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Review Articles

Plant Reviews

Therapeutic potential and health benefits of *Sargassum* species

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ABSTRACT

Sargassum species are tropical and sub-tropical brown macroalgae (seaweed) of shallow marine meadow. These are nutritious and rich source of bioactive compounds such as vitamins, carotenoids, dietary fibers, proteins, and minerals. Also, many biologically active compounds like terpenoids, flavonoids, sterols, sulfated polysaccharides, polyphenols, sargaquinoic acids, sargachromenol, pheophytine were isolated from different *Sargassum* species. These isolated compounds exhibit diverse biological activities like analgesic, anti-inflammatory, antioxidant, neuroprotective, anti-microbial, anti-tumor, fibrinolytic, immune-modulatory, anti-coagulant, hepatoprotective, anti-viral activity etc., Hence, *Sargassum* species have great potential to be used in pharmaceutical and neutralceutical areas. This review paper explores the current knowledge of phytochemical, therapeutic potential, and health benefits of different species of genus *Sargassum.*

Key words: Brown seaweed, *Sargassum*, sulfated polysaccharide, therapeutic potential

INTRODUCTION

As more than 70% of the world's surface is covered by oceans, the wide diversity of marine organisms offer a rich source of natural products, which make up approximately one half of the total global biodiversity and are rich reservoirs of structurally diverse bio-functional components. Among marine organisms, marine algae are rich sources of structurally diverse bioactive compounds with various biological activities.[1,2]

Marine algae are heterogeneous group of plants with a long fossil history. Two major types of algae can be identified: The macroalgae occupy the littoral zone, and the microalgae are found in both bentheic and littoral habitats and also throughout the ocean waters as phytoplankton. Marine macroalgae or seaweeds are found in the coastal region between high tide to low tide and in the sub-tidal region up to a depth where 0.01% photosynthetic light is available and can be classified into three classes: Brown algae (Phaeophyta), Green algae (Chlorophyta), and Red algae (Rhodophyta). Brown seaweeds are predominantly brown due to the presence of the carotenoid fucoxanthin, and the primary polysaccharides present include alginates, laminarins, fucans, and cellulose. Green seaweeds are dominated by chlorophyll a and b, with ulvan being the major polysaccharide component. While in Red seaweeds, principal pigments are phycoerythrin and phycocyanin and the primary polysaccharides are agars and carrageenans.[3,4] The importance of seaweeds for human consumption is well known since 300 BC in China and Japan. These two countries are the major seaweed cultivators, producers, and consumers in the world. In the Indian Ocean region countries like Malaysia, Indonesia, Singapore, Thailand, Korea etc., seaweeds are used in salad, jelly, soup etc., However, in India, seaweed consumption is negligible except in the preparation of porridge from *Gracilaria* species and *Acanthophora* species in coastal states of Kerala and Tamil Nadu.[5] Seaweeds are rich in soluble dietary fibers, proteins, minerals, vitamins, antioxidants, phytochemicals, and polyunsaturated fatty acids, with low caloric value.[6] They are an excellent source of vitamins A, B_1, B_2, B_3, B_{12}, C, D, E. Their amino acid content is well-balanced and contains all or most of the essential amino acids needed for life and health.[5] Moreover, biologically active compounds isolated from marine macroalgae exhibit various biological activities such as antioxidant,[7,8] anti-viral,[9] anti-allergic,[10] anti-inflammatory,[11,12] anti-cancer,[13] anti-coagulant[14] *etc.*

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Sargassum, a genus of brown seaweed, commonly known as gulf-weed or sea holly belonging to family Sargassaceae, order Fucales, subclass Cyclosporeae, and class Phaeophyceae, contains approximately 400 species.[15,16] *Sargassum* species are found throughout tropical and subtropical areas of the world and are reported to produce metabolites of structural classes such as terpenoids, polysaccharides, polyphenols, sargaquinoic acids, sargachromenol, plastoquinones, steroids, glycerides etc., which possesses several therapeutic activities. As it possesses many pharmacological properties, it has been considered as a medicinal food of the twenty-first century, and research is being carried out on it to reveal its other pharmacological properties. This review focuses on pharmacological activities with potential health benefits of different *Sargassum* species.

THERAPEUTIC POTENTIAL OF *SARGASSUM* SPECIES

In vitro antioxidant activity

Oxidative stress is the result of an imbalance between pro-oxidant and antioxidant homeostasis that leads to the generation of toxic reactive oxygen species (ROS).[17] ROS such as hydroxyl, super oxide, and peroxyl radicals are formed in human tissue cells, which attack macromolecules such as membrane lipids, proteins, and DNA, lead to many health disorders such as cancer, diabetes mellitus, age-related degenerative conditions, neurodegenerative and inflammatory diseases with severe tissue injuries.[18-20] Antioxidants may have a positive effect on human health as they can protect human body against damage by ROS. *In vivo,* cells have their own inherited antioxidative defense system, in the form of various enzymatic, as well as non-enzymatic pathways, for removing the ROS. Among enzymatic pathways, O_2 are dismutated by superoxide dismutase (SOD) to H_2O_2, catalase (CAT) reduces H_2O_2 to water and molecular oxygen. Glutathione peroxidase (GPX) catalyzes the reduction of H_2O_2 to water and organic peroxide to alcohols at the expense of reduced glutathione (GSH), while glutathione-S-transferase conjugates xenobiotics with glutathione for excretion. Among the non-enzymatic substances, β-carotene, vitamin-A, vitamin-E, and vitamin C scavenge free radicals.[21] Among the sources of natural antioxidants, marine seaweeds are now being considered to be a rich source of antioxidants. Antioxidant activities of *Sargassum* species have been determined by various methods such as 1,1-diphenyl-2-picryl hydrazyl (DPPH) radical scavenging, 2,2'-azinobis-3-ethylbenzo thizoline-6-sulfonate (ABTS) radical scavenging, NO scavenging, lipid peroxide inhibition, superoxide and hydroxyl radical scavenging assays.

Kim *et al.*[22] reported the sulfated polysaccharides of *Sargassum fulvellum* is more potent NO scavenging and DPPH scavenging activity than commercial antioxidants such as α-tocophorol. According to Hwang *et al.*,[23] the DPPH free radicals scavenging activity, superoxide anion scavenging activity measured using the xanthine- xanthine oxidase system and Fe^{3+} reducing activity of hot-water extract from *Sargassum hemiphyllum* showed a linear dose-depending relationship with an IC_{50} = 1.58 mg/ml, 2.41 mg/ml and 0.41 mg/ml, respectively. The antioxidant activities of *Sargassum hemiphyllum* may be due to high level of total phenolic compounds. The water-soluble natural antioxidants from another seaweed *Sargassum thunbergii* exhibited the DPPH free radical scavenging activities, and the scavenging activity of the radicals increased with increasing concentrations of the extract,[24] the thunbergols (tetraprenyltoluquinols) and sargothunbergol (chromene) isolated from the *Sargassum thunbergii* were scavengers of the DPPH radical.[25,26] Sargachromanols (meroterpenoids), isolated from the brown alga *Sargassum siliquastrum,* exhibited significant activity in the DPPH assay.[27] Also, extracts from *Sargassum siliquastrum* showed DPPH free radical scavenging activity, suppression of lipid peroxidation, and scavenging activity of superoxide radicals.[28] In addition, the plastiquinones, isolated from brown alga *Sargassum micracanthum,* displayed significant antioxidant activity.[29,30] Furthermore, total methanolic extract and ethyl acetate fraction of *S. marginatum* exhibited significant antioxidant activity in DPPH scavenging activity, deoxyribose scavenging activity, and hydroxyl radical scavenging activity in dose-dependent manner.[8]

Cholinesterase inhibitory activity

Dementia is a chronic progressive mental disorder, which adversely affects memory, thinking, comprehension, calculation, and language. Some of the commonest types of dementia are Alzheimer's disease, Parkinsonism, and Myasthenia gravis.[31] Alzheimer's disease (AD) is an irreversible, progressive neurodegenerative disease, which resulting in memory loss, behavior disturbances, personality changes, and a decline in cognitive abilities.[32] Substantial reduction in activity of the enzyme choline acetyltransferase (ChAT) responsible for the synthesis of acetylcholine (ACh) is the key marker enzyme in AD. Parkinson's disease, a neurodegenerative disease of the substantia nigra (an area in the basal ganglia), which involves a breakdown of nerve cells in the motor area of the brain, is also characterized by reduction in ChAT activity.[33] Myasthenia gravis, a chronic autoimmune disorder, is characterized by reductions in levels of ACh at the neuromuscular junction.[34] All these disorders are related to abnormalities in the central cholinergic system, which shows a decline in ACh level. The inhibition of acetylcholinesterase (AChE) enzyme, which catalyzes the breakdown of ACh, may be one of the most realistic approaches to the symptomatic treatment of these disorders.[35]

Natarajan *et al.*[36] reported that methanolic extract of *Sargassum* showed strong inhibition at IC_{50} value of 1 mg/ml and 0.6 mg/ml on Cholinesterase activity with Acetylthiocholine iodide (ATCI) and Butyrylthiocholine iodide (BTCI) as substrate. Two farnesylacetone derivatives (identified as (5E,10Z)-6,10,14-trimethylpentadeca-5,10-dien-2,12-dione and (5E,9E,13E)-6,10,4-trimethylpentadeca-5,9,13-trien-2,12-dione) were isolated from the Korean brown alga *Sargassum sagamianum* and showed moderate acetylcholinesterase and butyrylcholinesterase inhibitory activities with IC_{50} values

of 65.0-48.0 and 34.0-23.0 mM, respectively.[37] However, two plastoquinones (sargaquinoic acid and sargachromenol), isolated from *Sargassum sagamianum,* showed moderate acetylcholinesterase inhibitory activity with IC_{50} 23.2 and 32.7 μM respectively, and for butyrylcholinesterase, sargaquinoic acid showed potent inhibitory activity with IC_{50} 26 nM.[38]

Neuroprotective (Neurite outgrowth promoting) activity

The neurotrophic factor, nerve growth factor (NGF), is fundamentally important to the differentiation, survival, and maintenance by stimulating neurite outgrowth in neuronal and rat phaeochromocytoma (PC12) cells.[39,40] Reduction of NGF levels in the brain ultimately causing aging and neurodegenerative conditions such as Alzheimer's disease.[41] The use of NGF-potentiating substance with small molecular weight has been suggested for the treatment of neurodegenerative diseases.[42] Furthermore, numerous animal tests have also shown that the administration of NGF can significantly ameliorate the neuronal degeneration in rat cerebral cortex and hippocampus after ischemic insults.[43] These results underlie the rationale for the use of NGF to treat neurodegenerative diseases.

Neurite outgrowth is a fundamental neuronal feature and plays an important role in neuronal development during embryogenesis and in the adult brain.[44] Pheophytin A, purified from the Japanese brown alga *Sargassum fulvellum,* is a novel neuro-differentiation compound. Pheophytin A at 3.9 μg/mL was observed to synergize with NGF in promoting neurite outgrowth in rat pheochromocytoma PC12 cells by a mechanism that appeared to involve activation of mitogen-activated protein kinase signaling.[45] Sargachromenol isolated from *Sargassum macrocarpum* was shown to markedly promote NGF-dependent neurogenesis in PC12D cells (ED_{50} 9 μM). Interestingly, mechanistic studies demonstrated that both the cyclic AMP-mediated protein kinase and mitogen-activated protein kinase 1/2 signal transduction pathways were required for neurite growth stimulated by sargachromenol.[46] Low molecular weight quinonic compound sargaquinoic acid isolated from *Sargassum macrocarpum* possesses a novel nerve growth factor-dependent neurite outgrowth promoting activity at the nanogram range. Kamei and Tsang investigated the signaling pathways involved using a pharmacological approach and concluded that sargaquinoic acid enhanced neurite outgrowth in PC-12 neuronal cells by involving both TrkA-mitogen-activated protein kinase and adenylate cyclase-protein kinase as a signal transduction pathways.[47] In a subsequent study, the neuroprotective effect of sargaquinoic acid was shown to be independent of nerve growth factor and phosphatidylinositol 3 kinase, a key signaling molecule.[48]

Anti-cancer and cytotoxic activity

Cancer is a leading cause of death worldwide and a diverse group of diseases characterized by the uncontrolled proliferation of anaplastic cells, which tend to invade surrounding tissues and metastasize to other tissues and organs. Cancer results from a mutation in the chromosomal DNA of a normal cell, which can be triggered by both external factors (tobacco, alcohol, chemicals, infectious agents, and radiation) and internal factors (hormones, immune conditions, inherited mutations, and mutations occurring in metabolism).[49]

Zandi *et al.*[50] reported that the cold water extract of *Sargassum oligocystum* showed the reasonable anti-cancer activity against tumor cells replication. The most potent activity has been shown at concentrations 500 μg/ml and 400 μg/ml of extract on Daudi and K562 cell lines, respectively. Polysaccharides from *Sargassum fusiforme* showed significant anti-tumor activity both *in vitro* and *in vivo*, and improved the immune function in tumor-bearing mice.[51] Also, two polysaccharide fractions, SP-3-1 and SP-3-2 from *Sargassum pallidum,* showed significant *in vitro* anti-tumor activity against the HepG2 cells, A549 cells, and MGC-803 cells.[52] Khanavi *et al.*[53] found that the hexane fraction of methanol extract of *Sargassum swartzii* had *in vitro* cytotoxicity against Caco-2 and T47D cells and increased the percentage of apoptotic cells among these cells. The activity of this fraction may be due to the meroterpenoids. Hydroxysargaquinone and Sargasals I and II fraction of a methanolic extract of *Sargassum turtile* has demonstrated significant and marginal cytotoxicity against cultured P-388 lymphocytic leukemia cells.[54] Furthermore, polysaccharide E3 isolated from *Sargassum latifolium* showed a selective cytotoxicity against lymphoblastic leukemia 1301 cells.[55]

Anti-pyretic, analgesic, and anti-inflammatory activities

The inflammatory process involves a series of events that can be elicited by numerous internal or external stimuli. Therapy of inflammatory diseases is usually directed at the inflammatory processes. Anti-inflammatory refers to the property of a substance or treatment that reduces inflammation.[56]

Dar *et al.*[57] reported that butanolic extract of *Sargassum wightii* collected during winter season was most effective (86.7%) in reducing carrageenan-induced edema in rats at a dose of 100 mg/kg as compared to reference drugs aspirin (79.4%) and ibuprofen (57.3%). The dichloromethane extract of *Sargassum fulvellum* inhibited an inflammatory symptom of mouse ear edema by 79.1%. The ethanol extract of *Sargassum thunbergii* also inhibited edema by 72.1%, when evaluated against yeast-induced pyrexia, tail-flick test, and phorbol myristate acetate-induced inflammation (edema, erythema, and blood flow) in mice.[11] Also, methanolic extracts of *Sargassum swartzii* at the dose of 500 mg/kg body weight showed analgesic effects in both acetic acid-induced writhing and hot plate-induced pain models, acute anti-inflammatory effect in both edemas in hind paw induced by carrageenan and peritonitis models. Furthermore, *S. swartzii* extract showed chronic anti-inflammatory effects at the dose of 175 and 350 mg/kg body weight in amiant-induced granuloma model in mice.[58] According to Hwang *et al.*,[59] fucoidan (sulfated polysaccharide) from *Sargassum hemiphyllum* showed *in vivo* and *in vitro* anti-inflammatory activity.

Hepatoprotective activity

Raghavendran *et al.*[60] reported the protective effects of *Sargassum polycystum* alcoholic extract on changes in liver mitochondrial enzymes against acetaminophen-induced toxic hepatitis in rats. Reports show that the *S. Polycystum* pre-treated rats showed an improved level of mitochondrial GSH, and prevented the excessive depletion of SOD and CAT with concomitant reduction in the levels of lipid peroxides when compared with acetaminophen-induced animals. Furthermore, extract prevent the severe impairment in the activities of tricarboxylic acid cycle enzymes, prevention in the excessive impairment of NADH dehydrogenase activity and improving the mitochondrial antioxidant defence system, thereby protecting the critical nucleophilic sites on the enzymes against toxic electrophilic metabolites. Sulfated polysaccharides from *Sargassum wightii* significantly restored the deformities due to cyclosporine A-induced oxidative liver injury in rats. Administration of sulfated polysaccharides repairs the activities of hepatic marker enzymes as it decreases the levels of lipid peroxidation, 8-hydroxy-2-deoxy guanosine and protein carbonyls, along with an increase in ATPase activities. Also, sulfated polysaccharides co-administration minimized the oxidants production by scavenging the free radicals.[61]

Anti-viral activity

Iwashima *et al.*[62] discovered that three plastoquinones isolated from *Sargassum micracanthum* inhibited cytomegalo virus (IC_{50} 0.49-2.6 μM) and measles virus (IC_{50} 2.7-3.1 μM). A sulfated polysaccharide (SP-2a) from *Sargassum* patens was found to significantly inhibit the *in vitro* replication of both the acyclovir-sensitive and -resistant strains of Herpes simplex virus type 1 (HSV-1), in dose-dependent manners, with 50% inhibitions occurring with 1.5-5.3 μg/ml.[63] Also, a sulfated polysaccharide (SP2) isolated from *S*. patens inhibit the replication of herpes simplex virus type 2 (HSV-2) dose-dependently by 38.5-96.1% of the control level, after incubations with 0.78-12.5 μg/ml of the polysaccharide.[64] Polysaccharides, ST-F characterized fucoidan, from *Sargassum* trichophyllum showed anti-viral activity against herpes simplex virus type 2.[65] Sulfated polysaccharide, fucoidan, and a guluronic acid-rich alginate derived from *Sargassum tenerrimum* showed activity against herpes simplex virus type 1 (HSV-1). Their inhibitory concentration 50% (IC50) values were in the range 0.5-15 μg/ml.[66]

Anti-coagulant activity

Disorders in blood coagulation can lead to an increased risk of bleeding (hemorrhage) or clotting (thrombosis).[67] Anti-coagulants are substances that prevent coagulation that is, they stop blood from clotting.[68] De Zoysa *et al.*[69] reported the isolation and characterization of fucose containing sulfated polysaccharide as an anti-coagulant agent from *Sargassum fulvellum*. Hot water extracts from *Sargassum horneri* showed high activated partial thromboplastin time (APTT) and exhibited the potent anticoagulant activity.[70]

Immunomodulatory activity

Immunomodulation is explained as any change in the immune response and may involve induction, expression, amplification of any part or phase in the immune response. Modulation may be very specific limited to a given antigen/agent with a great effect on immune response.[71] *In vitro* and *In vivo* effect of ethyl acetate fraction *Sargassum ilicifolium* was tested for immunomodulatory activities. *In vitro* study revealed that *S. ilicifolium* has stimulated chemotatic, phagocytic, and intracellular killing of human neutrophils at a dose of 100 μg/ml. Whereas, *In vivo* studies have shown prominent immunostimulatory effect at a dose of 100 mg/kg p.o. The said activity was due to presence of terpenes and steroids.[72] The hot-water extract of *Sargassum hemiphyllum* showed the activity of cell proliferation (174%) at 120 μg/ml, and IgM secretion (132%) at 120 μg/ml when assayed in HB4C5 cells (human hybridomas producing monoclonal antibody against human lung cancer). Furthermore, extract showed significant proliferation activity (141%) and phagocytosis activity (148%) at 80 μg/ml when assayed in J774 (murine macrophage-like) cell line. These result revealed the significant immune-stimulating activity of *Sargassum hemiphyllum.*[23]

Other biological activities

Other pharmacological activity includes fibrinolytic, anti-diabetic, anti-bacterial, anti-plasmodial, Skin-whitening, gastric-protective activity etc., Two bioactive products identified as 1-O-palmi toyl-2-O-oleoyl-3-O-(α-D-glucopyranosyl)–lycerol (POGG) and 1-O-myristoyl-2-O-oleoyl-3-O-(α-D-glucopyranosyl)–glycerol (MOGG) obtained from *Sargassum fulvellum* showed fibrinolytic activity in the reaction system of pro-u-PA and plasminogen.[73] According to Kim *et al.,*[74] Sargaquinoic acid and sargahydroquinoic acid from *Sargassum yezoense* able to increase Peroxisome proliferator-activated receptor α/γ (PPARα/γ) transcriptional activity. PPARs are members of the nuclear hormone receptor superfamily of ligand- activated transcription factors, and are currently appreciated as potential therapeutic targets for the treatment of diabetes and dyslipidemia. Hot water extract of *Sargassum polycystum* in dose of 100 mg/kg maintains the acidity of gastric juice and improves the gastric mucosal injury in rats.[75] Extracts of *Sargassum polycystum* and *Sargassum silquastrum* exerted *in vitro* inhibitory activity against tyrosinase and melanin production, which could be developed to a skin-whitening agent in cosmetics industry.[76,77]

CONCLUSION

A large number of studies are reported that *Sargassum* species contain sulfated polysaccharide, plastoquinone, phlorotannins, flucoxanthin, fucoidan, sargaquinoic acid, sargachromenol, steroids, terpenoids, and flavonoids etc., Furthermore, these bioactive compounds and various extracts showed significant therapeutic potential and could be introduced for the preparation of novel functional ingredients in pharmaceuticals for the treatment and or prevention of several disorders. Therefore, further research studies are needed to exploit its maximum

therapeutic potential in the field of medicinal and pharmaceutical sciences for novel and fruitful application.

