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Medicinal Applications, Phytochemistry and Pharmacology of *Hymenodictyon excelsum* (Roxb.) Wall: A Review

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Abstract

Hymenodictyon excelsum Roxb. Wall (Rubiaceae) has been used in traditional medicine for a wide range of ailments related to digestive, endocrine, reproductive, and respiratory systems. Additionally, it is also used in gastrointestinal tract and urinary tract infection. This review gathers the fragmented information available in the literature regarding morphology, ethnomedicinal applications, phytochemistry, and pharmacology of *H. excelsum*. Relevant information on *H. excelsum* was compiled from electronic databases such as Academic Journals, Ethnobotany, Google Scholar, PubMed, Science Direct, Web of Science, and library search. Worldwide ethnomedical uses of H. excelsum are recorded which have been traditionally practiced for the treatment of different types of health disorders. Phytochemical research have led to isolation and characterization of different types of bioactive compounds in H. excelsum and pharmacological studies have shown some promising pharmacological activities. *H. excelsum* has emerged as a good source of traditional medicine for the treatment of various ailments. It is a promising candidate in pharmaceutical biology for the development/ formulation of new drugs and future clinical uses.

Keywords: *Hymenodictyon excelsum*; Traditional medicinal uses; Phytochemistry; Pharmacology

Introduction

Hymenodictyon is a genus of flowering plants in the family Rubiaceae comprising of about 30 species. *Hymenodictyon* was named by Nathaniel Wallich in 1824 in an addendum to William Roxburgh's Flora Indica, an edition published by Carey and Wallich after Roxburgh's death. The generic name is derived from two Greek words, hymen, 'membrane', and diktyon, 'net'. It refers to the wing that surrounds each seed. Molecular phylogenetic studies have shown that *Hymenodictyon* is paraphyletic over the Madagascan genus Paracorynanthe. In *Hymenodictyon* and *Paracorynanthe*, the stipules bear large deciduous glands called colleters. The corolla tube is narrow at the base, gradually widening toward the apex. The fruit is a woody capsule. The species belonging to this genus are having oppositely arranged serrated leaves, small, clustered flowers and many seeded capsules. The genus comprises trees and shrubs distributed mostly in tropical and sub-tropical parts of Asia and Africa [1]. Some of the species are commercially useful for tanning and dyeing purposes while remaining are only useful for the timber wood.

Hymenodictyon excelsum Roxb. Wall. syn *H. orixense* Roxb. Mobb. belonging to the family Rubiaceae and commonly known as Bhorsal, Kukurkat, Bhaulan, Bauranga, Pottaka, Kusan, Kadambu (India), Kuthan (Burma), and Lala (Thailand), is a medium to tall growing, deciduous tree, 10-12 m in height, usually with a straight cylindrical bole, a rounded crown, grey-brown-tinged bark, oblong, ovate, or elliptic, glabrous green leaves, greenish-white, fragrant flowers and ellipsoid capsules containing winged seeds. Bark is mostly furrowed and rough, 10-20 cm thick, exfoliating in irregularly shaped, softish scales. Stipules are linear to lanceolate or ovate to lanceolate, c. 15 mm long, apex acuminate, deciduous, pubescent. Leaves are deciduous; petioles 10-60 mm long, green-white-tinged, puberulous; blades ovate, elliptic to lanceolate or oblong to lanceolate, pale green above, lightgreen-tinged beneath, glabrous to puberulous above, pubescent to puberulous beneath, membranaceous, apex acuminate, base acute to cuneate; margins glabrous, ciliate; midribs drying yellow-red-tinged, sometimes brown-black-tinged, puberulous above, puberulous to pubescent beneath;

secondary veins seven to ten pairs per side, colour unknown, inconspicuous above, conspicuous beneath, glabrous; without domatia.

