to reveal the book buried facts of this traditional medicine through modern scientific approach. In the knowledge of our literature survey, this is the first review to be done on the M. pubescens plant from overall Tamil Nadu.

Keywords: Morinda pubescens, Traditional use, Phytochemistry, Therapeutic values, Ethnomedicinal plant

INTRODUCTION

Morinda pubescens (M. pubescens) plant discovered by J. E. Smith is a Rubiaceae species, with extensive distribution in Southern Asia: it displays a full repartition in westwards to eastern slopes of Ghats and predominates the arid regions of Southern Deccan and Southern Travancore. According to the plantlist.org, Morinda pubescens is the unresolved name to refer to this plant which later accepted as a synonym of Morinda coriacea Buch Ham. The other scientific names such as Morinda tinctoria (Roxb), Morinda tomentosa (Roxb) relegated to synonymy [1]. Commonly, the plant is described under many different names including the Morinda tree, Brime stone tree or wild ash root [2-4].

Traditionally, all parts of the plant especially the leaves and root, are widely used by indigenous people for medicating a full spectrum of ailments and diseases ranging from the topical application to heal wounds, inflammation, gout and stomach pains to oral administration for diabetes, malaria, fever, rheumatism and infectious diseases. Several in vitro and in vivo studies provided diverse evidence supporting most of the traditional therapeutic claims of M. pubescens. Bioassay-guided phytochemical screening of M. pubescens extracts led to the identification of afluence of bioactive principles such as flavonoids, alkaloids, phenolic acids with noteworthy therapeutic implications. However, besides extensive use in folk medicine, there are numerous other possible applications of M. pubescens; the most investigated being as green manure and green dye adsorbent.

With the upward popularity of M. pubescens, there are significant concerns about its efficacy, toxicity, and allergenicity. Therefore, a comprehensive review of the current understanding of this plant is needed to provide a source of information for anyone potentially interested in, but also to pinpoint research gaps for future investigation. To this end, we systematically retrieved and critically summarized the extant literature on the pharmacology and toxicology of M. pubescens and its relationship with local/traditional use and phytochemistry. The botanical characterization of M. pubescens performed as well.

Morphological features

M. pubescens can be gaudily depicted as a flowering shrub-like species, growing up to over 6-10 cm high. The flowers are white, and several together united at the base into a small head. The head (capitulum) is 3.5 cm long and appearing leaf-opposed or subtended by reduced leaf. The capitulum bears white corolla (15 mm), short-limbed calyx, oblong lobes and anthers (6-8 mm and 5 mm), and stigma two-lobed with styles (18 mm). Flowering occurred in March, and each mature stem can bear several flowers. M. pubescens leaves (6-20 cm) can be described as elliptic to linear-lanceolate or obovate, petiolate (2.5 cm) and alternately to oppositely arranged. The plant has branchlets often with a characteristic thin pallid to yellowish bark: it is usually glabrous above and pale in the inferior part possessing fissured thick bark. Drupes are coalescent into ovoid fleshy head possessing oblong seeds, stony pyrenes, and oblong seeds. Young fruits occur in April with green color and mature in June with black [5-8].

Ecogeographical features

Geographically the M. pubescens distribution extends from Southern Deccan and Carnatic to Southern Travancore in dry forests whereas wet wards to eastern slopes of Ghats at low levels [5]. Reportedly, the plant is native to Southern Asia and then spread to other parts of Asia such as Sri Lanka, the Malay Archipelago, and the drought-prone area of Omanabad, Andaman, and the Nicobar Islands. As well as in Bandar ban, Chittagong and Dinaipur in Bangladesh [6, 9]. In the mainland of India, where it grows wild as a weed in roadisides, wastelands, crop fields, and homesteads along the coastal areas of Jhabua, Kerala, Karnataka, Pune, Maharashtra, and Tamil Nadu. Indeed it has also found to be cultivated in Boda hills, Eastern Ghats of Kolli hills for the medicinal purpose [8, 10].