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Phytochemistry and Pharmacology of *Berberis* Species

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ABSTRACT

The genus *Berberis* (Berberidaceae) includes about 500 species worldwide, some of which are widely cultivated in the north-eastern regions of Iran. This genus consists of spiny deciduous evergreen shrubs, characterized by yellow wood and flowers. The cultivation of seedless barberry in South Khorasan goes back to two hundred years ago. Medicinal properties for all parts of these plants have been reported, including: Antimicrobial, antiemetic, antipyretic, antioxidant, anti-inflammatory, anti-arrhythmic, sedative, anti-cholinergic, cholagogic, anti-leishmaniasis, and anti-malaria. The main compounds found in various species of *Berberis*, are berberine and berbamine. Phytochemical analysis of various species of this genus revealed the presence of alkaloids, tannins, phenolic compounds, sterols and triterpenes. Although there are some review articles on *Berberis vulgaris* (as the most applied species), there is no review on the phytochemical and pharmacological activities of other well-known species of the genus *Berberis.* For this reason, the present review mainly focused on the diverse secondary metabolites of various species of this genus and the considerable pharmacological and biological activities together with a concise story of the botany and cultivation.

Key words: *Berberis*, pharmacological effects, phytochemistry, zereshk

INTRODUCTION

The genus *Berberis* (Berberidaceae) includes about 500 species that commonly occur in most areas of central and southern Europe, the northeastern region of the United States and in South Asia including the northern area of Pakistan.[1,2] There are five species of this plant in Iran, two of them (*B. orthobotrys* and *B. khorassanica)* exclusively growing in the northern, eastern, and south eastern highlands of Iran (Alborz, Qaradagh in Azerbaijan, Mountains of Khorasan, Barez Mountain in Kerman).[3,4]

Berberis species, called "zereshk" in Persian language, are widely cultivated in Iran. The South-Khorasan province (especially around Birjand and Qaen) is the major field of cultivation for zereshk in the world.[5] Medicinal properties for all parts of these plants have been reported [Table 1], including tonic, antimicrobial, antiemetic, anti-pyretic, anti-pruritic, antioxidant, anti-inflammatory, hypotensive, anti-arrhythmic, sedative, anti-nociceptive, anti-cholinergic, cholagogic, and have been employed in cholecystitis, cholelithiasis, jaundice, dysentery, leishmaniasis, malaria, gall stones, hypertension, ischemic heart diseases (IHDS), cardiac arrhythmias and cardiomyopathies.[2-6] Also, barberry has been used to treat diarrhea, reduce fever, improve appetite, and relieve upset stomach.[7]

Among the several species of this genus, *Berberis vulgaris* is well known and its fruits have been used in the preparation of a special dish with rice and also in *Berberis* juice.[8-10] Sometimes it has been used as a tea made from the bark of the plant.[7] Besides nutritional consumption, various parts of this plant including roots, bark, leaves and fruits have been employed in folk and traditional medicine for a long time in Iran.[7] The stem and root barks are used for their cathartic, diuretic, febrifuge, anti-bilious, and antiseptic properties. Also, the decoction of leaves is used as anti-scorbutic in dysentery, scurvy angina, and sore throat.[11] This article reviews mainly the phytochemical compounds of various species of *Berberis* together with the highlighted pharmacological and biological properties.

Plant characteristics

The *Berberis* genus consists of spiny deciduous evergreen shrubs, characterized by yellow wood and flowers,[9] dimorphic and long shoots together with the short ones (1-2 mm). The leaves on long shoots are not involved in photosynthesis but develop into three-spine thorns and finally short shoots with several leaves

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Table 1: Pharmacological and biological activity of the various species of Berberis genus

Plant name	Pharmacological/biological effect	Reference
B. vulgaris	Antihistaminic, anticholinergic, anti-inflammatory and anti-nociceptive effects	(16)
B. croatica	Antimicrobial activity	(10)
B. aristata	Cytotoxic activity, anticancer activity, laxative and useful in rheumatism; hypoglycemic activity, anti-osteoporotic activity	(17-19)
B. koreana	Cytotoxic activity	(20)
B. aetnensis	The plants is useful in rheumatic complaints and other types of chronic inflammations and antimicrobial activity	(21)
B. heterophylla	Antimicrobial activity	(22)
B. umbellate	Useful in treatment of cholera, acute diarrhea, amoebiasis and latent malaria	(23)
B. lyceum	Useful in treatment of eye diseases, liver and heart diseases, antihistaminic activity, stomachic, astringent, antipyretic and diaphoretic properties, anti-hyperglycemic effects	(24)
B. aquifolium	Antibacterial activity	(25)
B. repens	Antibacterial activity	(25)
B.integerrima	Antibacterial activity	(26)
B. hispanica	Increase of antibody production, immunosuppressive	(27)
B. thunbergii	Antimicrobial activity	(28)

Table 2: The main isolated compounds reported from different species of berberis. Structures of the compounds below are shown in Figure 1

Compound name	Plant source
Lupeol	*B. vulgaris*
Oleanolic acid	*B. vulgaris*
Stigmasterol	*B. vulgaris*
Stigmasterolglucoside	*B. vulgaris*
Berberamine	*B. vulgaris*
Palmatine	*B. vulgaris*
Berberine	*B. vulgaris*
Oxyberberine	*B. vulgaris*
Columbamine	*B. vulgaris*
Isocorydine	*B. vulgaris*
Lambertine	*B. vulgaris*
Magniflorine	*B. vulgaris*
Oxycanthine	*B. vulgaris*
N-(p-trans-Coumaroyl) tyramine	*B. vulgaris*
cannabisin G	*B. vulgaris*
(±)-lyoniresinol	*B. vulgaris*
2,5-bis-(2'-methoxy-5'-methylphenyl)-furan	*B. umbellata*
1,4-bis-(2'-hydroxy-5'-methylphenyl)-butan-l: Cdione	*B. umbellata*

contd...

Table 2: The main isolated compounds reported from different species of berberis. Structures of the compounds below are shown in Figure 1

Compound name	Plant source
Berbamine	*B. aristata*
(+)-N-methylcoclaurine	*B. montana*
(-)-pronuciferine	*B. montana*
(+)-9-hydroxynuciferine	*B. montana*
(+)-orientine	*B. montana*
2-norberbamunine	*B. stoloniferais*
Berbamunine	*B. stoloniferais*
Aromoline	*B. stoloniferais*
Isotetrandrine	*B. stoloniferais*
23-trans-p-coumaroyloxy- 2a, 3a-dihydroxyolean-12-en-28-oic acid	*B. koreana*
23-cis-p-coumaroyloxy-2a, 3a-dihydroxyolean-12-en-28-oic acid	*B. koreana*
5'-methoxyhydnocarpin-D	*B. aquifolium* *B. fremontii* *B. repens*
Pheophorbide- a	*B. aquifolium* *B. fremontii* *B. repens*
Jatrorrhizine	*B. umbellate*

(1-10 cm long, simple, and either entire, or with spiny margins) involved in photosynthesis. Many deciduous species such as *B. thunbergii* and *B. vulgaris* indicate pink or red autumn color, while the leaves are brilliant white beneath in some Chinese evergreen species (*B. candidula* and *B. verruculosa*), and dark red to violet foliage is found in horticultural variants of *B. thunbergii*. On a single flower-head, the flowers are appears alone or in racemes. They are yellow or orange, 3-6 mm long, with both six sepals and petals (usually with similar color) in alternating whorls. The *Berberis'* fruits are small berries (5-15 mm) which turn red or blue after ripening.[12,13]

In the lifecycle of *Berberis*, there are sexual and asexual reproduction processes which enable the plant to survive in harsh conditions. The distinctive yellow flowers of these plants appear in clusters and hang downwards from the stem. The reproductive organs of the flower are protected from rain by three inner concave sepals as well as six petals that completely enclose the stamens and anthers.[14]

The land under cultivation

Cultivation of zereshk in Iran is limited to the South-Khorasan province, especially around Birjand and Qaen. About 72% of the production is in Qaen and about 32% in Birjand. According to evidence the cultivation of seedless barberry in South-Khorasan goes back to two hundred years ago. The export of *Berberis* fruits is not considerable, because appropriate packaging is not available which affects the appearance and color of barberries. Besides this problem, barberry is not so familiar to people outside Iran.[15]

Pharmacological and biological effects

So far, many pharmacological and biological effects of various species of *Berberis* have been reported, some of which are summarized below in Table 1.

Phytochemistry

The main compounds, found in various species of *Berberis*, [Table 2] are berberine and berbamine [Figure 1]. Phytochemical analysis of the crude extract of *B. vulgaris* revealed the presence of alkaloids, tannins and phenolic compounds.[2] The triterpenes: lupeol (1), separated from its fruits, and oleanolic acid (2), isolated from ethanolic extract; the sterol: stigmasterol (3), obtained from hexane extract, and stigmasterol glucoside (4), from ethyl acetate extract; the alkaloids: berberamine (5), palmatine and (6) berberine (7), were reported for the first time from *B. vulgaris*.[11] Other important alkaloids: oxyberberine (8), columbamine

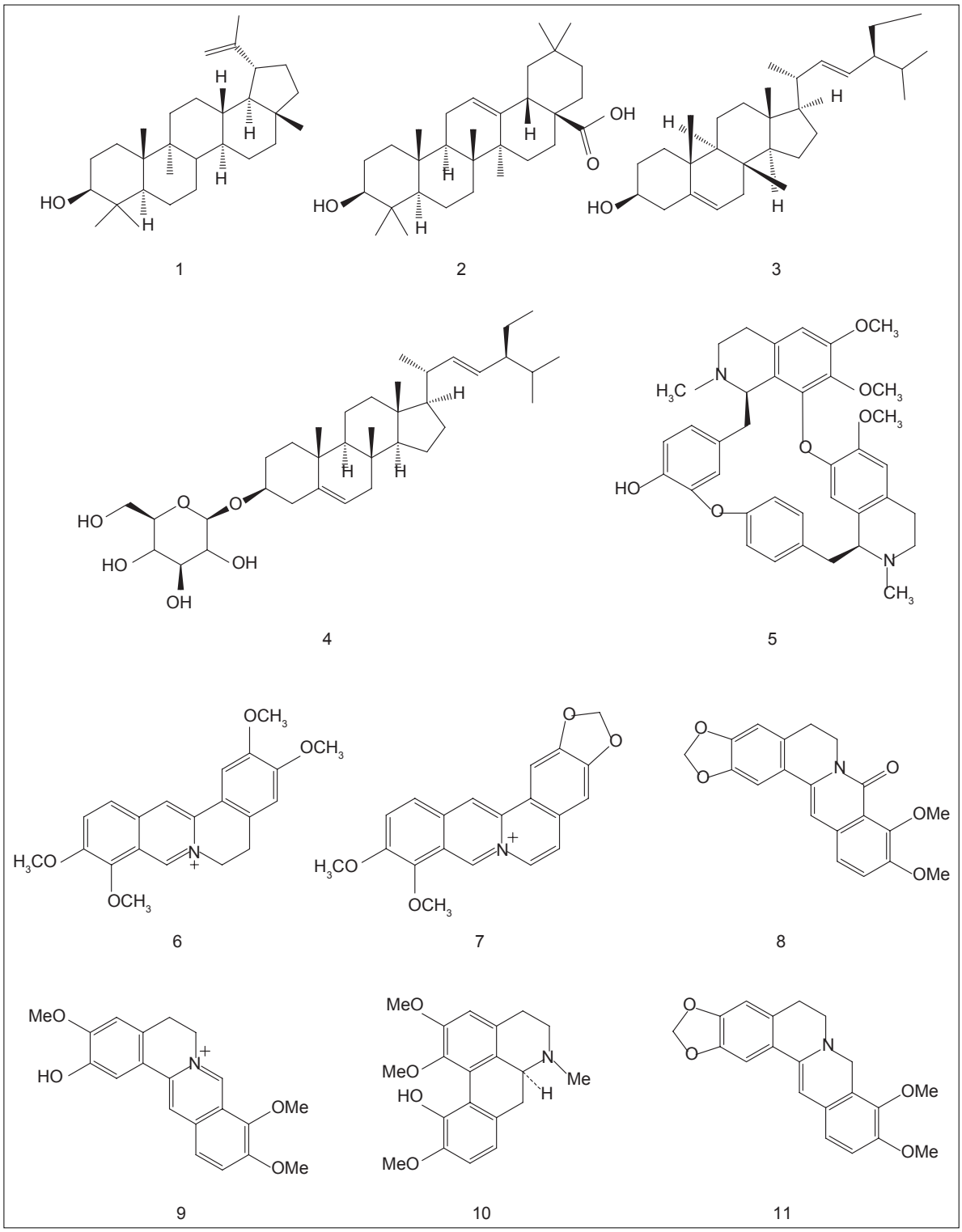

Figure 1: The structures of some phytochemical compounds isolated from various species of *Berberis*

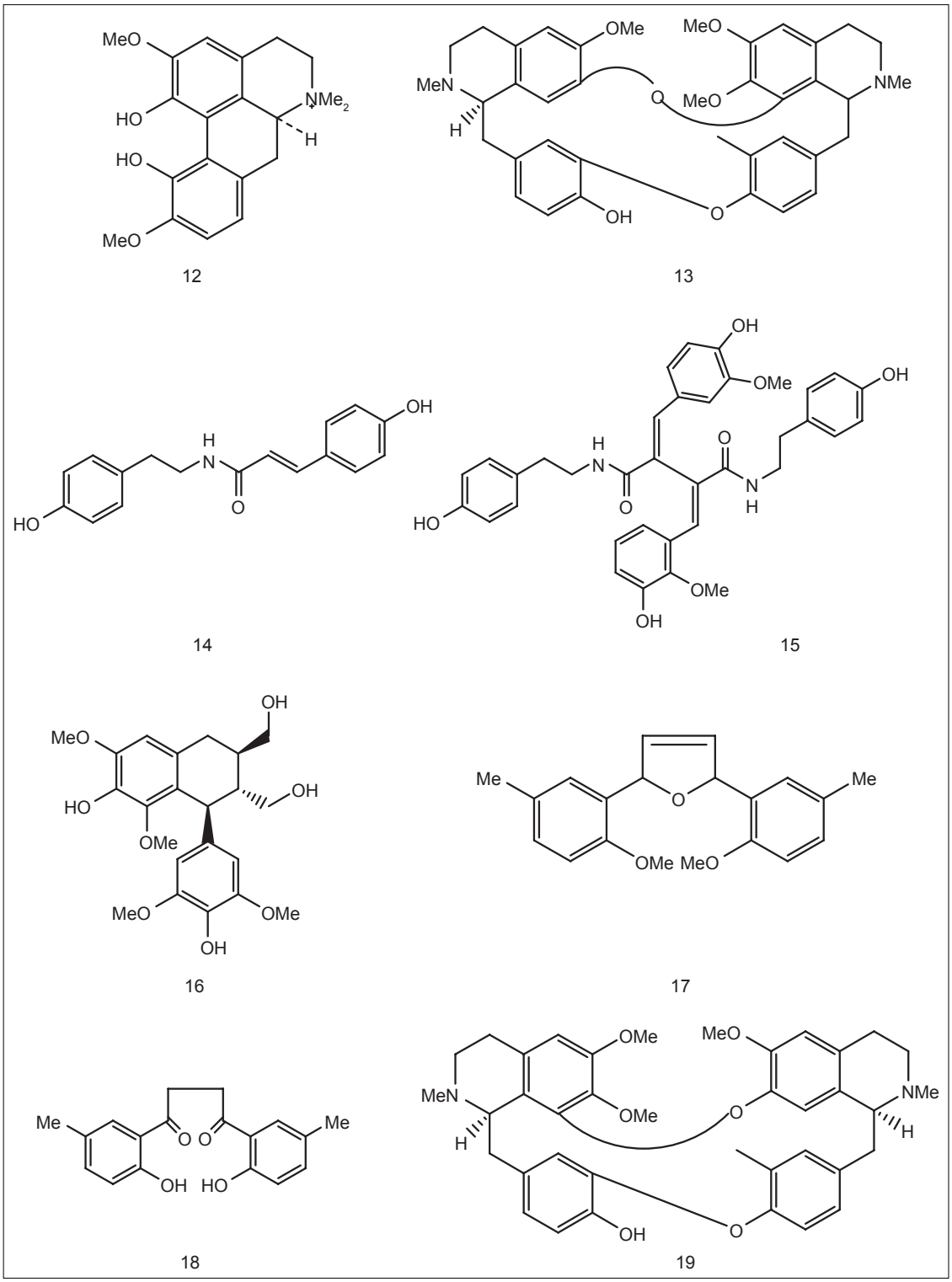

Figure 1: The structures of some phytochemical compounds isolated from various species of *Berberis*

(9), isocorydine (10), lambertine (11), magniflorine (12) and bisbenzlisoquinolines *e.g.,* oxycanthine (13)[7] have been reported from this plant. Cytoprotective compounds including N-(*p-trans*-coumaroyl) tyramine (14), cannabisin G (15), and (±)-lyoniresinol (16)[29] have been isolated from ethyl acetate extract of *B. vulgaris* [Figure 1]. The compounds: 2,5-bis-(2'-methoxy-5'-methylphenyl)-furan (17) and 1,4-bis-(2'-hydroxy-5'-methylphenyl)-butan-l: cdione (18) were isolated and identified from the ethanolic extract of *B. umbellate* roots [Figure 1].[30-34] Chromatographic separation of the crude alkaloid fraction of *B. chitria* afforded a new aporphine (isoquinoline) alkaloid as an amorphous solid

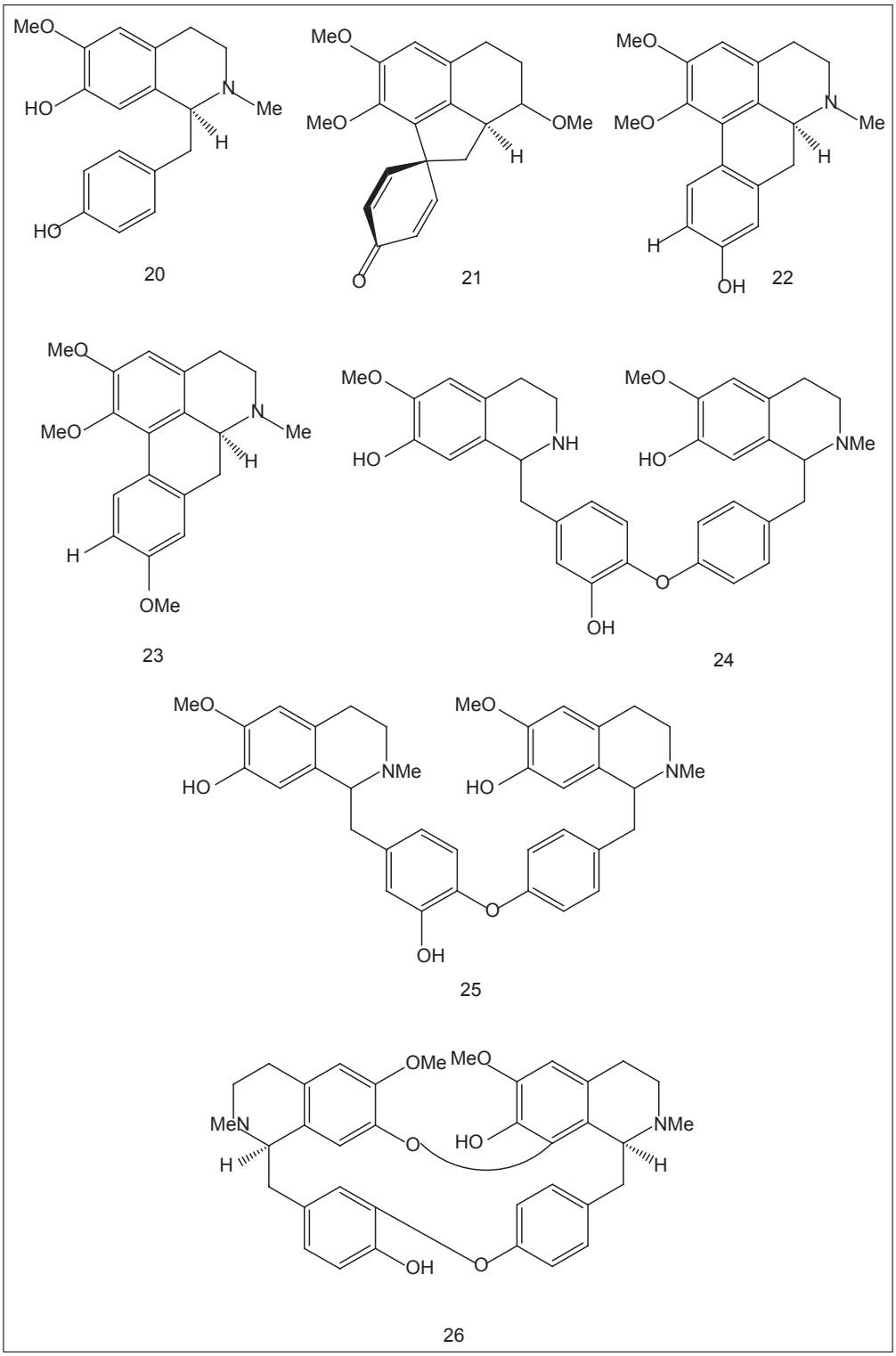

Figure 1: The structures of some phytochemical compounds isolated from various species of *Berberis*

named: O-methylcorydine-N-oxide.[31] *B. aristata* contains also a valuable isoquinoline alkaloid berbamine (19).[17]