Leaves are ovate-elliptic or almost rounded 10-24 cm long, 7-12.5 cm wide, pointed at both ends, and hairy on both surfaces. Flowers whitish or yellowish green are stalked, fragrant, about 0.5 cm long, and borne in terminal, drooping panicles. Capsule is oblong-elliptic; Corolla-tube is slender and 5-lobed. Fruit, a capsule, is ellipsoid, 2 to 2.5 cm long, growing on recurved, thick pedicels 5 to 12 mm long. Seeds are many, flat, winged all around the margin, about 1 cm long, including the wing [2-4]. The wood of *H. excelsum* is soft and has limited use, mostly for boxes. The wood is used as planks in building houses and boats; for making boxes, packing cases, pencils, toys model making and matches [5]. In India, it is used as a cheaper grade of wood for making furniture, wrapper bobbins and wool boards. The bark obtained is useful for tanning purposes while leaves are useful for dyeing and as fodder for cattle [6].

Distribution

H. excelsum is mainly found in secondary forests at low altitudes, often about cliffs near the sea. It is distributed throughout Oceania and Southeast Asia. It occurs in Nepal, Burma, Java Bangladesh, Cambodia, Indonesia, Malaysia, Thailand, Philippines, Vietnam and Philippines. It is distributed throughout India, and in the Himalayan region of India [7-8] except Jammu and Kashimi [2].

Traditional Medicinal Uses

Primarily bark and leaves of *H. excelsum* have been used in traditional medicine systems across the world for treatment of various ailments. bark exhibits wide spectrum of medicinal value. Various plant parts reported to be used in burning sensation in chest, emaciation, and carbuncle and useful in fever, sores, smallpox, atrophy and lactation complaints. It also increases taste and appetite. Decoction used in diarrhoea [9-10]. In traditional medicine system bark and leaves of the plant are attributed to various medicinal properties. Bark has been used as an astringent and febrifuge and for treatment of fever and tumours, while the leaves are used to treat ulcers, sialitis, sore throat, tonsillitis and inflammatory conditions [11-12]. The Inner bark of the plant is traditionally used as febrifuge, astringent and antiperiodic, especially for tertian ague. It is also used as a substitute for quinine and for night blindness. The crushed and powdered bark is orally used for treating hemorrhoids (piles). According to Ayurveda, bark is hot, pungent, bitter, increases taste and appetizer. It is good for throat and cures all tumours. In India, the bitter bark is used as astringent and febrifuge; root, wood and stem-bark used as for fevers and to relieve thirst. It is also known for its wound healing property [13-14]. As antiperiodic, bark used as substitute for cinchona bark. Inner bark is bitter; outer layer of the bark is tasteless. Its bark is used as an astringent and febrifuge, while its leaves are used to treat jaundice, fever, ulcer, sialitis, sore throat, tonsillitis, and inflammation [15]. Powder of the root is given with cow's milk in bodily inflammation. Bark is used as powder to kill tapeworms and to cure dysentery [16].

Phytochemistry

H.excelsum has been investigated for its considerable number of important phytoconstituents [17-22]. The chemical constituents previously reported to be found in this plant were coumarins [23] and anthraquinones [24]. The stem bark contains tannin, toxic alkaloid hymenodictine, a bitter substance, aesculin**(1)**, an apioglucoside of scopoletin, hymexelsin [10,19]. Anthraquinones, rubiadin**(2)** and its methyl ether, lucidin **(3)**, damnacanthal **(4)**, nordamnacanthal**(5)**, 2-benzylzanthopurpurin**(6)**, anthragallol, soranjidol and morindone(7) have also been isolated from roots [4]. Hymenodictyoline obtained from *H. excelsum* is one of the few alkaloids which do not contain oxygen. Aesculin (β-methylaesinietin), scopoletin**(8)**, hymenodictyonim (a toxic alkaloids); alanine, arginine, cystine, glycine, leucine, fruitore, galactose, glucose from barks; anthragallol, 6-methyalizarin, subiadin and its 1-methylester, soranjidol, isolated from roots [12]. Studies have also reported acetylenic fatty acids, a new triglyceride, and 11 known compounds, among them, ursolic acid**(9)**, oleaqnolic acid, uncarinic acid E, β-sitosterol [23]. The roots of *H. excelsum* also reported to contain anthragallol, 6-methylalizarin, soranjidiol, morindone and triterpenes including 3β-hydroxy-11-oxours-12-en-28-oic acid; 3β-hydroxy-27-p-(Z)- coumaroyloxyolean-12-en-28-oic acid; 3-oxo-11α,12α-epoxyurs-13β,28-olide; 3β-hydroxy-11α,12α-epoxyurs-13β,28-olide; 3β-hydroxyurs-11-en-13(28)-lactone; oleanolic acid; uncarinic acid E (3β-hydroxy-27-(E)-p-coumaroyloxyolean-12-en-28-oic acid, 3β-(formyloxy)-urs-12-en-28-oic acid [25] (Figure 1).