Ethnopharmacological relevance

For centuries, indigenous Indian cultures have used herbal medicine traditionally to treat a myriad of maladies. One of the most vital and infrequent ancient book buried ethnomedicinal plant is M. pubescens [11, 12]. Ayurveda, Siddha, Unani, Tibbi, and Amchi are natural systems of medicine which have writings on the use of Morinda plant [13, 14]. Perhaps, there are reports that South Indian ancestors perceived the therapeutic values of M. pubescens and used in Siddha and Ayurveda medicinal systems [15]. Besides, as early as 1605, in Kerala, it has been long recognized as traditional medicine named “Paphanak.” Moreover, complex traditional formulations,
"Paphanadi tailam" and "Paphanadi ghrtam" prepared from the plant used in the treatment of different ailments [5, 16]. It was traditionally used as folk medicine by tribes as astringent and for curing rheumatism, cholera, hypertension, diabetes, blood cleansing and treatment of renal toxicity symptoms [17-19]. Furthermore, the bark used in the treatment of eczema, fever, ulcers, and leaves for digestive disorders in children [20]. Root is bitter, styptic, constipating, anti-inflammatory, antibiotic, alycetic and tonic for physical obstructions, renal dropy, and ascites whereas leaves serve as the excellent fomentation for haemorrhoidal pains and piles [5, 21]. Indeed, reports also have shown the extract of its leaves, stems, and fruits used in the treatment of gastropathy, gastralgia, stomach ulcer, wounds, gout, inflammation, hernia, sarcocele, and fever [22-24]. Stem bark decoction has been used orally by rural people of Kurnool District as well as Seshachalam hills located at Andra Pradesh, locally named, Mulugu chettu and Togaru chettu to cure rheumatic diseases and jaundice [25, 26]. Leaf paste has been used by local people of Maharashtra and tribal people of Tirunelveli hills in southern India for healing wound among various medicinal plants [27, 28]. Besides, Siddha healers of Katpadi taluk in the Vellore district of Tamil Nadu prescribe leaf preparations such as Nuna tailam and Nuna kadugu for leucoderma [29]. Moreover, the leaf boiled in water and the decoction is administered to children for two days to cure dysentery by villagers around Gin gee hills of Viltapuram District [30]. The traditional uses of M. pubescens have been summarized in table 1 as follows:

### Table 1: Traditional remedial values

<table>
<thead>
<tr>
<th>M. pubescens plant part</th>
<th>Mode of preparation</th>
<th>Therapeutic effect</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaves</td>
<td>Infusion, Poultice, Decoction, paste</td>
<td>Children's digestive disorder, haemorrhoidal pains, and piles, wound healing, dysentery, leucoderma</td>
<td>[20, 5, 27-30, 77]</td>
</tr>
<tr>
<td>Bark</td>
<td>NS</td>
<td>Eczema, fever, ulcers</td>
<td>[40]</td>
</tr>
<tr>
<td>Root</td>
<td>Infusion</td>
<td>Anti-inflammatory, visceral obstructions, renal dropy and ascites</td>
<td>[5, 21]</td>
</tr>
<tr>
<td>Leaves stem and fruits</td>
<td>NS</td>
<td>Gastropathy, dyspepsia, diarrhoea, stomach ulcer, wounds, gout, inflammation, hernia, sarcocele and fever</td>
<td>[22-24]</td>
</tr>
<tr>
<td>Stem bark</td>
<td>Decoction</td>
<td>Rheumatic diseases and jaundice</td>
<td>[25, 26]</td>
</tr>
</tbody>
</table>