B. montana contained four monomeric isoquinoline alkaloids: The benzyl isoquinoline (+)-N-methylcoclaurine (20), the proaporphine (-)-pronuciferine (21), and the aporphines (+)-9-hydroxynuciferine (22) and (+)-orientine (23), all of which were separated from methanol extract of this plant [Figure 1].[32] *B. stolonifera* is another species of *Berberis* which was investigated for biosynthetic pathway, and resulted in isolation of five bis-benzyl isoquinoline alkaloids from dried callus and suspension cultures as: 2-norberbamunine (24), berbamunine

(25), and aromoline (26), berbamine (19) and isotetrandrine (27) [Figure 1].[33]

Several triterpenoids such as 23-*trans-p*-coumaroyloxy- 2a, 3a-dihydroxyolean-12-en-28-oic acid (28) and 23-*cis-p*-coumaroyloxy-2a, 3a-dihydroxyolean-12-en-28-oic acid (29) were isolated and structurally elucidated from *B. korean* [Figure 1].[20]

The active inhibitors 5'-methoxyhydnocarpin-D (30) and pheophorbide- a (31) have been isolated from the leaves of *B. aquifolium*, *B. fremontii* and *B. repens* respectively.[25] Furthermore,

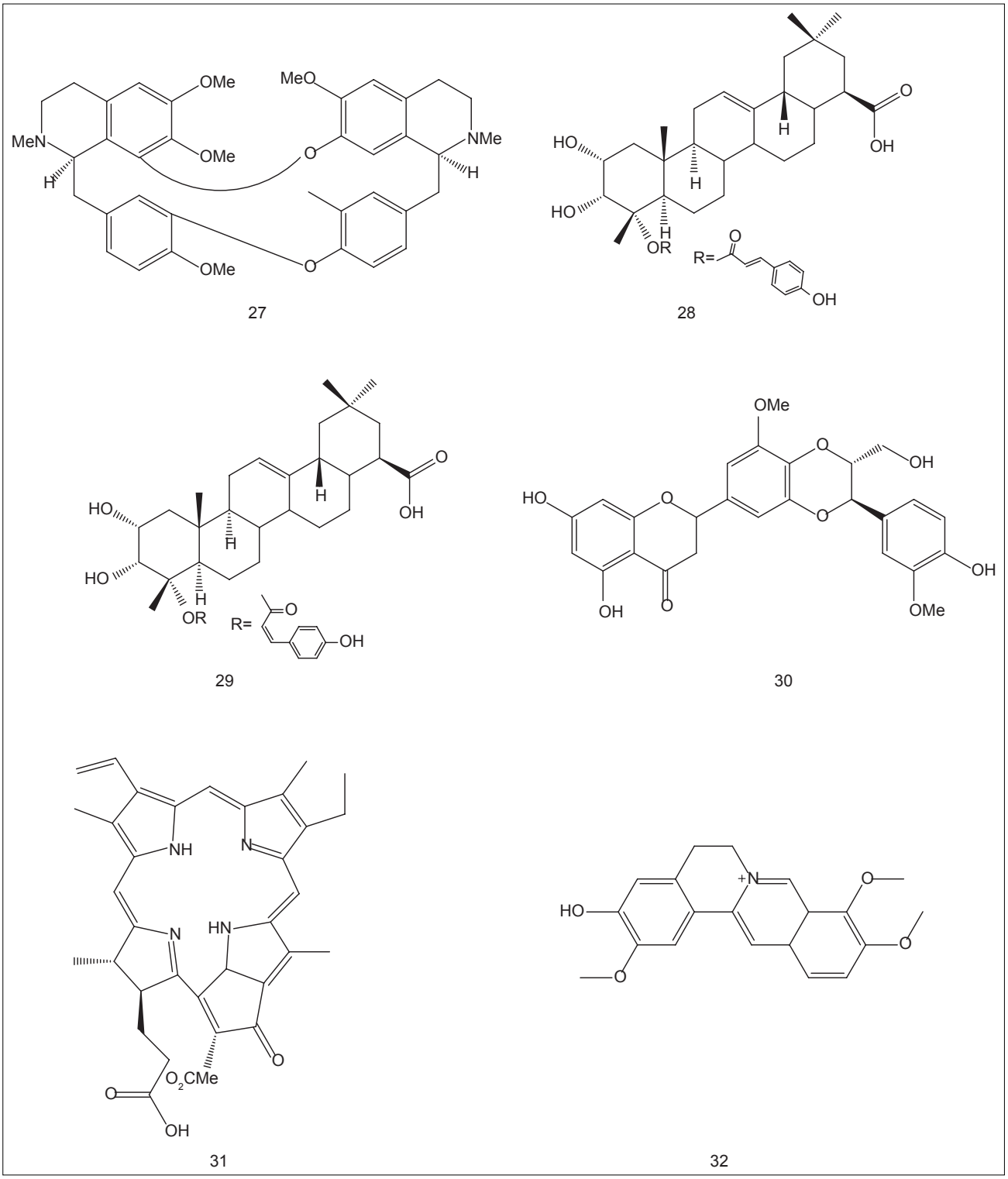

Figure 1: The structures of some phytochemical compounds isolated from various species of *Berberis*

Jatrorrhizine (32) as aporotoberberine alkaloid has been separated from *B. umbellate*.[23] Tetrahydro isoquinoline alkaloids are another noteworthy alkaloid group reported from *B. tinctoria*.

CONCLUSIONS

Crocus sativus, *Cuminum cyminum* and *Berberis vulgaris* are important medicinal food plants growing widely in Iran and also cultivated for their nutritional purposes and economic significance.[35,36] "Zereshk" is a Persian common name for the genus *Berberis* that has been frequently consumed as a food additive and also traditionally as a remedy in Iran. In traditional and folklore medicine, it has been used for its many pharmacological and biological activities, which make it an effective remedy for various kinds of illnesses. The literature reviews revealed the presence of quinoline and isoquinoline alkaloids together with sterols and triterpenes. Bereberine and other similar alkaloids have been identified as the main responsible natural compounds for diverse medicinal properties.

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Role of Ayurveda in management of oral health

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ABSTRACT

Oral diseases continue to be a major health problem world-wide. Oral health is integral to general well-being and relates to the quality-of-life that extends beyond the functions of the craniofacial complex. The standard Western medicine has had only limited success in the prevention of periodontal disease and in the treatment of a variety of oral diseases. Hence, the search for alternative products continues and natural phytochemicals isolated from plants used in traditional medicine are considered to be good alternatives to synthetic chemicals. The botanicals in the Ayurvedic material medica have been proven to be safe and effective, through several hundred to several thousand years of use. The exploration of botanicals used in traditional medicine may lead to the development of novel preventive or therapeutic strategies for oral health. The present scientific evidence based review is focused on the possible role of Ayurveda in the management of various orofacial disorders.

Key words: Ayurveda, dentistry, oral health, orofacial disorders

INTRODUCTION

Oral diseases continue to be a major health problem world-wide.[1] Dental caries and periodontal diseases are among the most important global oral health problems, although other conditions like oral and pharyngeal cancers and oral tissue lesions are also of significant concern.[2] Oral health is integral to general well-being and relates to the quality-of-life that extends beyond the functions of the craniofacial complex. The link between oral diseases and the activities of microbial species that form part of the micro biota of the oral cavity is well-established.[3] The global need for alternative prevention and treatment options and products for oral diseases that are safe, effective and economical comes from the rise in disease incidence (particularly in developing countries), increased resistance by pathogenic bacteria to currently used antibiotics and chemotherapeutics, opportunistic infections in immunocompromised individuals and financial considerations in developing countries.[4,5] Despite several chemical agents being commercially available, these can alter oral micro biota and have undesirable side-effects such as vomiting, diarrhea and tooth staining.[6,7] Furthermore, the standard Western medicine has had only limited success in the prevention of periodontal disease and in the treatment of a variety of oral diseases. Hence, the search for alternative products continues and natural phytochemicals isolated from plants used in traditional medicine are considered as good alternatives to synthetic chemicals.[8]

Ayurveda is the ancient Indian system of health-care and longevity. It involves a holistic view of man, his health and illness. Ayurvedic treatment is aimed at patient as an organic whole and treatment consists of salubrious use of drugs, diets and certain practices.[9] Currently, Ayurveda is widely practiced in the Hindustan peninsula (India and the neighboring countries) and in recent years, has attracted much attention in economically developed countries such as those in Europe and in the United States and Japan.[10] There are approximately 1250 Indian medicinal plants[11] that are used in formulating beneficial measures according to Ayurvedic or other ethnicity. This 5000-year-old system of medicine recommends treatments with specific herbs and minerals to cure various diseases. The botanicals in the Ayurvedic material medica have been proven to be safe and effective, through several hundred to several thousand years of use.[12] The exploration of botanicals used in traditional medicine, may lead to the development of novel preventive or therapeutic strategies for oral health.[13] As most of the oral diseases are due to bacterial infections and it has been well-documented that medicinal plants confer considerable anti-bacterial activity against various microorganisms including bacteria's responsible for dental caries.[14]

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The dentist needs to be more informed regarding the use, safety and effectiveness of the various traditional medicines and over-the-counter products. As this is hardly explored part for the field of dentistry, there is a need for integration of professional dental treatment modalities and complementary alternative medical (CAM) systems to provide the best and unique from each system to patients as a complementary therapy and an alternative choice of treatment.[15] Considering the importance of various traditional or CAM systems, the present scientific evidence based review of literature is focused on the possible role of Ayurveda in the management of various orofacial disorders.

MATERIALS AND METHODS

In this review of the literature, we only considered those studies that include individual plants or mixtures of plants consistent with the philosophy of Ayurveda. The databases searched for the current review were Medline, Natural Products Alert Database, and related databases, such as AYUSH Research Portal, National Library of Ayurveda Medicine, Systematic Reviews in Ayurveda, Ayurveda Database, Web of Science, Indus Medicus and Google Scholar; by consulting existing bibliographies; by using both forward and backward reference chaining techniques; and by tracking recent activities in the field of Ayurveda, which is primarily concerned with prevention and management of orofacial disorders. In addition, we also collected literature on traditional medicine and searched some Indian journals not included in Medline. References that were primarily anecdotal or that were only peripherally related to the topic were excluded.

Ayurveda and the concept of health

Sushruta Samhita, the surgical compendium of Ayurveda, defines health as "the equilibrium of the three biological humors (*doshas*), the seven body tissues (*dhatus*), proper digestion and a state of pleasure or happiness of the soul, senses and the mind."[16]

A balance among the three *doshas* is necessary for health. Together, the three *doshas* govern all metabolic activities. When their actions in our mind-body constitution are balanced, we experience psychological and physical wellness. When they go slightly out of balance, we may feel uneasy. When they are more obviously unbalanced, symptoms of sickness can be observed and experienced.[17,18]

Ayurveda and orofacial diseases

According to the *Shalyatantra* and *Shalakyatantra* (one of the branches of Ayurveda), 65 varieties of oral diseases can arise in seven anatomic locations-eight on the lips, 15 on the alveolar margin, eight in connection with the teeth, five on the tongue, nine on the palate, 17 in the oropharynx and three in a generalized form.[19]

For the treatment of these diseases Ayurveda advocates procedures such as oral cleansing, extractions, excisions, flap surgeries etc., Along with the treatment of orofacial diseases, Ayurveda recommends some daily use therapeutic procedures for the prevention of and maintenance of oral health. These include: *Dant Dhavani* (Brushing), *Jivha Lekhana* (Tongue scrapping) and *Gandoosha* (gargling) or oil pulling and tissue regeneration therapies. Some of the scientifically proven beneficial effects of these procedures are described below:

- *Dant Dhavani* (brushing): *Avurveda* recommends chewing sticks in the morning as well as after every meal to prevent diseases. Ayurveda insists on the use of herbal brushes, approximately nine inches long and the thickness of one's little finger. These herb sticks should be either "*kashaya*" (astringent), "*katu*" (acrid) or "*tikta*" (bitter) in taste. The method of use is to crush one end, chew it and eat it slowly.[20] The *neem* (*margosa* or *Azadirachta indica*) is a famous herbal chewing stick. Fresh stems of *liquorice* (*Glycyrrhiza glabra*), *black catechu* or the *cutch tree* (*Acacia Catechu* Linn.),[21] *Arjuna* tree (*Termmalia arjuna*), *fever nut* (*Caesalipinia bouduc*) and *milkweed plant* (*Calotropis procera*)[22] can also be used for brushing. Chewing on these stems is believed to cause attrition and leveling of biting surfaces, facilitate salivary secretion and possibly, help in plaque control while some stems have an anti-bacterial action.[22] Present-day research has shown that all the chewing sticks described in ancient *Avurveda* texts (Circa 200 BC) have medicinal and anti-cariogenic properties.[23]
- *Jivha Lekhana* (tongue scrapping): It is ideal to use gold, silver, copper, stainless steel for the scrapping of the tongue. Tongue scrapping stimulates the reflex points of the tongue. Removes bad odor (halitosis). Improves the sense of taste, stimulate the secretion of digestive enzymes. Removes millions of bacteria growth (approximately 500 varieties) Clinical evidence also shows that use of tongue scrapers on a regular basis, has a significant Improvement on eliminating anaerobic bacteria and decreases bad odor.[24]
- *Gandusha* (gargling) or oil pulling: Oil pulling is an ancient Ayurveda procedure that involves swishing oil in the mouth for oral and systemic health benefits. It is mentioned in the *Avurvedic* text *Charaka Samhita* where it is called *Kavala* or *Gandusha* and is claimed to cure about 30 systemic diseases ranging from headache, migraine to diabetes and asthma. Oil pulling has been used extensively as a traditional Indian folk remedy for many years to prevent decay, oral malodor, bleeding gums, dryness of throat, cracked lips and for strengthening teeth, gums and the jaw.[25,26] Oil pulling therapy can be done using oils like sunflower oil or *sesame* oil.[27] Oil pulling therapy is very effective against plaque induced gingivitis both in the clinical and microbiological assessment.[28,29]
- Tissue regeneration therapies: In *Avurveda*, the well-known herb, *Amla* (*Phyllanthus emblica*) is considered a general rebuilder of oral health. *Amla* works well as

a mouth rinse as a decoction. One to two grams per day can be taken orally in capsules for the long-term benefit to the teeth and gums. *Amla* supports the healing and development of connective tissue when taken internally.[30] Regular use of *Bilberry* and *hawthorn berry* fruits stabilize collagen and strengthens the gum tissue.[31] *Liquorice* root promotes anti-cavity action, reduces plaque and has an anti-bacterial effect.[30] Herbs such as *yellow dock root*, *alfalfa leaf*, *cinnamon bark* and *turmeric root* are taken internally to strengthen *Astidharu*, for example, the skeleton and the joints, have proven to be good for long term health of teeth.[31]

Ayurvedic herbs with various oral health related properties

Ayurvedic medications have stood the test of time and since time immemorial been used for various ailments. Recently, there is renewed interest in use of various Ayurvedic drugs for oral and dental health. Various plants and natural products have been used for their pharmacological applications viz. antiulcer genic, wound healing, anti-inflammatory, antimicrobial, antioxidant properties etc.[31-33] In this section, we have tried to review the recent studies undertaken to use of natural products for oral diseases and also have looked into the multitude prospects and perspectives of Ayurveda in the management of orofacial diseases. Various clinical implications of commonly used Ayurvedic herbs in the management of orofacial diseases are summarized in Table 1.

CONCLUSION

Oral diseases are one of the most important problems in public health and are on the rise in developing countries. Most of the oral diseases are caused due to the bacterial infections. The anti-bacterial activity of medicinal plants are due to the presence of potential bioactive compounds, which help to reduce bacterial load in the oral cavity and thus prevent the formation of plaque, dental caries and ulcers. Use of indigenous plants in oral health and hygiene has a long history in different parts of the world. Therefore, this knowledge is likely to vanish soon as many of these ethno-phytotherapeutic remedies are followed only by a few in rural areas. New generation is ignorant of this traditional knowledge. Because of younger generation's lack of knowledge on the identification, collection, preservation and processing of the plant species for medicinal use it is therefore very crucial to conserve these ethno-cultural practices before they are lost definitively.

In this paper, an attempt has been made to review various herbal plants mentioned in Ayurveda that can be used as an adjunct for the maintenance of oral health. The literature showed that there are numerous Ayurvedic drugs, which can be used in prevention as well as management of oral diseases. Many Ayurvedic herbal plants, which are reviewed, possess antimicrobial, anti-inflammatory, analgesic, antiulcer genic activities when screened according to the modern parameters. However, among them very negligible amount of herbals

Table 1: Plants with their oral health related indications

Plants and their scientific use for oral health
Amala (*Emblica officinalis*): It has an antioxidant as well as astringent property which has been proven to be effective in the treatment of toothache, gingival inflammations,[34] *apthous stomatitis*[35] and other types of mouth ulcers
Anar/Dalima (*punica granatum*): Topical applications of *pomegranate* preparations have been found to be particularly effective for controlling oral inflammation as well as bacterial and fungal counts in periodontal disease[36-38] and *Candida*-associated denture stomatitis.[39] The *ellagitannin, punicalagin*, is thought to be responsible for *pomegranate's* antibacterial activity[36]
Launga/Clove (*Syzygium aromaticum*): *Clove* oil is commonly used to relief pain of dental caries. *Eugenol* is considered as an active component (including *beta caryophyllene*).[40] *Eugenol* is also widely used in conjunction with root canal therapy, temporary fillings and general gum pain, dental abscesses and in other gum diseases[41]
Datiwan (*Alucita bidentata*): *Datiwan's* stem and leaves are mainly used. The root juice is used in Nepal for the treatment of toothache. The stem of the plant is used as a toothbrush and is said to be good in the treatment of pyorrhea[31]
Gotu kola (*Centella asiatica*): It is effective in the treatment of mouth ulcers. It is known to heal wounds and promote connective tissue growth. *Asiaticoide* and *hypaphorine* are believed to be responsible for this action.[42] According to Sastravaha *et al.*, *Centella asiatica* showed a significant improvements in decreasing plaque, periodontal pocket depth and attachment level at 3 months[43]
Grita Kumari (*Aloe vera*): It has unexpectedly shown an interesting property of dentin formation. Jittapiromsak *et al.* investigated the effect of *acemannan* (extracted polysaccharide of *aloe vera*) on dentin formation. In this, PDPCs were treated with *acemannan*. The results revealed that *acemannan* significantly increased pulp cell proliferation, BMP-2, ALPase activity, DSP expression and mineralization. The *acemannan*-treated group also exhibited a complete homogeneous calcified dentin bridge and good pulp tissue organization; the data suggested that *acemannan* promotes dentin formation by stimulating PDPCs proliferation, differentiation, extracellular matrix formation and mineralization[44]
Guduchi (*Tinospora cordifolia*): It has an anti-inflammatory, antioxidant, immune-modulator, properties. A significant difference was observed in a study with respect to improvement in salivary flow and in reduction in severity of mucositis in radiotherapy patients thus proving the role of *guduchi* as a radioprotector[45]
Jasmine (*Jasminum grandiflorum*): The leaves are used in the treatment of odontalgia, fixing loose teeth, ulcerative stomatitis and oral wounds. The leaves also possess a potential antiulcer activity, which may be attributed to its antioxidant mechanism of action. Thus may be tried in the treatment oral ulcers[46]
Kantakari (*Solanum xanthocarpum*): *Dhoopana* with seeds of *kantakari* has been used for treatment of dental caries. This anti caries activity is attributed to the chemical constituents such as *solanocarpine, carpesterol, solanocarpidine, solasodine, solasonine* and *solamargine*[40]
Nimbu (*Lemon*): Lemon solution is a natural source of citric acid (Ph 1.68) with lower acidity. Because of its wide anti-bacterial efficiency (including *Enterococcus faecalis*), a freshly prepared *lemon* solution is recommended as a root canal medicament[47]

contd...