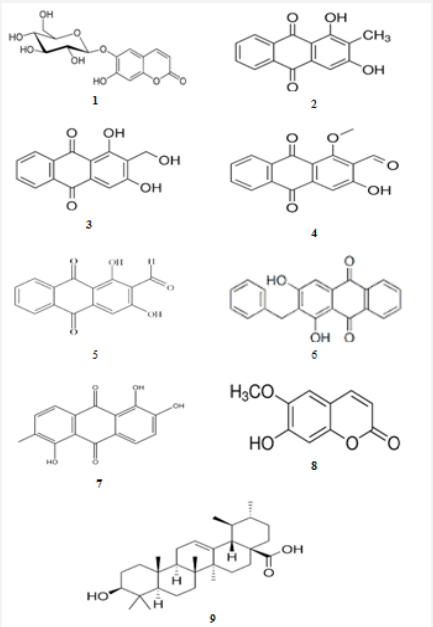

Figure1: Aesculin, Rubiadin, Lucidin, Damnacanthal, Nordamnacanthal, 2-benzylzanthopurpurin, Morindone, Scopoletin and Ursolic acid

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Pharmacology

The plant and some of its active chemical constituents have been investigated for various pharmacogical properties. The leaves and bark of the plant have been reported to have antimicrobial, anticoagulant, anti-inflammatory [26] and sun-screening activity [27]. Furthermore, antioxidant, antimicrobial, anti-inflammatory, analgesic, depressing, antipyretic, atherothrombolytic and moderately antiamylase activities of *H. excelsum* extracts have been reported [28]. A precise description of various pharmacological activities is derailed hereunder.

Antimicrobial Activity

H. excelsum bark exhibited a bactericidal effect against S. aureus at a concentration of 500µg/ml. The acetone extract 100mg/ml showed inhibition zone of 24mm against *Pseudomonas aureginosa* which is more than control assuring a good anti-bacterial activity against the bacterium [29]. Methanolic bark extract of *H. excelsum* also showed antimicrobial evidence against Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Mycobacterium smegmatis and Candida *albicans* and the leaves for antiinflammatory activity [30]. Inhibitory effect of the methanolic extract of *H. excelsum* bark assessed against some important and frequently occurring pathogenic fungi viz., *Alternaria alternate, Aspergillus flavus, Cladosporium cladosporidies, Drechslera halodes* and *Fusarium moniliforme* by agar-well diffusion method showed significant antifungal the bark extract in a dose dependant manner. The extract at concentration of 40mg/ml showed growth inhibition almost at par with synthetic fungicide, Carbendazim [31].

Anti-inflammatory Activity

In vitro anti-inflammatory activity studied using inhibition of protein denaturation and human red blood cell (HRBC) membrane stabilization methods. Inhibition of protein denaturation was found to be 82.64 ± 0.6 % at a dose of 250 µg/ml that indicated remarkable *in vitro* anti inflammatory activity [32]. Methanol extract of *H. excelsum* bark reported to exhibit significant anti-inflammatory activity tested by egg albumin induced rat paw edema model and found comparable to the standard anti-inflammatory drug Piroxicam [33]. Hydro alcoholic extract of leaves of the plant evaluated for anti-inflammatory activity by carrageenan induced oedema method. The percentage inhibition of oedema at 4th hour of the dose 200mg/kg was 42.62%, and the dose 400mg/kg was 62.63%, the standard 61.78% [34].