### NS: not specified

#### Phytochemistry of M. pubescens

Chemical studies of M. pubescens leaves in different solvents have identified major active compounds, para-hydroxy quinine [31], octonyl glucopyranose, phytol, hexonyl glucopyranose, phytolacetate, artenol, identified major active compounds, para-hydroxy quinine [31], octonyl glucopyranose, phytol, hexonyl glucopyranose, phytolacetate, artenol, identified major active compounds, para-hydroxy quinine [31], octonyl glucopyranose, phytol, hexonyl glucopyranose, phytolacetate, artenol, identified major active compounds, para-hydroxy quinine [31], octonyl glucopyranose, phytol, hexonyl glucopyranose, phytolacetate, artenol, identified major active compounds, para-hydroxy quinine [31], octonyl glucopyranose, phytol, hexonyl glucopyranose, phytolacetate, artenol, identified major active compounds, para-hydroxy quinine [31], octonyl glucopyranose, phytol, hexonyl glucopyranose, phytolacetate, artenol, identified major active compounds, para-hydroxy quinine [31], octonyl glucopyranose, phytol, hexonyl glucopyranose, phytolacetate, artenol, identified major active compounds, para-hydroxy quinine [31], octonyl glucopyranose, phytol, hexonyl glucopyranose, phytolacetate, artenol, identified major active compounds, para-hydroxy quinine [31], octonyl glucopyranose, phytol, hexonyl glucopyranose, phytolacetate, artenol, identified major active compounds, para-hydroxy quinine [31], octonyl glucopyranose, phytol, hexonyl glucopyranose, phytolacetate, artenol, identified major active compounds, para-hydroxy quinine [31], octonyl glucopyranose, phytol, hexonyl glucopyranose, phytolacetate, ar

#### Antimicrobial activity

Microbial diseases continued to be significant threats to the world regardless of efforts and progress in developing modern medicine [49, 50]. Currently, the ever-increasing threat from drug-resistant microbes's calls for a global effort to search on novel solutions [51] which can also base on natural products from plants that are selected by documented ethnomedicinal use [53]. In this regard, recently many studies have been carried out with the aim of highlighting the capacity of many extracts of M. pubescens to prevent the growth of microbial strains due to the presence of active antimicrobial agents such as phenols, triterpenoids, and tannins. Tyagi et al., (2015) showed the significant antibacterial effect of ethanol and chloroform extracts of M. pubescens bark against the selected microbial strains such as S. aureus, B. cereus, E. coli, P. aeruginosa. Indeed aqueous extract was ineffective against all tested microbes compared to the effect of reference standard ofloxacin [9]. Besides, the wood extract of M. pubescens used as a dye in fabric at pH 8, potentially inhibited S. aureus and C. albicans comparably no zone formation noticed in the cotton fabric without stain [53]. Moreover, acetone extract of M. pubescens fruit inhibited most of the salivary microflora samples with a maximum zone of inhibition when compared with definite standard chlorhexidine. The authors suggested the extract as a therapeutic remedy for the hard tissue diseases of the oral cavity in children [54]. On the contrary, other authors reported little or no inhibitory effect on micro foulers such as Klebsiella sp., Aeromonas sp., Pseudomonas sp., Bacillus sp., by ethanol extract of M. pubescens leaves [55]. Furthermore, studies on M. pubescens leaves, and stem showed the highest antimicrobial activity in solvents such as ethanol against S. aureus and E. coli [56]. Besides petroleum ether, chloroform, methanol, water against S. aureus, B. s. ubtilis, P. aeruginosa, K. pneumoniae, and S. typhi among which acetone exhibited maximum inhibition against P. aeruginosa comparable with antibiotics tetracycline and chloramphenicol [45, 46]. Indeed, a recent study has shown that silver nanoparticles synthesized by M. pubescens roots were found to be highly toxic against bacterial strains such as S. aureus and E. coli at an increasing dose of concentration. The authors concluded that the antibacterial activity resides on the large surface area of nanoparticles for interaction with microbes [57].

#### Pharmacological evidence

Studies conducted on cell lines, microorganisms, and model animals of human diseases showed a broad spectrum of bioactivities for different parts and varying extracts of M. pubescens. The antidiabetic, antioxidant, anticancer, antimalarial and wound healing effects do stand out, but there is also a stunning array of other relevant biological effects. Below are critically summarized the main findings of the pharmacological activities of M. pubescens retrieved from the literature.