Table 1: Contd...

Amra/Mango (*Magnifera indica*): *Mango* leaf contains ascorbic and phenolic acids. Studies have shown that mango leaves possess anti-bacterial properties against anaerobic dental microflora such as *Prevotella intermedia* and *Porphyromonas gingivalis* and can be effectively used as adjunct for maintenance of oral hygiene[48]
Mukhjali (*Drosera peltata*): Leaves are traditionally used for the treatment of dental caries, Didry *et al.*, showed that chloroform extracts of the aerial plant parts showed broad spectrum activity against numerous bacteria of the oral cavity, with greatest activity against *S. mutans* and *S. sobrinus*.[49] plumbagin was identified as the active component of this extract
Neem (*Azadirachta indica*): Anti-bacterial, antifungal, antiviral, antioxidant, anti-inflammatory, analgesic, immunostimulant properties of *neem* are well-established.[50] Anti-plaque activity of *neem* stick was demonstrated by Bandyopadhyay *et al.* It has both mechanical as well as chemotherapeutic antiplaque agents. Presence of *gallotannins* during the early stages of plaque formation could effectively reduce number of bacteria responsible for periodontitis.[51] Furthermore, the mouth rinse prepared from *neem* leaves has shown efficacy in treatment of periodontitis[52]
Nilgiri (*Eucalyptus globulus*): *Eucalyptus* extract containing chewing gum showed a significant positive effect on plague accumulation, gingival index, bleeding on probing and periodontal depth probing.[53] *Eucalyptus* containing *macrocarpals* have also shown anti-bacterial activity against cariogenic bacteria.[52,53] It also displaces saliva into the alkaline range[54]
Orange: Orange oil is mainly composed of *dlimonene*, some long chain aliphatic hydrocarbon alcohols and aldehydes like *octanal*. It is suggested to use in gutta-percha softening and in dissolving endodontic sealers[3]
Rumi mastagi/mastic gum (*Pistacia lentiscus*): Used as a remedy for oral malodor. It has shown great activity against *Porphyromonas gingivalis* by using disc diffusion assays[56]
Tila/Sesame (*Sesamum indicum*): Ashokan *et al.* found that the oil pulling therapy done by using *sesame* oil, significantly reduces the plaque index, modified gingival scores and total colony count of aerobic microorganisms in the plaque of adolescents with plaque-induced gingivitis[27]
Triphala: It contains the dried fruits of three medicinal plants *Terminalia chebula, Terminalia belerica* and *Phyllanthus embelica*.[57] It has shown a very promising anti-caries[58] and anti-plaque properties, it is also used for strengthening the gums[59] as a root canal irrigant[60]
Tulsi (*Ocimum sanctum*): *Studies have shown that* 4% *Tulsi* extract mouth rinse effectively reduces the salivary *Streptococcus mutans* counts[61]
Harita/Turmeric (*Curcuma longa linn.*): There are many uses of *turmeric* in dentistry. The active component is *curcumin*. *Turmeric* can be used in relief of pain, gingivitis, periodontitis, as colorant in pit and fissure sealant, in dental plaque detection,[62,63] etc., It is suggested that *turmeric* extracts can be extensively used in the treatment of potentially malignant lesions in oral cavity.[64] It effectively inhibits metastasis of melanoma cells and may be especially useful in deactivating the carcinogens in cigarette smoke and chewing tobacco[65,66]

PDPC=Primary human dental pulp cells, BMP-2=Bone morphogenetic protein 2, DSP=Dentin sialoprotein

extracts are used in clinical practice and the rest of others are not practiced because of their unknown toxicological effects. The clinical studies should be encouraged to assess the efficacy as well as toxicity of herbal drugs.

The traditional knowledge of Ayurveda should be integrated with the modern dentistry. For this, the active principles of plants should be incorporated into modern oral health-care practices and dentists should be encouraged to use natural remedies in various oral health treatments. This will make dentistry much safer, affordable and more accessible for the lower socio-economic groups in society.

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A current update on the phytopharmacological aspects of *Houttuynia cordata* Thunb

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ABSTRACT

The present review is an attempt to put an insight into a medicinal plant *Houttuynia cordata* Thunb, which is indigenous to North-East India and China. It is an aromatic medicinal herb belonging to family *Saururaceae* and is restricted to specialized moist habitats. The review provides detailed information regarding the morphology, distribution, phytochemistry, ethnopharmacological uses and also describes various pharmacological activities reported on the plant *H. cordata*. The review describes therapeutic efficacy of the whole plant and its extracts, fractions and isolated compounds in different diseased condition. Among the important pharmacological activities reported includes, anti-mutagenic, anti-cancer, adjuvanticity, anti-obesity, hepatoprotective, anti-viral, anti-bacterial, anti-inflammatory, free radical scavenging, anti-microbial, anti-allergic, anti-leukemic, chronic sinusitis and nasal polyps activities. Thus, the present review will act as a source of referential information to researchers to perform clinical studies on isolated compounds that may serve the society and will help in improving human health care system.

Key words: Anti-viral, aristolactams, *Houttuynia cordata*, *Saururaceae*

INTRODUCTION

In most of the developing countries, 70-95% of the population rely on traditional medicines for primary health-care and out of these 85% of people use plants or their extracts as the active substance.[1] The search for new biologically active compounds from plants usually depends on the specific ethnic and folk information obtained from local practitioners and is still regarded as an important source for drug discovery. In India, approximately 2000 drugs are of plant origin.[2] In view of the widespread interest on using medicinal plants, the present review on *Houttuynia cordata* Thunb. provides up-to-date information with reference to botanical, commercial, ethnopharmacological, phytochemical and pharmacological studies that appears in the literature. *H. cordata* Thunb. belongs to the family *Saururaceae* and is commonly known as Chinese lizard tail. It is a perennial herb with stoloniferous rhizome having two distinct chemotypes.[3,4] The Chinese chemotype of the species is found in wild and semi-wild conditions in the North-East of India from April to September.[5-7] *H. cordata* is available in India, especially in Brahmaputra valley of Assam and is utilized by various tribes of Assam in the form of vegetable as well as in various medicinal purposes traditionally.[8]

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TAXONOMICAL CLASSIFICATION

Kingdom: *Plantae*; Phylum: *Magnoliophyta*; Class: *Magnoliopsida*; Sub-class: *Magnoliidae*; Order: *Piperales*; Family: *Saururaceae*; Genus: *Houttuynia* Thunb.; Species: *H. cordata*.[9]

BOTANICAL DESCRIPTION

The plant *H. cordata* is an aromatic medicinal herb with creeping root stock. It grows about 20-50 cm in height with leaves measuring 4-8 cm in length, 3-6 cm in width and are broad, ovate-cordate. Stipular sheath are 1-2.5 cm, 1/4-1/2 as long as petiole, usually ciliate, base enlarged and slightly clasping; petiole 1-3.5 cm, glabrous. Leaf blades are broadly ovate or ovate-cordate, 4-10 cm long, 2.5-6 cm wide, thinly papery, densely glandular, usually glabrous. Sometimes they are pubescent at vein axils, usually purplish abaxial, base cordate, apex shortly acuminate; veins 5-7, basal or innermost pair arising ca. 5 mm above the base, if 7-veined, then outermost pair very slender or inconspicuous; reticulate veins ± conspicuous. Inflorescences 1.5-2.5 cm long,

3-6 mm wide; peduncles 1.5-3 cm, subglabrous; involucral bracts oblong or obovate, 10-15 mm long, 5-7 mm wide, apex rounded. Flowers are naked with dense spikes, subtended by four white and petalloid bracts, involucres, non-petal, yellow inflorescences ca. 1-3 cm long, three stamens, flowering in June-July.[10] Rhizomes are creeping, thin while basal part of stems creeping rooted in whorls at nodes, apical part erect, glabrous or pubescent on nodes, sometimes purplish red.[11] The chromosomal number of *H. cordata* was reported as $2n = 96$.[12]

ETHNOMEDICAL USES

In the North-East region of India, whole plant of *H. cordata* is eaten raw as a medicinal salad for lowering the blood sager level and is commonly known by the name Jamyrdoh.[13] Moreover, leaf juice is taken for the treatment of cholera, dysentery, curing of blood deficiency and purification of blood.[14] Young shoots and leaves are eaten raw or cooked as a pot-herb. A decoction of this plant is used internally for the treatment of many ailments including cancer, coughs, dysentery, enteritis and fever. Externally, it is used for the treatment of snake bites and skin disorders. The leaves and stems are harvested during the growing season and are used as fresh decoctions. The leaf juice is also used as antidote and astringent.[15] The root, young shoots, leaves and sometimes the whole plant is traditionally used to cure various human ailments throughout South-East Asia. In Indo-China region, the entire plant is considered for its cooling, resolvent and emmenagogue properties. The leaves are recommended for the treatment of measles, dysentery and gonorrhea. The plant is also used in the treatment of eye troubles, skin diseases, hemorrhoids, relieving fever, resolving toxin, reducing swelling, draining pus, promoting urination and in certain diseases of women.[16]

PHARMACOLOGY

H. cordata possess a number of medicinally important activities such as anti-leukemic,[17] anti-cancer,[18] adjuvanticity,[19] anti-oxidant[20] and inhibitory effects on anaphylactic reaction and mast cell activation.[21] Moreover, *H. cordata* has also been utilized for the treatment of herpes simplex virus type 1 (HSV-1), influenza virus, human immunodeficiency virus type 1,[22] and chronic sinusitis and nasal polyps.[21]

Anaphylactic inhibitory activity

Oral administration of *H. cordata* water extract inhibited compound 48/80-induced systemic anaphylaxis in mice. Water extract of *H. cordata* at 100 mg; p.o. also inhibited the local allergic reaction, passive cutaneous anaphylaxis (PCA), activated by anti-dinitrophenyl (DNP) immunoglobulin E (IgE) antibody in rats. It also reduced the compound 48/80-induced mast cell degranulation and colchicine-induced deformation of rat peritoneal mast cells (RPMC). Moreover, *H. cordata* water extracts dose-dependently inhibited histamine release and calcium uptake of RPMC induced by compound 48/80 or anti-DNP IgE. The same extract also increased the level of intracellular cyclic adenosine monophosphate (cAMP) and inhibited significantly the compound 48/80-induced cAMP reduction in RPMC. These results suggest that water extracts of *H. cordata* may be beneficial in the treatment of mast cell-mediated anaphylactic responses.[21]

Anti-mutagenic activity

Aqueous extracts of *H. cordata* has been reported to possess anti-mutagenic effect on benzo (a) pyrene, aflatoxin B1 and oxidized frying oil (OFO), which demonstrated a dose-dependent response using the Ames test in Sprague-Dawley rats, which were fed with a diet of 0, 2, or 5% *H. cordata* and 15% fresh oil or OFO for 28 days. After administration of OFO, it was observed that there was a significant decrease in polyphenol content in plasma which increased in the faces showing an apparent decrease in absorption of polyphenol. On treatment with *H. cordata*, the polyphenol content in plasma improved, which may be due to the presence of higher polyphenol concentration in the aqueous extracts of *H. cordata*.[23]

Anti-inflammatory activity

Essential oil from *H. cordata* was reported to exhibit anti-inflammatory activity by a mechanism of action similar to that of non-steroidal anti-inflammatory drugs (NSAIDs). They inhibited the release of lipopolysaccharide (LPS)-induced prostaglandin E_2 (PGE_2) from mouse peritoneal macrophages (IC_{50} value: 44.8 μg/mL). Moreover, the inhibitory activity of *H. cordata* essential oil elicited a dose-dependent inhibition of cyclooxygenase-2 (COX-2) enzyme activity (IC_{50} value: 30.9 μg/mL). *H. cordata* essential oil was also found to elicit reduction in LPS-induced COX-2 messenger ribonucleic acid (mRNA) and protein expression, but did not affect COX-1 expression. NSAID and specific COX-2 inhibitor NS398 functioned similarly in LPS-induced mouse peritoneal macrophages.[24]

Water extracts of *H. cordata* exhibits anti-inflammatory activity on lipoteichoic acid (LTA)-induced inflammation in dermal fibroblasts by blocking the tumor necrosis factor-α (TNF-α) pathway. *H. cordata* (20 μg/mL) suppressed the level of LTA-induced TNF-α, mRNA and LTA-induced COX-2 protein by up to 40% and 52% respectively. Moreover, TNF-α-induced COX-2 expression was also down-regulated by *H. cordata* treatment up to 65%.[25]

Ethanolic extract of whole plant of *H. cordata* (10 μg/mL for 24 h) showed marked effect in treating mast cell-induced inflammatory diseases by a significant decrease in chemotactic index (63%) of human mast cells (HMC-1) in response to stem cell factor by inhibiting the nuclear factor-kappa B (NF-κB) activation.[26]

Anti-inflammatory activity of *H. cordata* injection (HCI), which constituted a mixture of essential oil from *H. cordata*, aqueous solution of sodium chloride solution and tween-80 was reported in carrageenan induced inflammation in the rat pleurisy model and by xylene in the mice ear edema model. The fluid volume,

protein concentration, C-reactive protein and cell infiltration were attenuated by HCI at all doses and touched bottom at a dose of 0.54 mL/100 g. This drug was also effective in inhibiting xylene induced ear edema and the percentage of inhibition came to 50% at a test dose of 80 μL/20 g.[27] Another anti-inflammatory study on supercritical extract of *H. cordata* (HSE) in a carrageenan-air pouch model showed that HSE (200 mg/kg; p.o.) exerts anti-inflammatory effects by inhibiting both TNF-α-nitric oxide (NO) and COX-2-PGE_2 pathways.[28]

Anti-viral activity

The optimal dosage of HCI showed direct inhibitory activity on cell infection by pseudorabies herpesvirus using Vero cells (a monkey kidney cell line) and swine testis cells as a model. While at high dosage *H. cordata* alone caused cell apoptosis.[29]

Aqueous extract of *H. cordata* showed immunomodulatory and anti-severe acute respiratory syndrome (SARS) activities. *H. cordata* also stimulated the proliferation of mouse splenic lymphocytes significantly and dose-dependently. By flow cytometry, it was revealed that *H. cordata* increased the proportion of $CD4^+$ and $CD8^+$ T cells. Moreover, it caused a significant increase in the secretion of interleukin (IL)-2 and (IL)-10 by mouse splenic lymphocytes. In the anti-viral aspect, *H. cordata* exhibited significant inhibitory effects on SARS coronavirus (SARS-CoV) 3C-like protease ($3CL^{pro}$) and RNA-dependent RNA polymerase.[30]

A 4-5 dioxoaporphin namely norcepharadione B isolated from the n-hexane fraction of *H. cordata* was found to possess good inhibitory activity against the replication of HSV-1.[31]

In particular, quercetin 7-rhamnoside (Q7R), a flavonoid present in *H. cordata*, has been reported to elicit anti-viral activities against porcine epidemic diarrhea virus (PEDV), which is the predominant cause of severe enteropathogenic diarrhea. Q7R actively inhibited PEDV replication with a 50% inhibitory concentration (IC_{50}: 0.014 μg/mL). The 50% cytotoxicity concentration (CC_{50}) of Q7R was over 100 μg/mL and the derived therapeutic index was 7142. Therefore, Q7R could be considered to be a lead compound for development of anti-PEDV drugs, which may be used to arrest the early stage of PEDV replication.[32]

Quercetin 3-rhamnoside (Q3R) from *H. cordata* possessed strong inhibitory effects on influenza A/WS/33 virus by reducing the formation of a visible cytopathic effect. Moreover, Q3R also inhibited virus replication in the initial stage of virus infection by indirect interaction with virus particles.[33]

One of the finding claimed that aqueous extract of *H. cordata* possess anti-viral activity against dengue virus serotype 2 (DEN-2), strain 16681. *H cordata* (10-100 mg/mL) was found to exhibit significant reduction in intracellular DEN-2 RNA production correlating with the decrease in dengue protein expression after pre- and post-incubation with HepG2 cells. Moreover, in the direct blocking mode, the extract bound with DEN-2 strongly inhibited the intracellular viral RNA replication with an effective dose (EC_{50}) of 0.8 mg/mL. Concentrations as low as 10-40 mg/mL of *H. cordata* extract also exhibited protective effect on virion release from infected monkey kidney cell line (LLC-MK2) cells.[34] Hot water extracts of *H. cordata* blocked HSV-2 infection through inhibition of NF-κB activation by the presence of major water extractable flavonoids quercetin or isoquercitrin at 10 μM.[35]

Anti-obesity effect

Administration of an aqueous extract of leaves of *H. cordata* (1 g/kg; p.o.) significantly inhibited the corn oil-induced increase in plasma triglyceride levels in mice. It also inhibited the oleic acid and glycerol induced increase in the levels of plasma non-esterified fatty acids and glycerol, respectively. Moreover, an anti-obesity effect of *H. cordata* leaf extract has also been reported in mice with high-fat-diet-induced obesity.[36]

Anti-bacterial activities

Water extract of *H. cordata* showed the anti-bacterial effects against *murine salmonellosis*. The anti-bacterial activity of *H. cordata* water extract was also examined in a *Salmonella enterica* serovar (*Salmonella typhimurium*) and was found to increase in a dose-dependent manner at concentrations from 25 to 100 mg/mL during 8-h incubation. Water extract of *H. cordata* also affected RAW 264.7 cells including morphologic changes and bacterial uptake, but there was no significant difference in bacterial replication in RAW 264.7 cells. With *H. cordata* water extract alone, NO production by RAW 264.7 cells did not increase, but when RAW 264.7 cells were infected by *S. typhimurium*, with or without extract, NO production with extract was 2-fold higher than that without extract. Treatment with aqueous extract of *H. cordata* did not affect inducible nitrous oxide synthase (iNOS) mRNA expression by RAW 264.7 cells, but when RAW 264.7 cells with extract were infected by *S. typhimurium*, iNOS mRNA expression was increased during 8-h incubation. Furthermore, water extract of *H. cordata* showed virulence reduction effects in *S. typhimurium*-infected BALB/c mice. After a lethal dose of *S. typhimurium*, the mortality rate in the extract untreated group was 100% at 7^{th} day, but at the doses 25, 50 and 100 μg/mL of extract groups were survived until 11, 17 and 23 days respectively. These data suggest that *H. cordata* water extract is stable and beneficial in the treatment of bacterial infection including intracellular replicating pathogens and may solve anti-microbial misuse and overuse.[37] Houttuynin (decanoyl acetaldehyde), a β-dicarbonyl compound, is reported as a major anti-bacterial constituent in the volatile oil of *H. cordata*.[38]

Effects on xenobiotic-metabolizing enzyme system of rodents

One of the finding on *H. cordata* claimed that the OFO feeding produced a significant increase in phase I and II enzyme systems, including the content of CYP450 and microsomal protein. The oil was also reported to play a significant role in activities of nicotinamide adenine dinucleotide phosphate reductase,

ethoxyresorufin O-deethylase (EROD), pentoxyresorufin O-dealkylase, aniline hydroxylase (ANH), aminopyrine demethylase (AMD) and quinone reductase (QR) (Phase-II enzyme) in Sprague-Dawley rats. In addition, the activities of EROD, ANH and AMD decreased and QR increased after feeding with *H. cordata* in OFO-fed group. Feeding with *H. cordata* diet also resulted in better regulation of the xenobiotic-metabolizing enzyme system.[39]

Anti-cancer activity

It is reported that *H. cordata* induced apoptotic cell death in human primary colorectal cancer cells through a mitochondria-dependent signaling pathway. *H. cordata* at 250 μg/mL showed chromatin condensation in the treated cells. Moreover, *H. cordata* increased reactive oxygen species production and decreased the mitochondrial membrane potential ($\Delta\Psi$ (m)) in examined cells. Mitochondria-dependent apoptotic signaling pathway was shown to be involved as determined by the increase in the levels of cytochrome c, Apaf-1 and caspase-3 and -9. The decrease in the level of $\Delta\Psi$ (m) was associated with an increase in the BAX/BCL-2 ratio which led to activation of caspase-3 and -9.[40]

Six bioactive alkaloids, aristolactam B, piperolactam A, aristolactam A, norcepharadione B, cepharadione B and splendidine were isolated by bioactivity-guided fractionation of a methanolic extract of the aerial part of *H. cordata*. All the isolates exhibited moderate cytotoxicity against the five human cancer cell lines (A-549, SK-OV-3, SKMEL-2, XF-498 and HCT-15) examined *in vitro*. Among them, splendidine was found to exhibit significant activity against each cell line and aristolactam B exhibited selective activity against XF-498 (central nerve system cell) (ED_{50}, 0.84 μg/mL).[18]