Antioxidant Activity

Methanol extract of *H. excelsum* bark showed effective free radical scavenging at higher concentrations [31, 35].

Antimalarial activity

The ethyl acetate extract of *H. excelsum* has shown dose dependent percentage inhibition of schizont maturation of *Plasmodium falciparum*, hence possess significant *in vitro* and *in vivo* antimalarial activity [36].

Anticoagulant activity

The chemical constituents of *H. excelsum* named scopoletin and its galactoside (each 25 mg/kg) reported to show slight increase in prothrombin time however, higher doses (100 mg/kg for the former, 200 mg for the latter) enhanced prothrombine time significantly suggesting their promising anticoagulant activity [27].

Antitumour Activity

H. excelsum is traditionally used for treatment of tumour as it contains phytochemicals of anthraquinone and coumarin group. The structure-activity relationship of coumarin and its derivatives has been studied and ascertained by semi empirical molecular orbital method [37].

Cytotoxic activity

Cytotoxic activity of *H. excelsum* bark extract was investigated against healthy mouse fibroblasts (NIH3T3), healthy monkey kidney (VERO) and four human cancer cell lines (gastric, AGS; colon, HT-29; and breast, MCF-7 and MDAMB-231) using MTT assay. High cytotoxicity across all cell lines tested was exhibited by bark extract. *H. excelsum* bark showed strong but non-selective cytotoxicity that support for the traditional use of the 'active' plant as anticancer agents [22]. Cytotoxic activity of methanolic extract of the bark of *H. excelsum* on DLA cells by trepan blue dye exclusion method and observed 100% cytotoxicity at 200µg/ml [30]. The anthraquinone and coumarin principles of *H. excelsum* have an anti-prostate cancer effect that has been proposed to be exerted by antagonistic effects on human androgen receptor [38]. Anti-proliferative activity of stem bark of the plant evaluated using the Ehrlich As cites Carcinoma (EAC) cells on Swiss albino mice have showed significant decrease in tumour volume, viable cell count, tumour weight and elevated the life span of EAC tumour bearing mice. Haematological profile such as RBC, haemoglobin, WBC and lymphocyte count reverted to normal level in treated mice. This revealed that the extract has potent dose dependent anticancer activity that is comparable to that of 5-fluorouracil [34].

Conclusion

An extensive literature survey revealed that *H. excelsum* is an important medicinal plant used for the ethnomedicinal treatment of fever, hemorrhoids, inflammation, abdominal disorders, infectious diseases, and many more throughout the world. Pharmacological studies carried out on the crude extracts, and individual chemical constituents of *H. excelsum* provide an experimental support for its various traditional medicinal uses. Recent studies have been focused on evaluating the antimicrobial (antibacterial), antifungal, anti-inflammatory, cytotoxicity, antioxidant activities. Most of the mentioned pharmacological studies were aimed at validating its traditional uses. It has been found that some of its traditional uses have been extensively explored by several research groups, like anti-inflammatory and antimicrobial activities. However, adequate experimental

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evidence are lacking to substantiate its various other traditional therapeutic applications that need further scientific validation.

Primarily bark and leaves of *H. excelsum* have been reported to be employed in the treatment of some ailments in varied geographical locations. The explanation for such a practice warrants further phytochemical and pharmacological studies. Furtherefore, majority of the pharmacological studies that have been done with crude extracts of various parts of the plant. Thus, it is difficult to reproduce the outcomes of these studies and to locate the precise bioactive metabolite. Hence, there is a need for phytochemical standardization and identification of further bioactive candidates. Phytochemical research carried out on *H. excelsum* has led to the isolation of few classes of plant metabolites. However, the vast traditional use and proven pharmacological activities indicate that an immense scope still exists for its phytochemical exploration. However, the potent bioactive secondary metabolite with potential for pharmacological effects e.g. anticancer, scavenging activity, etc. as described by earlier researchers. Therefore, there is a vast scope for establishing a relation between given phytoconstituents and biological activities. The outcome of the future research in the above-mentioned areas will provide a convincing support for the future clinical uses of *H. excelsum* in modern medicine.

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