- **NS:** not specified

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The chloroform extract of *M. pubescens* fruit when tested on the strains *B. oryzae*, *F. udum*, *C. lunata*, *P. infestans*, *R. solani*, and *M. phaseolina* induced 100% inhibition in *R. solani* and *B. oryzae* through the reduction of new and dry weights of mycelial growth. Besides, extract had significant Minimum Inhibitory Concentration (MIC) in the range of as well as reduced fungal respiration rate as compared with control [12]. Whereas, the maximum zone of inhibition observed after the treatment of *C. albicans* and *A. niger* with ethanol and chloroform extracts from *M. pubescens* bark compared to the effect of the reference standard [9]. Moreover, the chloroform extract of stem and leaf displayed significant antifungal activity against a wide range of fungal strains with the maximum zone of inhibition in *R. oryzae* [45].

Antimalarial activity

Malaria is one of the most significant human parasitic diseases in the world and has claimed more children life worldwide than any other conditions. Since there are no adequate vaccines and plant drugs, have been employed for centuries. The need for the assessment of traditional anti-malarials is urgent, particularly in the light of widespread resistance of malarial strains to the operationally useful present day antimalarials. In this regard, the filter-sterilized ethanol extracts of *M. pubescens* leaf and bark investigated for antimalarial activity against *P. falciparum* displayed significant antimalarial activity [58]. On the contrary, the methanol extract of *M. pubescens* leaves was found to be ineffective for the larvicidal activity of *C. Quinquefasciatus* [59].

Radical scavenging activity

Nowadays there is frequent and increase in search for new compounds from medicinal herbs with antioxidant potential which inhibit free radicals responsible for oxidative damage to biomolecules such as lipids, proteins, and nucleic acids, which eventually causes diabetes, aging, injury of kidney, liver, and cancer in humans. Besides the antioxidant vitamins such as vitamin E and C, there are other compounds as vitamin E and C, there are other compounds as artenol, linoleic acid, caproic acid, caprylic acid, β-sistosterol, campesta-

Anticancer activity

Cancer is a significant prevalence of health concern and treatment poses a problem and is frequently unproductive. As such, continuous efforts in the search for novel agents and therapies to perk up survival are obligatory. A substantial number of plant extracts and isolated compounds possess significant anti-proliferative or pro-apoptotic effects [68]. By supporting the arawal, extracts of *M. pubescens* of Rubiaceae family has been shown to sensitize liver and lung tumor cell lines, but not Vero human fibroblasts. The critical mechanism by which *M. pubescens* could combat tumor formation is the induction of cell cycle arrest and apoptosis. Apoptosis is a highly complicated and elaborate mode of cell death that requires precise regulation of different intracellular signaling pathways to ensure the continuation of the transmission of the death signal [69]. The characteristic executioners of apoptosis are intracellular cysteine proteases called caspases, stored in most cells as zymogens or pro-caspases [70]. These caspases are activated by intrinsic and extrinsic pathways which later mediate cleavage of proteins which are essential for cell viability that result in morphological hallmarks of apoptosis [71]. On this subject, a recent study has shown chloroform extract of *M. pubescens* leaves, and its isolated compound crocin diphenyl pyrrolidinone showed significant anti-proliferative activity against caspase-3 and caspase-9 protein levels to 1.3 folds than the healthy cells and augmented p53 expression in human hepatoma HepG2 cells [32]. Furthermore, hexane extract of *M. pubescens* leaves, and the isolated compound hyoscyamine dose-dependently decreased the cell viability in HepG2 cells. Besides, hyoscyamine induced caspase-3 mediated apoptosis. Up-regulation of p53 gene expression provided the cue for apoptotic activity of hyoscyamine [53]. Moreover, the antiproliferative and pro-apoptotic effects of an ultra-protein extract of *M. pubescens* leaves in A549 lung tumor cell line extensively documented in vitro. And that supported by the increase in apoptosis resulting in the cytoplasmic and chromatin condensation, nuclear breakdown, and shrinkage of the cell. Followed by fragmentation into membrane-bound apoptotic bodies, eventually subjected to rapid phagocytosis by surrounding cells, whereas similarly treated standard Vero cell line had shown 98% cell viability with no apoptosis induction [72]. The anti-proliferation activity again proved with another study as *M. pubescens* leaf synthesized nanoparticles decreased the cell viability of Human Epithelium cells of liver cancer in MTT assay [60].