Anti-allergic activity

Aqueous extracts of *H. cordata* (10 or 100 mg/kg; p.o.) show a significant effect on mast cell-mediated anaphylactic reaction, which is involved in many allergic diseases such as asthma and allergic rhinitis. *H. cordata* aqueous extract inhibited the compound 48/80-induced systemic anaphylaxis in mice. It also inhibited the local allergic reaction, PCA, activated by anti-DNP IgE antibody in rats. Compound 48/80-induced mast cell degranulation and colchicine-induced deformations of RPMC were also reduced by the *H. cordata* extract. Moreover, the extract dose-dependently inhibited histamine release and calcium uptake of RPMC induced by compound 48/80 or anti-DNP IgE. Aqueous extract of *H. cordata* increased the level of intracellular cAMP and inhibited significantly the compound 48/80-induced cAMP reduction in RPMC.[21]

Ethanolic extract of *H. cordata* showed beneficial therapeutic effects on the T helper 2-mediated or allergic skin disorders. Ethanolic extract inhibited the expression of IL-4 and (IL)-5 in response to phorbol 12-myristate 13-acetate (PMA) and calcium ionophore (CaI) in Jurkat T cells and the HMC-1 line, HMC-1. IL-4-5 and TNF-α (TNF-γ)-induced thymus activation regulated chemokine (TARC) production was also blocked by ethanolic extract of *H. cordata* in skin fibroblast CCD-986 sk cells. Stimulants included in PMA, phytohemagglutinin and CaI, increased the mRNA level of CC chemokine receptor 4 (CCR4), a receptor of TARC, in Jurkat T cells and the ethanolic extract weakly blocked the increased mRNA level. However, the stimulants and *H. cordata* ethanolic extract had no effect on the CCR4 protein level. The ethanolic extract also inhibited the TARC-induced migration, as well as basal migration of Jurkat T cells.[41] It has been also reported that water extract of *H. cordata* suppressed anaphylactic reaction and IgE-mediated allergic response through inhibition of cytokines and multiple events of FcεRI-dependent signaling cascades in mast cells.[42]

Anti-diabetic activity

H. cordata water extract was also reported to exhibit significant decrease in the urinary protein, urinary albumin, monocyte chemo-attractant protein expression level and renal connective tissue growth factor (CTGF). It also showed a significant improvement in insulin resistance after giving 8 weeks of treatment to streptozotocine (STZ) induced type II diabetic mellitus rats.[43,44]

A recent study has shown that the volatile oil from *H. cordata* restored the alterations in blood glucose, insulin, adiponectin and CTGF levels in diabetic rats, induced by the combination of a high-carbohydrate and high-fat diet and STZ injection, which may be attributed to the reduced insulin resistance, adiponectin and CTGF levels.[45]

Anti-oxidant activity

Methanolic extract of *H. cordata* in an *in vitro* model has shown to possess free radical scavenging activity using 2, 2-diphenyl-1-picrylhydrazyl (DPPH), ferric reducing anti-oxidant power and trolox equivalent anti-oxidant capacity assays.[46] Anti-oxidant activity of *H. cordata* is mainly attributed to the presence of chlorogenic acids and its derivatives, catechin and procyanidin B, which were also characterized using on-line liquid chromatography-electrospray ionization mass spectrometer coupled with DPPH assay.[47]

One of the finding showed anti-oxidant activity of fermentation product of five indigenous plants *Phyllanthus emblica* Linn, *Morinda citrifolia* Linn, *H. cordata* Thunb. *Terminalia chebula* Retz and *Kaempferia parviflora* Wall. On oxidative stress in Wistar rats with STZ-induced type II diabetes. Fermentation product at the dose level 2 and 6 mL/kg body weight/day for 6 weeks significantly ($P < 0.05$) decreased the diabetes-associated oxidative stress to a large extent through the inhibition of lipid peroxidation.[48]

Dietary effects

A recent investigation has reported that methanolic extract of *H. cordata* powder (1 g/kg p.o.) increased growth performance, dry matter, nitrogen digestibility, white blood cell concentration, meat longissimus muscle area and thiobarbituric acid reactive substances value in finishing pigs.[49]

PHYTOCHEMISTRY

Phytochemical investigations on plant *H. cordata* up to 2012 have reported number of phytoconstituents present in the plant. Various types of chemical constituents such as aristolactams, 5,4-dioxoaporphines, oxoaporphines, amides, indoles, ionones, flavonoids, benzenoids, steroids and different volatile oils have been isolated from *H. cordata*. Houttuynoside A[31] and houttuynamide A[31] have also been isolated from this plant. Among the isolated compounds, some have been evaluated for their anti-oxidant and anti-tyrosinase activity. Cepharadione B showed strong inhibitory activity against tyrosinase with an IC_{50} value of 170 mM. Quercitrin, quercetin-3-*O*-β-D-galactop yranoside showed excellent DPPH radical-scavenging property with IC_{50} values of 31 and 63 mM, respectively.[31] Table 1 and Figure 1 demonstrate detailed information regarding the phytoconstituents with their specific classes isolated from *H. cordata*.

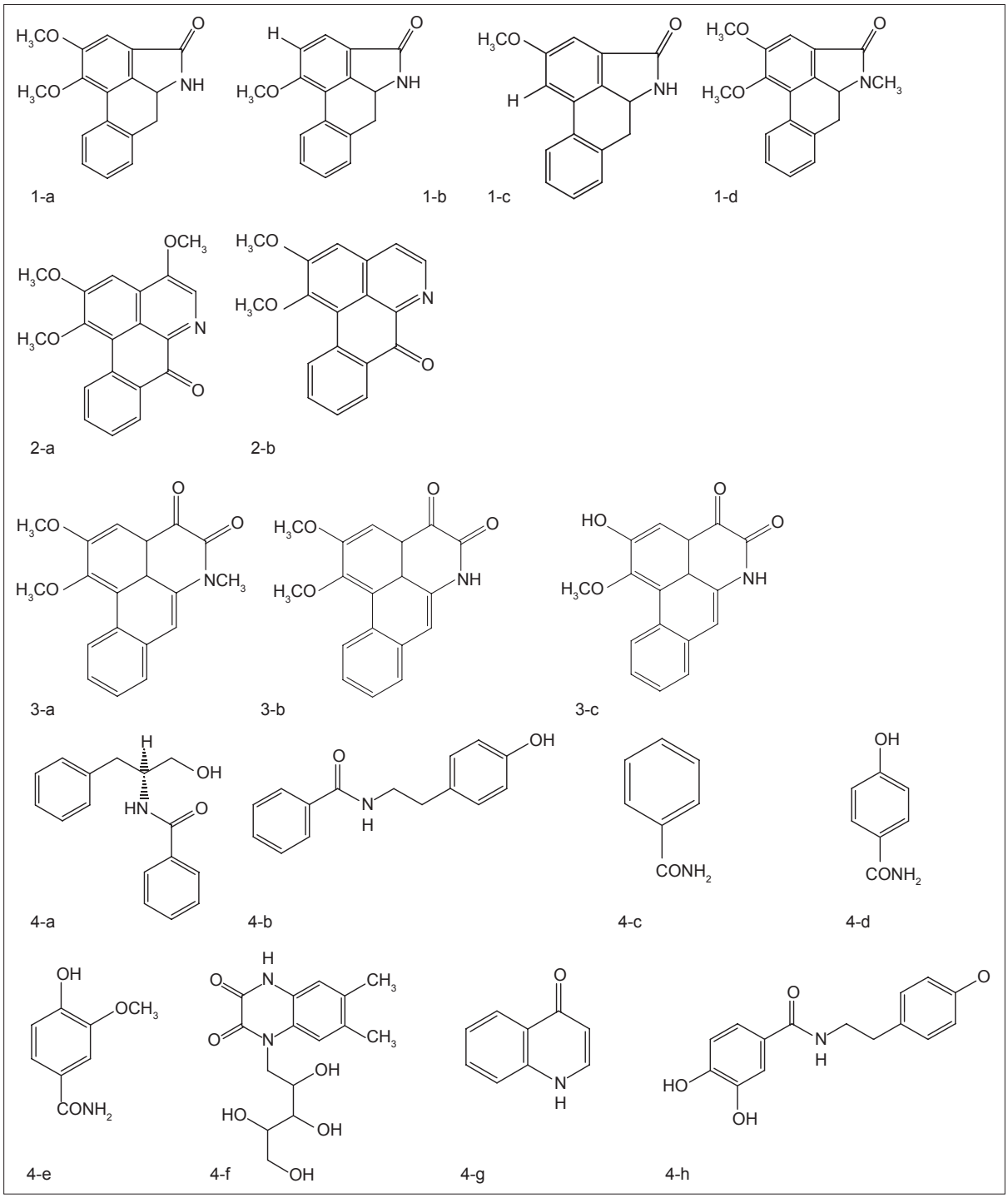

Figure 1: Phytoconstituents isolated from *Houttuynia cordata*

Contd...

CONCLUSION

According to Florae Reipublicae Popularis Sinicae and Flora Sichuanica, *H. cordata* Thunb. (Yuxingcao in Chinese) is the only species in the genus *Houttuynia*.[87,88] Its medicinal importance is well-described in Chinese system of medicine in fever, to

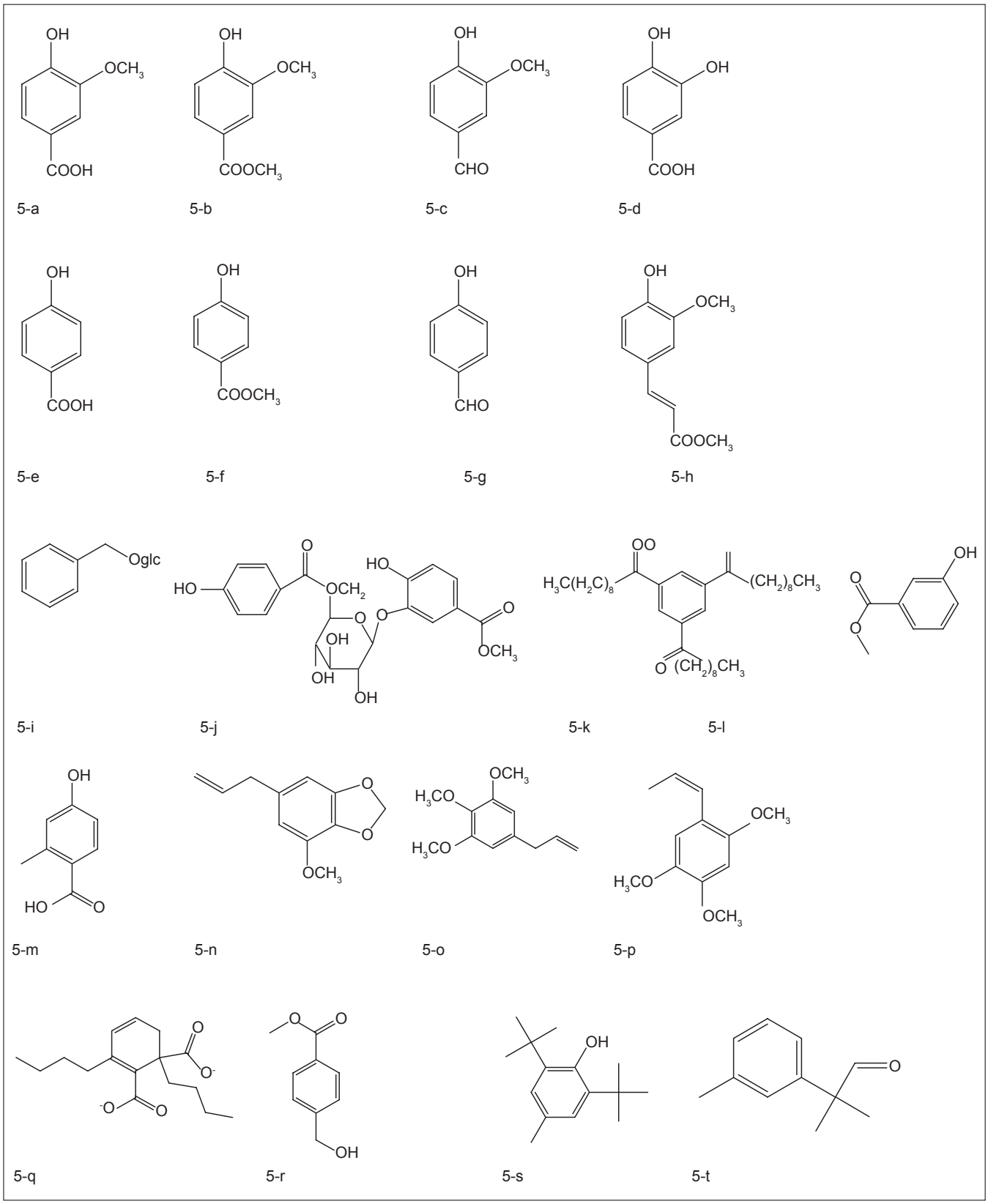

Figure 1: Phytoconstituents isolated from *Houttuynia cordata*

ease malnutrition, clearing of body toxins, anti-bacterial and in treatment of lung carbuncles. In addition, the plant is widely used as vegetable in North-Eastern parts of India and China and has been identified as one of the most potential medical and edible plant genetic resources by the Chinese State Health Department. Thus, the information provided in the present review may act as

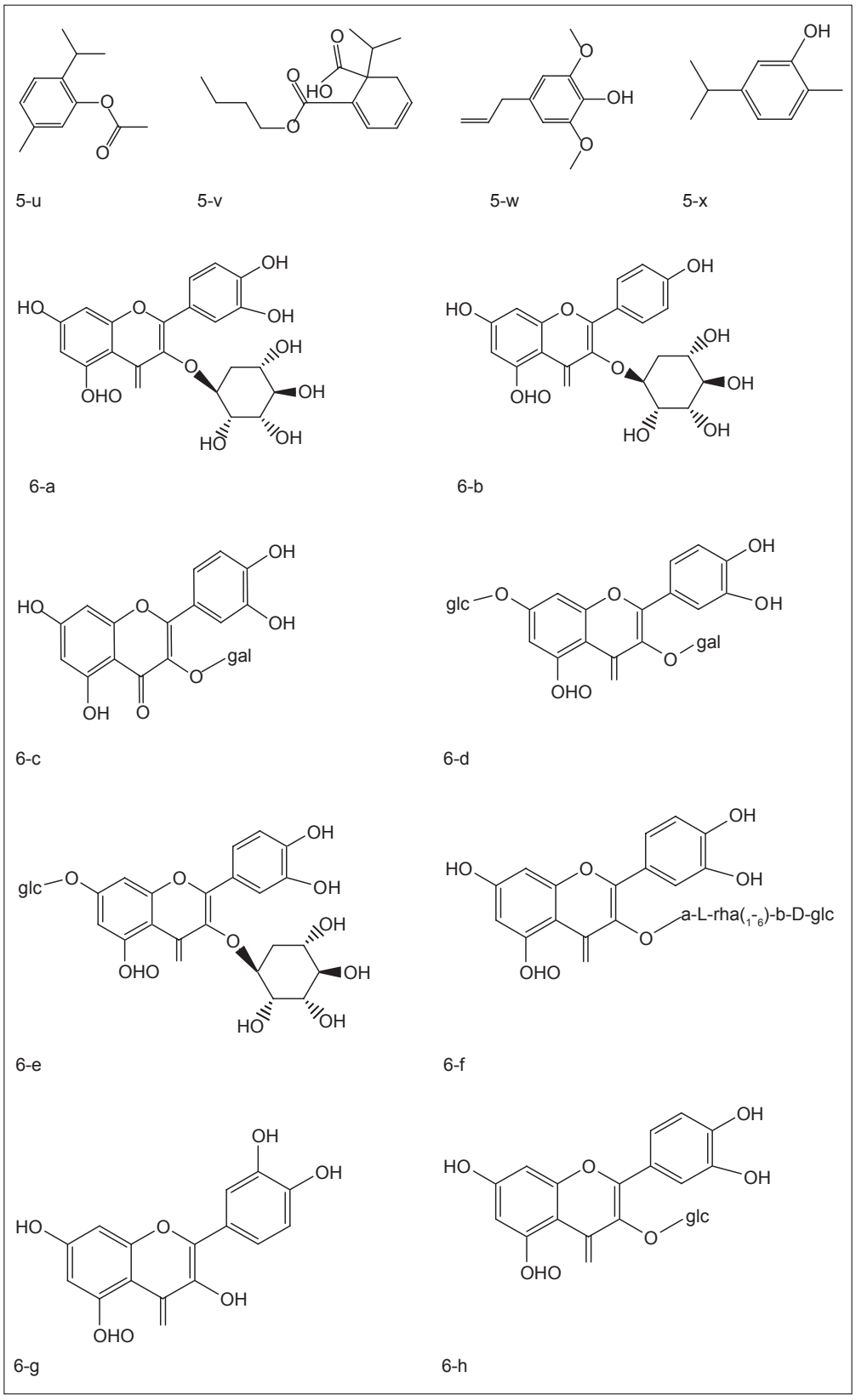

Figure 1: Phytoconstituents isolated from *Houttuynia cordata*

a contributing factor to the fact that at least 25% of all modern medicines are derived, either directly or indirectly, from medicinal plants, primarily through the application of modern technology to traditional knowledge.[1]

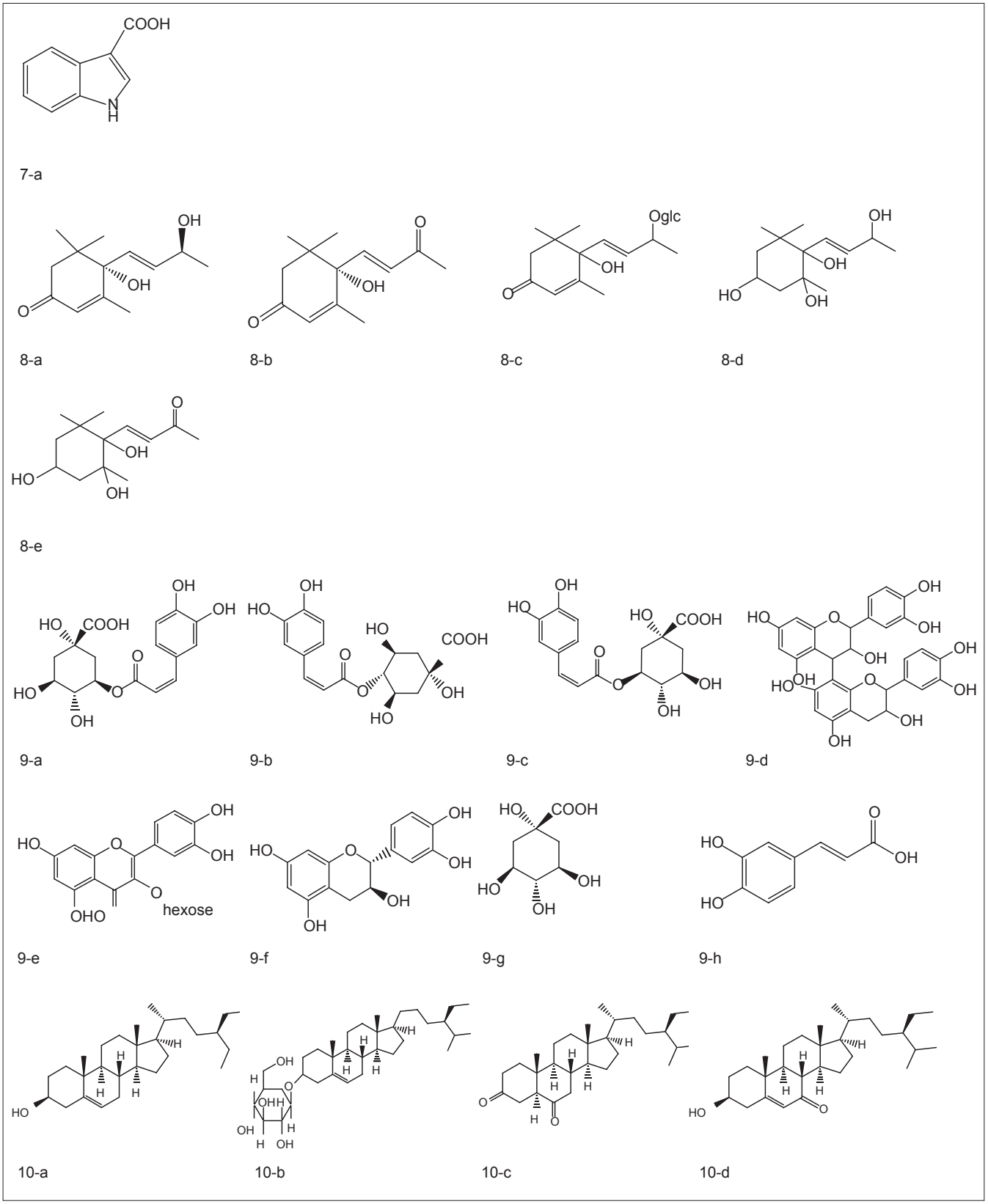

Figure 1: Phytoconstituents isolated from *Houttuynia cordata*

H. cordata offers an overall greater therapeutic value. The plethora of activities reported for the extracts, fractions and compounds isolated from *H. cordata* provide promising evidence for future research, which could achieve an important place in the world of modern drugs. Isolation on a large scale, chemical transformations and synthesis of the active compounds will

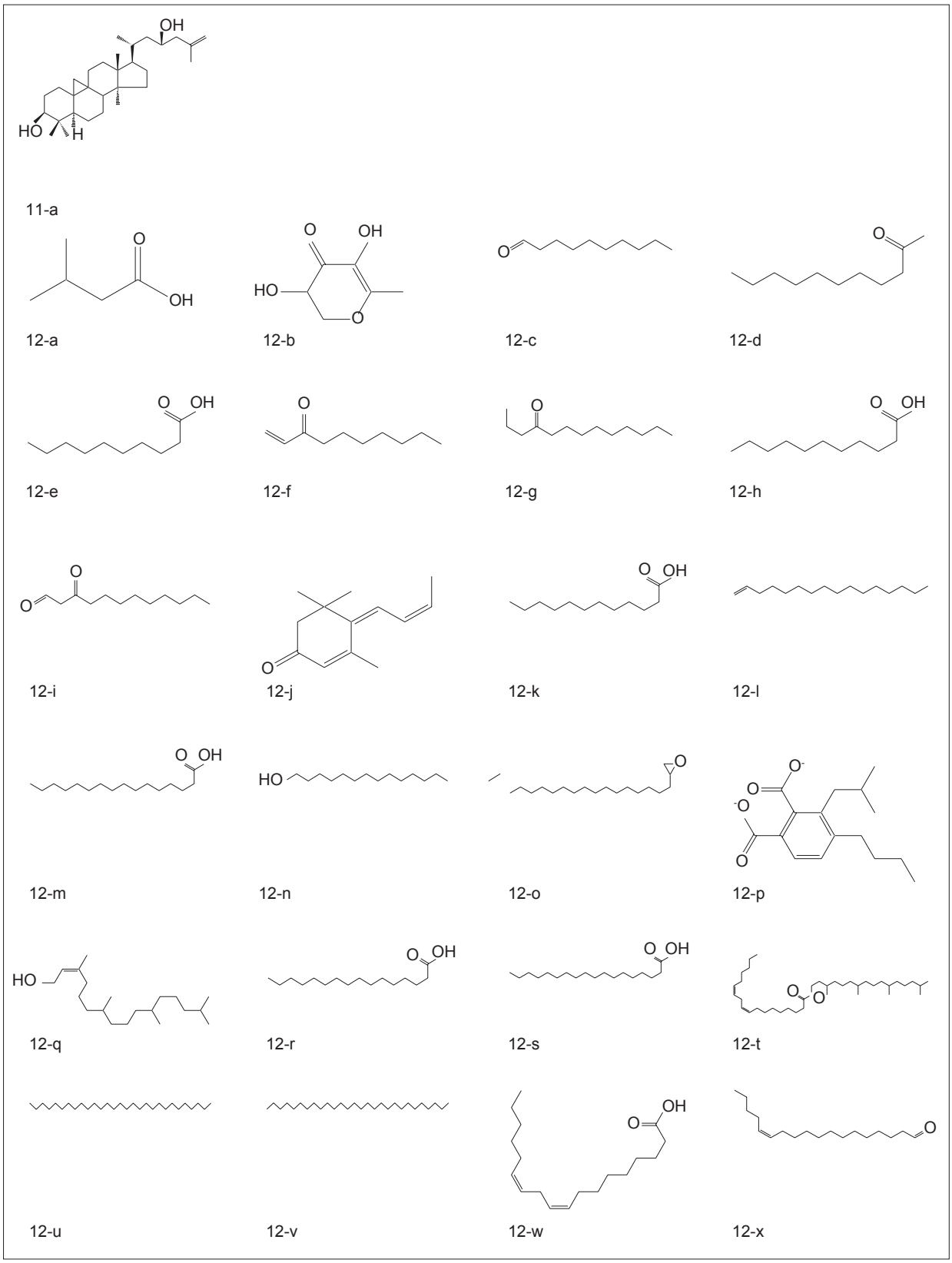

Figure 1: Phytoconstituents isolated from *Houttuynia cordata*

definitely enhance their pharmacological value. The provided information will also help in developing pharmacophores of many isolates that have not yet been identified and will also help in performing clinical trials using various active compounds against a variety of diseased conditions. Thus, the present review will elaborate the significance of *H. cordata* in human health-care system and will promote natural product research to its optimum height.

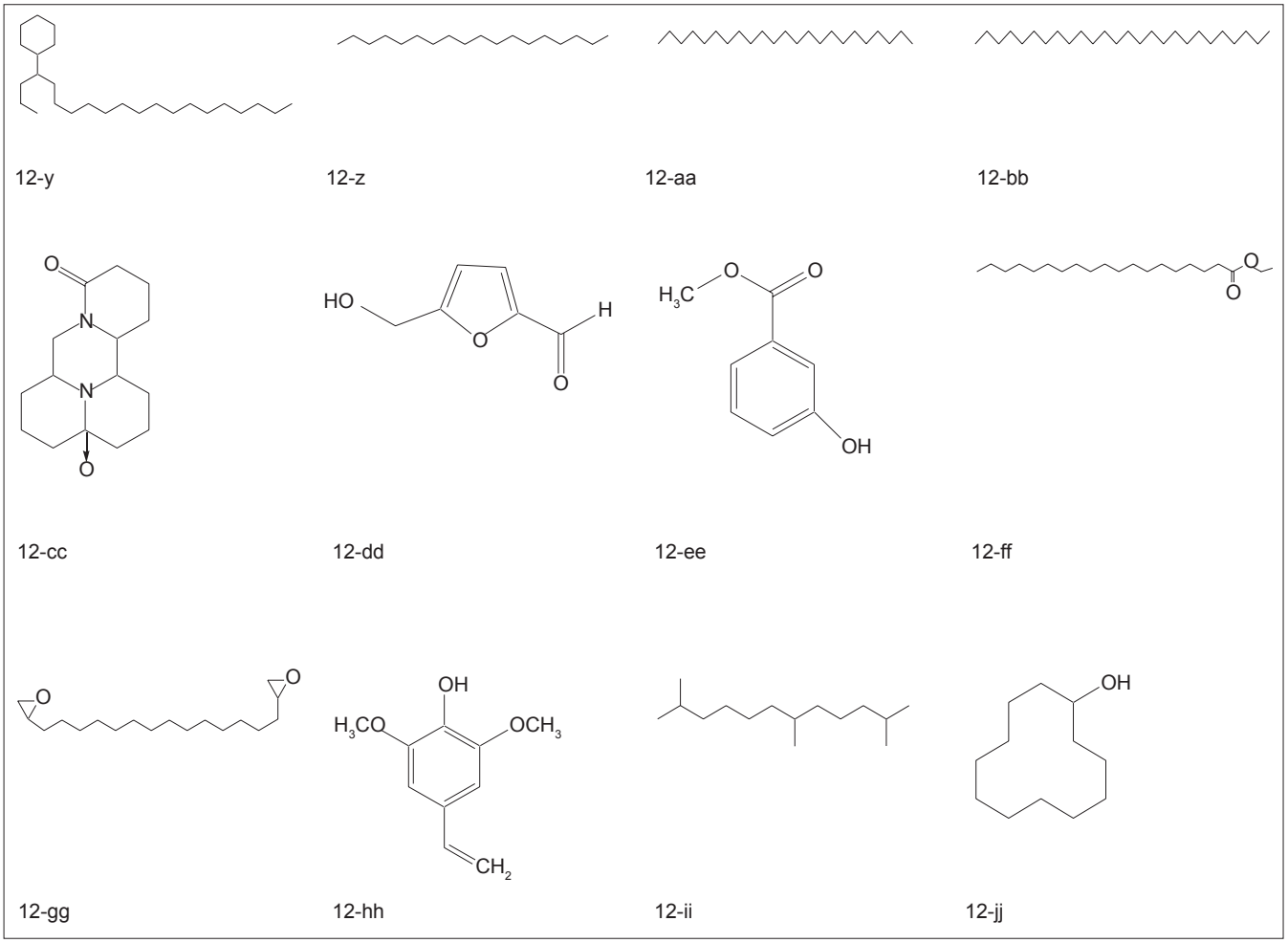

Figure 1: Phytoconstituents isolated from *Houttuynia cordata*

Table 1: List of phytoconstituents isolated from *H. cordata* till year 2012

Si No.	Phytoconstituents	Part of plant used for isolation	Reference
1	Aristolactams		
	a. aristolactam B II (Cepharanone B)	Dried aerial parts	a. [18,50]
	b. Aristolactam A II	Dried aerial parts	b. [18,50]
	c. Piperolactam A	Dried aerial parts	c. [18,50]
	d. Caldensin	Whole plant	d. [31,51]
2	Oxoaporphines		
	a. Splendidine	Dried aerial parts	a. [22]
	b. Lysicamine/oxonuciferine	Whole plant	b. [52]

Table 1: Contd...

Si No.	Part of plant used for isolation	Part of plant used for isolation	Reference
3	5,4-Dioxoaporphines		
	a. Cepharadione B	Dried aerial parts	a. [18,50]
	b. Norcepharadione B		b. [18,53]
	c. Noraritolodione		c. [22,53]
4	Amides		
	a. *N*-(1-hydroxymethyl-2-phenylethyl) benzamide	Whole plant	a. [54]
	b. *N*-(4-hydroxyphenylethyl) benzamide		b. [55]
	c. Phenyl carboxamide		c. [56]
	d. 4-Hydroxybenzamide		d. [57]
	e. 4-Hydroxy-3-		e. [58]

Contd...

Table 1: Contd...

Si No.	Part of plant used for isolation	Part of plant used for isolation	Reference
	methoxybenzamide		
	f. 6,7-Dimethyl-1-ribitol-1-yl-1, 4-dihydroquinoxaline-2,3-dione		f. [59]
	g. (1*H*)-quinolinone		g. [60]
	h. Houttuynamide A		h. [31]
5	Benzenoids		
	a. Vanillic acid	Whole plant	a. [31,61]
	b. Methyl vanillate		b. [31,62]
	c. Vanillin		c. [31,62]
	d. Protocatechuic acid		d. [31,63]
	e. 4-Hydroxybenzoic acid		e. [64]
	f. Methylparaben		f. [65]
	g. *p*-Hydroxybenzaldehyde		g. [67]
	h. *Cis*- and *trans*-methyl ferulate		h. [31,68]
	i. Benzyl-β-D-glucopyranoside		i. [31,69]
	j. Houttuynoside A		j. [31]
	k. 1,3,5,-Tridecanoylbenzene		k. [66]
	l. Methyl-3-hydroxybenzoate		l. [70]
	m. Methylaparaben		m. [66]
	n. Myristicin		n. [71]
	o. Elemicine		o. [71]
	p. α-Asarone		p. [71]
	q. 1,3-Dibutylphthalate		q. [70,72]
	r. Methyl-4-hydroxymethylbenzoate		r. [72,73]
	s. 2,6-Bis-(1,1-dimethyl)-4-methylphenol		s. [72]
	t. m-Tolyl-dimethylacetaldehyde		t. [72,73]
	u. Thymylacetate		u. [72]
	v. Butyl-2-isopropyl phthalate		v. [70,73]
	w. 2,6-Dimethoxy-4-(2-propenyl) phenol		w. [70]
	x. 2-Methyl-5-(1-methylethyl) phenol		x. [72]
6	Flavonoids		
	a. Quercitrin	Dried aerial parts	a. [18,74]
	b. Afzelin		b. [75,76]
	c. Hyperin		c. [76]
	d. Quercetin-3-O-β-D-galacto pyranosyl-7-O-β-D-glactopyra noside		d. [75,76]
	e. Quercetin-3-O-α-L-rhamno pyranosyl-7-O-β-D-glucopyran oside		e. [76]
	f. Rutin		f. [77,74]
	g. Quercetin		g. [78,31]
	h. Isoquercitrin		h. [79]
7	Indoles		
	a. Indole-3-carboxylic acid	Whole plant	a. [31,80]
8	Ionones		
	a. Vomifoliol	Whole plant	a. [66]
	b. Dehydrovomifoliol		b. [31,81]
	c. Reseoside		c. [31,82]
	d. 6-(9-Hydroxy-but-7-ethyl)-1, 1,5-trimethylcyclohexane-3,5,6-triol		d. [31,83]
	e. 7-(3,5,6-Trihydroxy-2,6, 6-trimethylcyclohexyl)-byt-3-en-2-one		e. [31,84]
9	Phenolic compound		
	a. Chlorogenic acid	Dried aerial part	[47]
	b. Crypto-chlorogenic acid		
	c. Neo-chlorogenica acid		
	d. Procynanidin B		
	e. Catechin		
	f. Quinic acid		
	g. Caffeic acid		
10	Steroids		
	a. β-Sitosterol	Rhizome	a. [61,77]
	b. β-Sitosteryl glucoside		b. [85]
	c. 5-α-Stigmastane-3,6-dione		c. [66]
	d. 3-Hydroxy-β-sitost-5-en-7-one		d. [66]
11	Triterpenoids		
	a) Cycloart-25-ene-3b, 24-diol	Whole plant	a. [31,86]
12	Volatile oil		
	a. 3-Methyl-butanoic acid	Whole plant	[70]
	b. 2,3-Dihydro-3,5-dihydroxy-6 methyl- 4*H*-pyran-4-one		
	c. Decanal		
	d. 2-Undecanone		
	e. *n*-Decanoic acid		
	f. 1-Decen-3-one		
	g. 4-Tridecanone		
	h. Undecanoic acid		
	i. Decanoyl acetaldehyde		
	j. Megastigmatrienone		
	k. Dodecanoic acid		
	l. 1-Hexadecene		
	m. *n*-Hexadecanoic acid		
	n. Pentadecanol		
	o. Hexadecyl-oxirane		
	p. Butyl-2-methylpropylphthalate		
	q. 3,7,11,15-Tetramethyl-2-hexadecen-1-ol		
	r. Palmitic acid		
	s. Octadecanoic acid		
	t. Phytol, (*Z*, *Z*) 9,12-octadecadienoic acid		
	u. Nonacosane		
	v. Octacosane		
	w. Linoleic acid		
	x. (*Z*)-13-octadecenal		
	y. (1-Propylheptadecyl) cyclohexane		
	z. Octadecane		
	aa. Tricosane		
	bb. Hexacosane		
	cc. *N*-oxide matrine		
	dd. 5-(Hydroxymethyl)-2-furancarboxalder		
	ee. 3-Hydroxy-benzoate methyl		
	ff. Nonadecanoate ethyl		
	gg. Tettadecyl oxirane		
	hh. 2,6-Dimethhoxy-4-(2-propenyl)-phenol		
	ii. 2,6,11-Timethyl-dodecane		
	jj. Cyxlododecanol		

Contd...

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A review on phytochemical, pharmacological, and pharmacognostical profile of *Wrightia tinctoria*: Adulterant of kurchi

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ABSTRACT

Wrightia tinctoria R. Br. belongs to family Apocynaceae commonly called as Sweet Indrajao, Pala Indigo Plant, Dyer's Oleander. "Jaundice curative tree" in south India. Sweet Indrajao is a small, deciduous tree with a light gray, scaly smooth bark. Native to India and Burma, Wrightia is named after a Scottish physician and botanist William Wright (1740-1827). Sweet Indrajao is called dhudi (Hindi) because of its preservative nature. The juice of the tender leaves is used efficaciously in jaundice. Crushed fresh leaves when filled in the cavity of decayed tooth relieve toothache. In Siddha system of medicine, it is used for psoriasis and other skin diseases. Oil 777 prepared out of the fresh leaves of the plant has been assigned to analgesic, anti-inflammatory, and anti-pyretic activities and to be effective in the treatment of psoriasis. The plant is reported to contain presence of flavanoid, glycoflavones-iso-orientin, and phenolic acids. The various chemical constituents isolated from various parts of the plant are reported as 3,4-Seco-lup-20 (29)-en-3-oic acid, lupeol, stigmasterol and campetosterol, Indigotin, indirubin, tryptanthrin, isatin, anthranillate and rutin Triacontanol, Wrightial, cycloartenone, cycloeucalenol, β-amyrin, Alpha-Amyrin, and β-sitosterol, 14α-methylzymosterol. Four uncommon sterols, desmosterol, clerosterol, 24-methylene-25-methylcholesterol, and 24-dehydropollinastanol, were isolated and identified in addition to several more common phytosterols. The Triterpinoids components of the leaves and pods of *Wrightia tinctoria* also isolated. This article intends to provide an overview of the chemical constituents present in various parts of the plants and their pharmacological actions and pharmacognostical evaluation.

Key words: Pharmacology, phytochemicals, therapeutic uses, *wrightia tinctoria*

INTRODUCTION

Wrightia tinctoria R.Br. (Family: Apocynaceae) commonly called "Indrajau" is distributed throughout the world and occurs abundantly in India. It is a deciduous tree with white fragrant flowers. The seeds and bark of this plant are used in Indian traditional medicine as anti-diarrheal and anti-dysenteric.[1] Sweet Indrajao is a small, deciduous tree with a light gray, scaly smooth bark. Native to India and Burma, Wrightia is named after a Scottish physician and botanist William Wright (1740-1827). From a distance, the white flowers may appear like snowflakes on a tree. The fruits pendulous, long-paired follicles joined at their tips. The hairy seeds are released as the fruit dehisces. The leaves of this tree yield a blue dye called Pala Indigo. Sweet Indrajao is called dhudi (Hindi) because of its preservative nature. Supposedly, a few drops of its sap in milk prevent curdling and enhance its shelf life, without the need to refrigerate. The wood of Sweet Indrajao is extensively used for all classes of turnery. It is made into cups, plates, combs, pen holders, pencils, and bed stead legs. It is commonly used for making Chennapatna toys.[2]

Medicinal uses: Ethnomedically, the bark of this plant is used as a galactagogue to treat abdominal pain, skin diseases and wounds,[3] as an anti-pyretic,[4] anti-dysenteric, anti-diarrheal- and anti-hemorrhagic[5] agents, and as an antidote for snake poison.[6] Seeds of this plant are also used as an aphrodisiac.[7] In view of the reported severe health hazards of estrogen, such as increased risk of endometrial hyperplasia and carcinoma,[8,9] breast cancer,[10] and thromboembolic diseases.[11] A large number

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of natural products showing promising anti-fertility activity in preliminary studies could not be pursued due to their associated estrogen-agonistic activity.[12]

The leaves are applied as a poultice for mumps and herpes. Sometimes, they are also munched to relieve toothache. In folk medicine, the dried and powdered roots of *Wrightia* along with *Phyllanthus amarus* (keezhanelli) and *Vitex negundo* (nochi) are mixed with milk and orally administered to women for improving fertility. The bark and seeds are effective against psoriasis and non-specific dermatitis. It has anti-inflammatory and anti-dandruff properties and hence is used in hair oil preparations.