Hypoglycemic activity

Plants, herbs and their derivatives owing to their broad spectrum of active principles signifying numerous chemical compounds hold promising potentials for their reliable usages in the treatment of diabetes. *M. pubescens* is one such candidate who has listed as traditional Indian herbal anti-diabetics [85]. In this regard, scientific studies prove the anti-diabetic effect of *M. pubescens*. *M. pubescens* fruit extract administered orally to alloxan induced diabetic female rats significantly reduced the blood glucose levels compared to control non-diabetic rats by alloxan. Besides, there was a significant reduction of biomarkers such as reduced GSH, GST, SOD, CAT in the liver and kidney of diabetic rats as compared with non-diabetic control rats. The authors also observed weight loss in diabetic rats as compared to non-diabetic control animals, whereas treatment with *M. pubescens* alcoholic extracts improved the animal weight as compared to diabetic animals [12]. *M. pubescens* is showing promising in vivo results as a natural anti-diabetic agent, the however safe range of doses and proven efficacy studies needed for further preclinical studies.

Prophylactic activity

Nowadays, studies have raised the possibility that *M. pubescens* might be useful in protecting against liver and kidney damage. Rats given the oral administration of *M. pubescens* fruit extract for 21 d followed by intraperitoneal injection of D-GaIN to induce liver damage prevented the increase of LPO and alteration in iron content in experimental animals. Besides, considerably increased the levels of GSH and vitamin E when compared to D-GaIN intoxicated animals. Pre-treatment with fruit extract to rats reduced the elevated levels of serum marker enzymes and also improves the levels of fucose, ceruloplasmin, and uric acid which were further confirmed by histopathological studies. The authors concluded that hepatoprotective potential might be due to the presence of alkaloids and phenols [73, 12]. In recent research, gentamicin-induced acute renal failure in male Wistar rats treated with water extract of *M. pubescens* bark and its ethyl acetate fractions once daily for ten days reversed the altered level of biochemical markers. And other parameters such as renal biomarkers creatinine, urea, uric acid, BUN, albumin, protein, and other parameters are kidney weight, body weight, urine volume and histopathology of the kidney to the near normal levels. The authors concluded that the ethyl acetate fraction exhibited the highest nephroprotective activity compared to water extract [74].

Wound rejuvenating activity

Traditional plants are fertile ground for materials used in wound healing and antiocoagulation. Myths in India use a large number of plants for treatment of cuts, wounds, ulcers, inflammation, and
burns. Plant extracts became popularized because of the lack of unnecessary side effects and effectiveness as crude preparations [75, 76]. Perhaps, reports are supporting that the topical application of leaf paste of *M. pubescens* has potential wound healing activity among various medicinal plants [77]. In this outlook, a study on chloroform extract of *M. pubescens* fruit investigated for its wound healing potential in male Albino rats. The extract showed a wound healing activity at a concentration-dependent manner through significantly increasing wound diminution and fresh hair growth in the entire wounded area within 15 d in animals treated with the compared with only 60% contraction without hair growth in olive oil treated control rats. The results suggested that mechanisms underlying this effect were fibroplasia, collagen synthesis, and wound contraction [78]. Furthermore, study with ointment prepared from *M. pubescens* roots extract in ethanol has been evaluated in Swiss albino mice using the wound excision model. The extracts exhibited faster-wound healing activity with increasing concentrations when compared to standard Povidone-iodine. The authors concluded that the wound healing property of *M. pubescens* might be due to its enhancing epithelization and collagen deposition mechanisms [79].

Toxicology

### CONFLICTS OF INTERESTS

All authors have none to declare.

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