Pharmacognostical evaluation

A preliminary pharmacognostical study on the leaves of *Wrightia tinctoria* (Roxb) R.Br. studied to determine various parameters of pharmacognostical standards such as ash values, extractive values, phytochemical tests, and microscopical characters of leaf powder. The shade-dried powder and various solvent extracts (*viz*., methanol, 70% ethanol, aqueous, dichloromethane, chloroform, ethyl acetate, and petroleum ether) have been analyzed for their phytoconstituents and fluorescence characters. The methanolic extract was found to contain presence of triterpenes. The data generated for the harmacognostical evaluation on *Wrightia tinctoria* leaves may be useful for establishing the standardization protocols. The HPTLC analysis data indicated that the collected *Wrightia tinctoria* leaves contain 47.6 mg of lupeol/g of the total methanolic extract.[13]

Pharmacognostical and physicochemical standardization of ethnopharmacologically important seeds of *Lepidium sativum* Linn. and *Wrightia tinctoria* R. Br. Performed. The morphological, microscopical, and physicochemical standards developed in this study will provide referential information for identification of these crude drugs and standardization. Quality control standardizations of the various medicinal plants used in traditional medicine is becoming more important today in view of the commercialization of formulations based on these plants. *Lepidium sativum* Linn. and *Wrightia tinctoria* R. Br. seeds are evaluated as per WHO recommendation, various physicochemical and phytochemical evaluation parameters for quality control of medicinal plants are performed. In view of their medicinal importance and taxonomic confusion, morphology and microscopy, physico-chemical parameters, fluorescence analysis, preliminary phytochemical screening, and quantitative estimation were performed to establish the salient diagnostic characters.[14]

The present paper deals with the pharmacognostical study of leaf of *Wrightia tinctoria* for its identification and to distinguish it from the co-existing weeds and adulterants. It has been used mainly for psoriasis and some other disorders. Since there is no proper information regarding this plant, efforts were devoted to study the pharmacognostical properties of this plant.[15]

Wrightia tinctoria (Indrajao), belonging to the family of Apocynaceae, is distributed in Rajasthan, Madhya Pradesh, and in Tamil Nadu. The plant is used in Siddha system for treating psoriasis, snake bites, and various inflammations. The present study is carried out to determine the pharmacognostical parameters and anti-microbial properties. It includes the transverse section, powder microscopy, physicochemical parameters, and anti-microbial studies.[16]

The bark of *W. tinctoria* is used as an adulterant for the well-known drug, *Holarrhena antidysenterica*. The pharmacognostic characters of *W. tinctoria* (collected from India) are presented. Such characters can be used to enable to identification of this herbal drug.[17]

H. antidysenterica and *H. pubescens*, an ingredient of the formulation Kurchi Bismuth Iodide, has often been confused and adulterated with another member of the same family, *W. tinctoria*. A comparative study was carried out on seeds of both medicinal plant species. Ash values, extractive values, and results of elemental analysis are reported, and physical characteristics of the seeds are described. The chloroform and methanolic extracts of both seeds showed anti-bacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa,* and *Escherichia coli*. The bitter value was determined as 11 000 for *H. antidysenterica*; *W. tinctoria* seeds are tasteless.[18]

Seeds of *H. antidysenterica* and *H. pubescens* are used in India for treating dysentery and a wide range of other digestive disorders. In appearance, they resemble those of *W. tinctoria,* which do not have the same medicinal properties. Data are presented on seed characteristics with distinguishing features.[19]

Pharmacological evaluation

Anti-psoriatic activity

The hydro-alcoholic extract of *Wrightia tinctoria* leaves was evaluated for anti-psoriatic activity by mouse tail test. Anti-psoriatic activity was performed at a dose 200 mg/kg body weight in mice (25-30 g). Isoretinoic acid (0.5 mg/kg) was used as the standard. Degree of orthokeratosis, drug activity, and the relative epidermal thicknesses were calculated and statistically analyzed. The extract was also evaluated for its antioxidant potential by DPPH, nitric oxide, and hydrogen peroxide radical scavenging assays. The extract produced significant ($P < 0.01$) degree of orthokeratosis compared to control, and the drug activity was found to be 70.18%, which is more potent than the standard (57.43%). The extract showed prominent antioxidant activity in all the assays. The present study concludes that the selected plant has anti-psoriatic activity and can be used for psoriasis treatment.[20]

Anti-diabetic activity

In the present study, investigation has been carried out to evaluate the effect of the different extracts of the leaves of *Wrightia tinctoria* on alloxan-induced diabetic rats of wistar strain. The experiment was carried out using six groups of albino rats.

Chloroform extract showed a significant anti-diabetic activity when compared to the standard drug glibenclamide.[21]

Anti-diabetic activity

The present work was undertaken to investigate various extracts of fruit of *Wrightia tinctoria* (Family- Apocynaeceae) for anti-diabetic activity in alloxan-induced diabetic rats. A comparison was made between the action of extracts and known anti-diabetic drug glibenclamide (10 mg/kg body weight). Oral administration of methanolic extract at a dose of 300 mg/kg/b. wt and ethyl acetate extract at a dose of 200 mg/kg/b. wt exhibited a significant ($P < 0.001$, $P < 0.001$) hypoglycemic activity in normal rats and significant ($P < 0.001$, $P < 0.001$) anti-hyperglycemic activity in alloxan-induced diabetic rats, respectively. The maximum reduction in blood glucose level was observed after 4 hours in case of methanolic and ethyl acetate extracts with a percentage protection of 37% and 42%, respectively. In long-term treatment of alloxan-induced diabetic rats, the degree of protection was determined by measuring blood glucose on 0, 1, 2, 4, 7, 14th day. Both the extracts showed a significant anti-diabetic activity comparable with that of glibenclamide. These results indicate that the *W. tinctoria* fruit extracts possess significant anti-diabetic activity.[22]

Anti-microbial properties

The present investigation focuses on *in vitro* anti-microbial properties and phytochemical analysis of aqueous and methanolic extracts of two different colored mature seed varieties of *Wrightia tinctoria*. The phytochemical screening revealed the presence of carbohydrates, reducing sugars, alkaloids, sterols, glycosides, phenolics, tannins, flavonoids, and amino acids. Greater effectivity was observed against gram-positive bacterial pathogens such as *Staphylococcus aureus* ATCC 25923, *S. aureus*, *S. citreus,* and *B. cereus* than the gram-negative strains. The methanolic seed extracts were largely inhibitory against pathogenic yeasts like *Trichophyton rubrum*, *Candida albicans*, *C. parapsilosis,* and *Cryptococcus*. The results indicated that the methanolic extract of the brown variety seeds is pharmacologically more active than that of the beige variety seeds. The aqueous extracts of both the seed varieties were moderately effective against *S. aureus* ATCC 25923 and *S. citreus* with no effect against the fungal strains.[23]

Anti-diabetic activity

In the present investigation, the methanolic extract of leaves of *Dodonaea viscosa* (D. viscosa) and pods of *Wrightia tinctoria* (*W. tinctoria*) were evaluated for anti-diabetic activity. The anti-diabetic activity was studied using the glucose uptake by isolated rat hemi-diaphragm *in vitro* model. The value of glucose uptake by rat hemi-diaphragm for *D. viscosa* was 13.80 ± 0.1697 and for *W. tinctoria* was 9.384 ± 0.3944 as compared to control (5.34 ± 0.12) and insulin 15.45 ± 0.12 in mg/g/min. The results strongly suggest that *D. viscosa* will be alternative choice for the treatment of diabetes mellitus caused in the consequences of resistance to stimulatory effect of insulin on Glut-4 protein.[24]

Anti-ulcer activity

The purpose of the present study was aimed at evaluating the anti-ulcer activity on leaves of *Wrightia tinctoria* on albino rat. The anti-ulcer activity of the *Wrightia tinctoria* methanolic extract (TM) and *Wrightia tinctoria* 70% ethanolic extract (T70E) were compared with carboxy methyl cellulose (CMC), pylorus control, aspirin, and standard famotidine, which was evaluated by employing aspirin plus pylorus ligation-induced ulcer model. The biochemical parameters like volume of gastric juice secretion, pH, free acidity, total acidity, and ulcer index and percentage inhibition were studied at the concentration of 200 mg/kg body weight. The plant methanolic extract showed significant gastro-protective activity of 65.89% when compared with the standard drug famotidine (20 mg/kg), which showed 75.34%. The result suggested that the methanolic extract of *Wrightia tinctoria* leaves possesses anti-ulcer effect. The observed effect may be due to the presence of bioactive constituents.[25]

Free radical scavenging activity

Attempt has been made to evaluate reducing power and free radical scavenging activity of ethanolic extract of *Wrightia tinctoria* Roxb bark and *Schrebera swietenoides* Roxb bark individually. *In vitro* antioxidant evaluation was done by measuring the reducing power and inhibition of superoxide production. The results suggest that the ethanolic bark extract of the *Wrightia tinctoria* Roxb and *Schrebera swietenoides* Roxb has the ability to suppress the oxidation, and it was also found that *Schrebera swietenoides* Roxb extract has more activity than *Wrightia tinctoria* Roxb extract.[26]

Toxicological profiles

The research work was conducted with the leaf solvent extracts of *Wrightia arborea* and *Wrightia tinctoria* to make toxicological profiles by employing Brine Shrimp Assay method (BSA) (*Artemia Salina LEACH*). The LC_{50} values were determined for both the plant solvent extracts respectively in mg/ml of active compounds and extracts. It was found that the leaf ethanolic and methanolic extracts were toxic for the Brine Shrimp Naupli. The results indicated that *Wrightia tinctoria* leaf ethanol (70%) extract and methanolic extract showed LC_{50} values of 471.604 and 517.038 mg/ml, respectively. While the *Wrightia arborea* leaf ethanol (70%) extract and methanolic extracts showed LC_{50} values of 498.213 and 531.082 mg/ml, respectively. The remaining solvent extracts showed no toxicity (as found more than 1000 mg/ml) in BSA method.[27]

Acute oral toxicity investigation

Abelmoschus manihot and *Wrightia tinctoria*, belonging to the botanical family Malvaceae and Apocynaceae, have been traditionally used by the locals in India for treatment of various ailments. The current study reports the outcome of acute oral toxicity investigation of *Abelmoschus manihot* and *Wrightia tinctoria* on ICR mice. No mortalities or evidence of adverse effects have been observed in ICR mice following acute oral administration at the highest dose of 2500 mg/kg crude extracts of *Abelmoschus manihot* and *Wrightia tinctoria*. This is the first report on the acute oral toxicity of *Abelmoschus manihot* and *Wrightia tinctoria,* and the findings of this study are in agreement with those of *in vitro*

experiments and thus provide scientific validation on the use of the leaves of *Abelmoschus manihot* and *Wrightia tinctoria*.[28]

Anthelmintic potential

The present communication deals with the comparative studies on anthelmintic potential of methanolic and aqueous extracts of *Cymbopogon citratus* and *Wrightia tinctoria* against *Pheritima posthuma*. Methanolic and aqueous extracts of both were used as test solutions. Piperazine citrate was used as standard drug and normal saline as a control. Study involved the determination of time of paralysis as well as time of death of worms. The results revealed that methanolic extract of *Cymbopogon citratus* leaves have better anthelmintic activity than that of *Wrightia tinctoria* extracts. Further, it will be interesting to isolate the active chemical constituents from both the plants.[29]

Anti-diabetic activity

The aim of this study is to evaluate the anti-diabetic activity of two Indian Ayurvedic herbs using an oral glucose tolerance test and blood insulin levels to understand the mechanism of action using the Zucker diabetic rat model. Herbal extracts of *Wrightia tinctoria* and *Parthenocissus quinquefolia* at a dose of (250 mg/kg body weight) were used throughout the study. Following a glucose challenge of 2 gm/kg using oral gavage, a timed glucose tolerance test was used to determine the ability of these extracts to alter glucose levels in diabetic animal model. The glucose-lowering activities of these extracts were then compared to the controls. Both tested herbal extracts have shown to exhibit significant ($P < 0.05$) hypoglycemic activity compared to the control. *W. tinctoria* and *P. quinquefolia* have an anti-diabetic activity, which reduced the blood glucose level in oral glucose tolerance test significantly compared with the control. To further understand their mechanism of action, blood insulin levels were also studied using an insulin Elisa assay. These studies revealed that the herbal extract of *P. quinquefolia* has direct correlation between glucose and insulin levels. However, *W. tinctoria* significantly lowered blood glucose levels ($P < 0.05$), while it did not show any correlation between blood glucose and insulin levels. Based on these findings, it can be concluded that hypoglycemic effects of *Wrightia tinctoria* are more complicated than *P. quinquefolia* and may involve other possible mechanism.[30]

Cytotoxic activity

The cytotoxic activity of the alcoholic extracts of some traditional plants of Chhattisgarh state, India used to treat cancer. *In-vitro* cytotoxic activity of alcoholic extracts of five plants i.e. *Artocarpus heterophyllus, Alangium salvifolium, Buchanania lanzan, Sesbania grandiflora,* and *Wrightia tinctoria* was studied against human breast cancer (MCF-7) and human leukemia (HL-60) tumor cell lines using the thiazolyl blue test (MTT) assay. From the result, it can be found that the *Sesbania grandiflora* extract has potent *in vitro* cytotoxic activity.[31]

Wound healing

In recent years, oxidative stress and free radicals have been implicated in impaired wound healing. *Abelmoschu manihot* (L.) Medik, Malvaceae and *Wrightia tinctoria* R.Br, Apocynaceae plants, widely used in Ayurveda, possesses anti-inflammatory and anti-microbial properties. The present study was undertaken to assess the potential of petroleum ether and methanolic extracts in wound healing in Wistar albino rats. The rats were divided into six groups of six animals each. Group 1 is normal wounded control, group 2 received standard drug, and the other 4 groups were treated with two different doses each of petroleum ether and methanolic extract of *A. manihot* and *W. tinctoria*. The wound healing parameters were evaluated by using incision wounds in extract-treated rats, standard, and controls. Both the doses of petroleum ether and methanolic extract significantly increased wound breaking strength when compared with the control group.[32]

Anti-inflammatory activity

In the present study, the bark of *Wrightia tinctoria* was investigated for anti-inflammatory activity by carrageenan-induced rat paw edema and cotton pellet-induced granuloma method. The various extracts showed inhibition of rat paw edema and percent granuloma changes at dose of 200 mg/kg when compared to control group. The activity was compared with that of standard drug diclofenac sodium (13.5 mg/kg/bw, p.o).[33]

Anthelmintic activity

The aim of the present study was to determine the anthelmintic activity of crude petroleum ether and chloroform extracts of leaves of *Wrightia tinctoria* using *Pheretima posthuma*. Three concentrations (2.5, 5.0, 7.5 mg/ml) of each extracts were studied in the activity, which involved the determination of time of paralysis and time of death of the worms. Piperazine citrate is used as standard reference and normal saline as control. The present study proves the potential usefulness of leaves of *Wrightia tinctoria* as comparable anthelmintic agent.[34]

Anti-fungal activity

Present study was designed to investigate the *in vitro* anti-fungal activity of certain medicinal plants and the pure compound indirubin isolated from *Wrightia tinctoria*. The hexane, chloroform, methanol, and ethanol extracts of six different plants were investigated against dermatophytes, non-dermatophytes, and yeasts. Chloroform extract of *Wrightia tinctoria* leaf was fractionated using column chromatography, and the major compound was identified using spectroscopic techniques. Anti-fungal activity was studied by spore germination test using agar dilution method. The minimum inhibitory concentration (MIC) was determined using broth micro dilution method. *Wrightia tinctoria* showed promising activity against dermatophytic and non-dermatophytic fungi. Leaf chloroform extract showed activity at 0.5 mg/ml against *Trichophyton rubrum*, *Epidermophyton floccosum*, *Aspergillus niger,* and *Scopulariopsis brevicaulis*. The major compound, identified as indirubin, exhibited activity against dermatophytes such as *Epidermophyton floccosum* (MIC = 6.25 μg/ml); *Trichophyton rubrum* and *Trichophyton tonsurans* (MIC = 25 μg/ml); *Trichophyton mentagrophytes* and *Trichophyton simii* (MIC = 50 μg/ml). It was also active against non-dermatophytes (*Aspergillus niger*, *Candida*

albicans, and *Cryptococcus* sp.) within a MIC range of 0.75-25 μg/ml. The indole compound indirubin from *Wrightia tinctoria* showed anti-fungal activity and may be useful in the treatment of dermatophytosis.[35]

Wrightia tinctoria was investigated for the preliminary phytochemical analysis and characterization by various instrumental techniques. Indole derivatives such as isatin, induribine, tryphanthrine, and fatty acids were identified. Methanolic extract of leaf parts of *Wrightia tinctoria* (WT) have been studied against replication of HCV in Huh 5.2 cells. The 50% effective concentration for inhibition of HCV in RNA sub-genomic replicon replication in huh 5-2 cells (luciferase assay) by CWT was found to be 15 μg/mL. The concentration that reduced the growth of exponentially proliferating Huh 5-2 cells by 50% was greater than 50 μg/Ml.[36]

Hematological, biochemical, histological, and antioxidant enzyme status

The effect of sub-acute administration of *W. tinctoria* bark extract on some hematological, biochemical, histological, and antioxidant enzyme status of rat liver and kidney investigated, following 21 and 45 days treatment. The animals were observed for gross physiological and behavioral responses, food and water intake, and body weight changes. Free radical scavenging activity and histopathology was done on liver and kidney samples. *W. tinctoria* showed significant hemopoiesis with increase in body weight signifying anabolic effect. It significantly reduced serum SGOT level and increased glucose levels. *W. tinctoria* caused increased SOD activity of liver along with catalase of both liver and kidney and decreased liver peroxidase ($P < 0.001$). These features indicate that *W. tinctoria* upto 1000 mg/kg daily dose is safe and has potential to be consumed for long time in management of various diseases.[37]

Anti-nociceptive activity

The pharmacological profile of hydro-alcoholic extract of *Wrightia tinctoria* (Roxb) R. Br. investigated in mice and rats using various models. The effects of the extract were observed in three different dose levels 300, 500, and 1000 mg/kg as extract does not show any sign of toxicity up to 3000 mg/kg dose. Investigations were carried out against thermal, chemical, and mechanical noxious stimuli to study anti-nociceptive activity and on pentobarbitone-induced hypnosis. Carrageenan-induced paw edema and cotton pellet-induced granuloma model were employed to test anti-inflammatory activity. The parameters taken for diuretic activity were urine volume and renal excretion of Na^+, Cl^-, and K^+ ions. Study revealed moderate analgesic effect against thermal ($P < 0.001$ to 0.01) and chemical ($P < 0.05$) noxious stimuli and anti-inflammatory activity ($P < 0.001$ to 0.01) at the 1000 mg/kg dose. Extract is devoid of any sedative activity. *Wrightia tinctoria* extract considerably increases urine volume, acting as strong kaliuretic.[38]

Anti-bacterial activity

The anti-bacterial activity of petroleum ether (60-80°), 95% alcohol, and 40% aqueous alcohol extracts of bark of *W. tinctoria* was evaluated against Gram-positive and Gram-negative organisms by cup plate diffusion method. The 95% alcohol and 40% aqueous alcohol bark extracts exhibited anti-bacterial activity against the tested organisms.[39]

Pregnancy-interceptive activity

The pregnancy-interceptive activity of the stem bark of *Wrightia tinctoria* R.Br. (Family Apocynaceae) investigated during the pre implantation, peri-implantation, and early post-implantation periods by oral route in adult female Sprague-Dawley rats. The ethanolic extract of the stem bark and its serial fractions were administered to female rats on days 1-7 or 1-5 post-coitum (Day 1: Day of sperm-positive vaginal smear) by the oral route. At autopsy on day 10 post-coitum, the number and status of corpora lutea and implantations were recorded. For estrogen-agonistic activity, immature rats ovariectomized 7 days earlier received the test extract or the vehicle once daily for 3 days and, at autopsy on day 4, uterine weight, status of vaginal opening, and extent of vaginal cornification were recorded. The ethanolic extract of the stem bark of *W. tinctoria* R.Br. inhibited pregnancy in 100% of rats when administered orally at a 250 mg/kg dose on days 1-7 or 1-5 post-coitum. On fractionation, the hexane-soluble, chloroform-soluble, water-soluble, and water-insoluble fractions showed 100% anti-implantation effect, while *n*-butanol-soluble fraction intercepted pregnancy in 75% of animals when administered in the days 1-5 post-coitum schedule. In immature rat bioassay, the active ethanolic extract and its fractions exhibited moderate to potent estrogen-agonistic activity, which might be responsible for their contraceptive action in this species. Findings demonstrate the anti-fertility activity of the ethanolic extract of the stem bark of *W. tinctoria* and its hexane-soluble, chloroform-soluble, water-soluble, and water-insoluble fractions. Studies that pursue promising natural products (to identify contraceptive agents from natural sources lacking potent estrogenic activity) towards a fruitful conclusion for development/lead generation should continue.[40]

Anti-ulcer activity

Evaluation of the anti-ulcer activity of *Wrightia tinctoria* bark extract investigated in induced acute gastric ulcers in rat.[41]

Wound-healing activity

The wound-healing activity of ethanol extract of *W. tinctoria* bark screened by using incision, excision, and dead space wound models and evaluated histopathological and biochemical changes of granuloma tissue. The bark powder of *W. tinctoria* was extracted with 95% ethanol by continuous heat extraction and was subjected to phytochemical investigation and screened for wound-healing activity in the incision, excision, and dead space wound models in rats. A supportive study made on granuloma tissue to estimate the hydroxyproline content and histopathological examination to determine the pattern of lay-down for collagen using Masson Trichrome stain. Triterpenoids, steroids, and saponins were present in ethanol extracts of barks of *W. tinctoria*. In the re-sutured incision wound model, the ethanol extract showed significant

breaking strength ($P < 0.01$) compared to the control. The ethanol extract promotes better wound-healing by increasing the percentage wound closure and decreasing epithelization time ($P < 0.001$) compared to the control. Statistically significant increase ($P < 0.001$) was observed in breaking strength and hydroxyproline content of ten-day-old granuloma of drug-treated animals compared to control animals in the dead space wound model. The results of the present study reveal that ethanol extract of bark of *W. tinctoria* have significant wound-healing activity. The pro healing action seems to be due to the increased synthesis of collagen, it's cross-linking as well as better alignment and maturation. This may be attributed to the presence of triterpinoids in the title plant.[42]

Phytochemical evaluation

The present paper deals with HPTLC finger printing studies on two ethnomedicinally important wrightia species, *viz*., *Wrightia tinctoria* and *Wrightia arborea*. The high performance thin layer chromatographic finger print parameters have been developed for methanolic lead extracts to fix standards. At shorter (254 nm) and longer (366 nm) wavelength, the resolution was better for these extracts and hence, these wavelengths can be taken for obtaining optimum HPTLC finger printing for this medicinal plant.[43]

777 Oil is a topically applied Ayurvedic formulation used for the effective treatment of psoriasis. The formulation is composed of leaf extract of *Wrightia tinctoria* and *Oleum Cocus nucifera*. A selective, sensitive, and reproducible HPLC method was developed for analyzing marker compound of *Wrightia tinctoria* (Rutin) in 777 Oil for routine standardization purpose. The chromatography was performed on Phenomenex C_{18} (250 × 4.6 mm, 5.0 μm particle) column using methanol-water (60:40, v/v) as mobile phase; adjusted to pH 3.0 by orthophosphoric acid. The flow rate was 1.0 mL/min. with detection at 360 nm. The values of retention times and capacity factor were 3.88 and 0.40, respectively. The calibration plot showed a good linear relationship between response curve and concentration in the range of 1.0-1000.0 μgmL^{-1} with regression coefficient 0.9998. The detection (LOD) and quantification (LOQ) limits were found 27.0 and 95.0 $ngmL^{-1}$, respectively. The statistical analysis proved that the method was precise, reproducible, selective, and accurate for the analysis of rutin in 777 Oil. The developed HPLC method is useful for the qualitative and quantitative estimation of rutin in 777 Oil and other products of traditional systems of medicine.[44]

Aim of this study was to identify and characterize the bioactive principles from the woody stem of *Wrightia tinctoria*. For isolation of the compounds, the powder of dried woody stem of *Wrightia tinctoria* was subjected to hot extraction with petroleum ether and subjected to chromatography. Three compounds (PEW-1, PEW-2, and PEW-3) were isolated and purified by chloroform. Mass spectrum of PEW-1, PEW-2, and PEW-3 showed a parent molecular ion [M^+] peak at mlz 426, which corresponds to the molecular formula $C_{30}H_{50}O$, 412 corresponds to $C_{29}H_{48}O$, and 400 corresponds to $C_{28}H_{48}O$. In the ^{1}H-NMR spectrum of PEW-1, H-3 proton appeared as a triplet of a double doublet (tdd) at δ 3.21, H-29 proton gives two multiplates at δ 4.71 and δ 4.56, in ^{1}H-NMR spectrum of PEW-2, H-3 proton appeared as a triplet of a double doublet (tdd) at δ3.62, and H-6 olefinic proton showed a multiplet at δ5.14. Two olefenic protons appeared downfield at δ 4.16 (m) and δ 4.14 (m). Six methyl proton appeared at δ 1.27, δ 1.19, δ 1.07, δ 1.00, δ 0.98, and δ 0.91 for methyl group and in the ^{1}H-NMR data of PEW-3, H-3 proton appeared at δ 3.21 as a triplet of a double doublet H-6 olefinic proton showed a multiplet at δ 5.10 and six methyl proton appeared at δ 1.27, δ 1.14, δ 1.09, δ 1.00, δ 0.98, and δ 0.95 for methyl group. From the physical, chemical, and spectral characteristics, PEW-1, PEW-2, and PEW-3 were concluded as lupeol, Figure 1 stigmasterol, and campetosterol.[45]

3,4-Seco-lup-20 (29)-en-3-oic acid, Figure 2 a rare triterpene, was isolated from *Wrightia tinctoria* R.Br (Family: Apocynaceae). It appeared promising to study the structural chemistry of this compound because of its unique bioactivity. X-ray diffraction analysis demonstrated that this compound consists of three six-membered rings and one five-membered ring. The first six-membered ring (A) is in the twist boat form while the remaining two six-membered rings (B, C) are in the chair form. The crystal of this compound belongs to the monoclinic crystal system and space group P21. Lattice constituents are as follows: a = 13.074 (6) Å, b = 11.972 (5) Å, c = 17.394 (7) Å; a = 90.00, b = 98.20 (13), c = 90.00; V = 2695 (2) Å3, d = 1.094 Mg/m3, Z = 4. The optimized geometry of the reported molecule has been calculated with the DFT/B3LYP theory using 6-31G (d, p) basis set.[46]

Chemical constituents were isolated from leaves of *W. tinctoria*, *W. tomentosa* [*W. arborea*], and *W. coccinea* (collected from India). Indigotin, indirubin, Figure 3 tryptanthrin, isatin**,** anthranillate, and rutin [rutoside] were isolated and identified as major constituents of *W. tinctoria* and *W. tomentosa*. Anthranillate and rutin were the major constituents of *W. coccinea*. Indigotin was found in fresh plant material, and indirubin was an artifact formed during the drying process after harvesting. Seasonal variation in the chemical constituents of leaves was studied using HPTLC and HPLC analyses; similar variation patterns in the 3 species were observed. The concentration of indigotin-indirubin combination steadily increased from August to November. In contrast, concentration of isatin and anthranillate increased in December and January, at the expense of indigotin-indirubin. Isatin was produced by the autoxidation of indigotin. Tryptanthrin concentration also

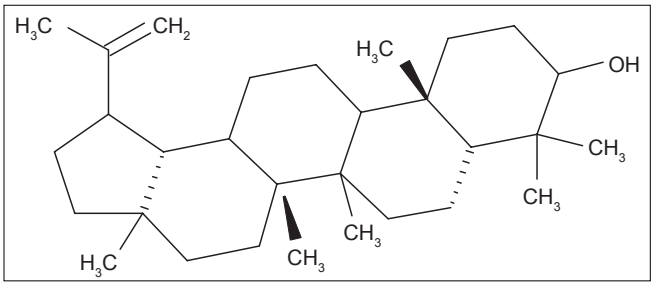

Figure 1: Lupeol

increased, periodically, in May (at the expense of isatin) and in January. Plausible pathways for the formation of these indole metabolites are appraised on the basis of circumstantial and synthetic evidence.[47]

Triacontanol and tryptanthrin Figure were newly isolated from *Wrightia tinctoria* leaves, collected from Pacha-Palode, Kerala, India, in July 1994.[48]

W. tinctoria is used in Indian traditional medicine to treat psoriasis, stomach pains, toothache, and as an anti-dysenteric. Wrightial, Figure 5 and 4 known compounds (cycloartenone, cycloeucalenol, β-amyrin, and β-sitosterol), were isolated from the MeOH extract of the immature seed pods of *W. tinctoria* (collected from the Mannanoor forest, Andhra Pradesh, India). The structure of wrightial was established from spectral analysis and by chemical correlation.[49]

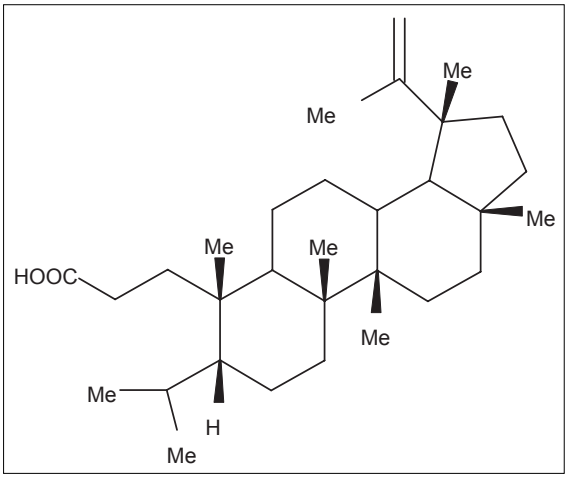

Figure 2: 3, 4-Seco-lup-20 (29)-en-3-oic acid

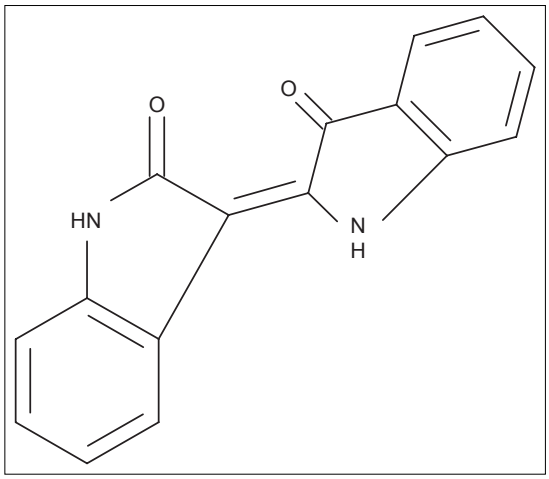

Figure 3: Indirubin

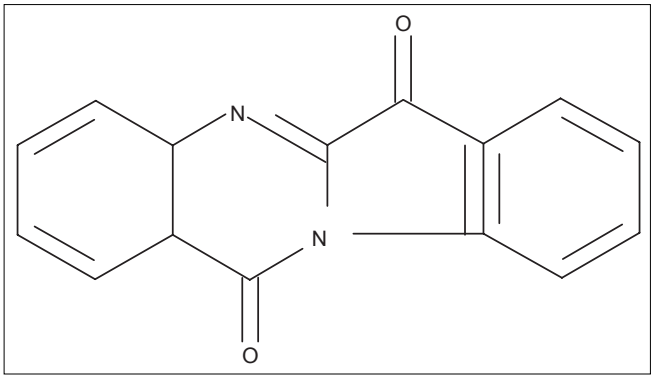

Figure 4: Tryptanthrin

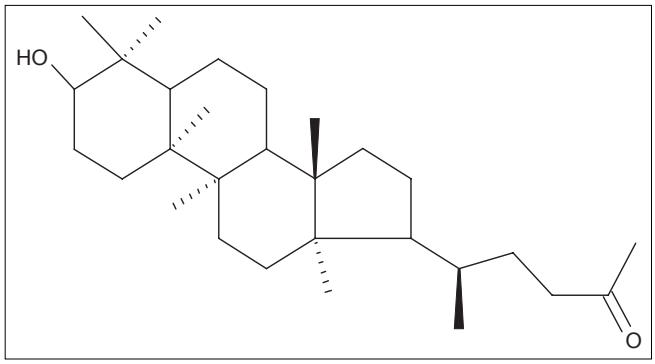

Figure 5: Wrightial

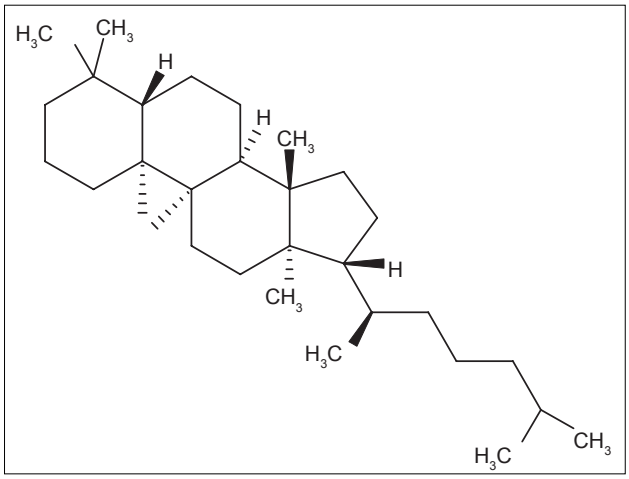

Figure 6: Cycloartenone

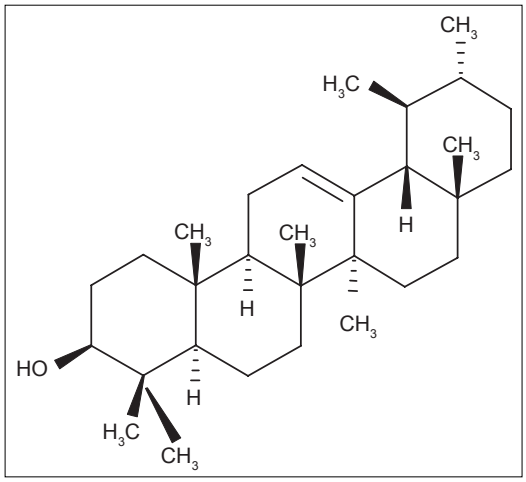

Figure 7: *Alpha-Amyrin*

W. tinctoria is used in traditional medicine to treat psoriasis. Cycloartenone Figure 6 and cycloeucalenol were isolated from the immature pods of this species, collected from Mannanoor Forest, Andhra Pradesh, India.[50]

The structure of a new sterol isolated from the unsaponifiable lipid fraction of the seed lipid was shown to be 14α-met hylzymosterol by comparison with a synthetic authentic compound. Four uncommon sterols, desmosterol, clerosterol, 24-methylene-25-methylcholesterol, and 24-dehydropollinastanol, were isolated and identified in addition to several more common phytosterols.[51]

The Triterpinoids components of the leaves and pods of *Wrightia tinctoria* isolated.[52]

Alpha-Amyrin Figure 7 was isolated from bark extracts of both *W. tomentosa* and *W. tinctoria*.[53]

CONCLUSION

This review shows that *Wrightia tinctoria* is an important medicinal plant with diverse pharmacological spectrum. Few novel chemical constituent isolated from the *Wrightia tinctoria* showed anti-cancer, anti-HIV, and anti-diabetic (type 2 diabetic) properties too. Further evaluation need to be carried out on *Wrightia tinctoria* in order to explore concealed areas and their practical clinical application, which can be used for the welfare of the mankind port in carrying out this study at the laboratory

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Phytopharmacological overview of *Tribulus terrestris*

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ABSTRACT

Tribulus terrestris (family Zygophyllaceae), commonly known as *Gokshur or Gokharu* or puncture vine, has been used for a long time in both the Indian and Chinese systems of medicine for treatment of various kinds of diseases. Its various parts contain a variety of chemical constituents which are medicinally important, such as flavonoids, flavonol glycosides, steroidal saponins, and alkaloids. It has diuretic, aphrodisiac, antiurolithic, immunomodulatory, antidiabetic, absorption enhancing, hypolipidemic, cardiotonic, central nervous system, hepatoprotective, anti-inflammatory, analgesic, antispasmodic, anticancer, antibacterial, anthelmintic, larvicidal, and anticariogenic activities. For the last few decades or so, extensive research work has been done to prove its biological activities and the pharmacology of its extracts. The aim of this review is to create a database for further investigations of the discovered phytochemical and pharmacological properties of this plant to promote research. This will help in confirmation of its traditional use along with its value-added utility, eventually leading to higher revenues from the plant.

Key words: Pharmacology, saponin, *tribulus terrestris*

INTRODUCTION

The genus *Tribulus*, belonging to family Zygophyllaceae, comprises about 20 species in the world, of which three species, viz. *Tribulus cistoides, Tribulus terrestris*, and *Tribulus alatus*, are of common occurrence in India.[1] Among them, *T. terrestris* (TT) is a well-patronized medicinal herb by Ayurvedic seers as well as by modern herbalists.[2] The plant is used individually as a single therapeutic agent or as a prime or subordinate component of many compound formulations and food supplements. It is an annual shrub found in Mediterranean, subtropical, and desert climate regions around the world, viz. India, China, southern USA, Mexico, Spain, and Bulgaria.[3,4]

Taxonomical classification

- Kingdom: Plantae
- Division: Phanerogams
- Subdivision: Angiospermae
- Class: Dicotyledonae
- Subclass: Polypetalae
- Series: Disciflorae
- Order: Giraniales
- Family: Zygophyllaceae
- Genus: *Tribulus*
- Species: *terrestris* Linn.

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PLANT PROFILE

TT is commonly known as *Gokshur* (Sanskrit); puncture vine, land (or small) caltrops (English); *Gokharu* (Hindi); *Bethagokharu* or *Nanagokharu* (Gujarathi); *Nerinjil* (Tamil); and *Khar-e-khusak khurd* (Urdu). It is distributed along a wide geographic perimeter. It is found all over India up to 11,000 ft in Kashmir, Ceylon, and all warm regions of both hemispheres. It is a common weed of the pasture lands, road sides, and other waste places, chiefly in hot, dry, and sandy regions including West Rajasthan and Gujarat in India.[5]

Botanical description *T. terrestris*

It is small prostrate, 10-60 cm height, hirsute or silky hairy shrub. Leaves are opposite, often unequal, paripinnate; pinnae from five to eight pairs, elliptical or oblong lanceolate [Figure 1]. Flowers are yellow in color. Its carpel fruits are of characteristic, stellate shape, somewhat round-shaped, compressed, five cornered, and covered with princkles of very light yellow color. There are several seeds in each crocus with transverse partitions between

them. The seeds are oily in nature. When fresh, the root is slender, fibrous, cylindrical, frequently branched, bearing a number of small rootlets and is of light brown color. Fruits and roots are mainly used as a folk medicine for the treatment of various ailments. Root occurs in pieces, 7-18 cm long and 0.3-0.7 cm in diameter, cylindrical, fibrous, frequently branched, bearing a number of small rootlets, tough, woody, yellow to light brown in color, surface rough due to the presence of small nodules; fracture fibrous; odor aromatic; taste sweetish astringent. The fruits of the herb are known as "Chih-hsing" in China or goat head in USA. The spiky fruit looks like the cloven hoof of a cow and, hence, is known as go-ksura (cow-hoof). Fruits are faint greenish yellow with spines [Figure 2]. They are globose, consisting of five, nearly glabrous, muriculate, wedge-shaped, woody cocci, each with two pairs of hard sharp spines, one pair longer than the other. Tips of spines almost meet in pairs together forming pentagonal framework around the fruit. Outer surface of the schizocarp is rough. There are several seeds in each coccus, with transverse partitions between them. Odor of fruits is faintly aromatic and taste is slightly acrid.

PROPERTIES AND ACTIONS MENTIONED IN AYURVEDA

- *Rasa* (taste based on activity): *Madhura* (sweet)
- *Guna* (properties): *Guru* (heavy to digest), *Snigdha* (unctuous)
- *Veerya* (potency): *Sheeta* (cooling)
- *Vipaka* (taste after digestion based on activity): *Madhura* (sweet)
- *Karma* (pharmacological actions): *Brumhana* (nourishing), *Vatanut* (pacifies *Vata-dsha*), *Vrusya* (aphrodisiac), *Ashmarihara* (removes urinary stone), *Vastishodhana* (cures bladder ailments).

CHEMICAL CONSTITUENTS

The preliminary phytochemical study of TT revealed the presence of saponins, flavonoids, glycosides, alkaloids, and tannins.[6] According to literature data, the saponin composition and the saponin content of TT from different geographic regions is different.[7] Kostova *et al.* studied the chemistry and bioactivity of saponins in TT. They reported that furostanol and spirostanol saponins of tigogenin, neotigogenin, gitogenin, neogitogenin, hecogenin, neohecogenin, diosgenin, chlorogenin, ruscogenin, and sarsasapogenin types are frequently found in this plant. In addition, four sulfated saponins of tigogenin and diosgenin type were also isolated. Majorly present are furostanol glycosides including protodioscin and protogracillin, of which protodioscin is the most dominant saponin and spirostanol glycosides are present in small quantities.[7,8] Wu *et al.* found that the quantity of main flavonoids is about 1.5 times that of main saponins. This indicated that the flavonoid contents in TT should be studied, developed, and further used.[9] Bhutani *et al.* isolated kaempferol, kaempferol-3-glucoside, kaempferol-3-rutinoside, and tribuloside [kaempferol-3-β-d-(6"-*p*-coumaroyl) glucoside] from leaves as well as fruits and identified them by spectroscopic analysis.[10] Louveaux *et al.* detected 18 flavonoids (caffeoyl derivatives, quercetin glycosides, including rutin and kaempferol glycosides) using high-performance liquid chromatography (HPLC) in four *Tribulus* species leaf extracts.[11] Yang *et al.* optimized the extraction condition using orthogonal experiment.[12] Matin Yekta *et al.* isolated three flavonoid glycosides, viz. quercetin 3-*O*-glycoside, quercetin 3-*O*-rutinoside, and kaempferol 3-*O*-glycoside from the aerial parts of *T. terrestris* L. var. *orientalis* (Kerner) G. Beck in the northeast of Iran.[13]

Raja and Venkataraman identified flavonoids from the petroleum ether and chloroform extracts of fresh fruits of TT from India using ethyl acetate: benzene (1:9) solvent system. These flavonoids were not detected in the fruit extracts of other variety, namely *T. alatus*. Hence, presence of such pharmacognostic constituents can be used as a diagnostic tool in the identification of the species and study of contamination/adulteration.[14,15] Tian Shung *et al.* isolated and characterized three new compounds, terrestribisamide, 25*R*-spirost-4-en-3, 12-dione, and tribulusterine, together with 10 known compounds, *N*-*p*-coumaroyltyramine, terrestriamide, hecogenin, aurantiamide acetate, xanthosine, fatty acid ester, ferulic acid, vanillin, *p*-hydroxybenzoic acid, and β-sitosterol, from the dried fruits of TT.[16] The alkaloids present are harmane and norharmane. The β-carboline alkaloid, tribulusterine, is present in minor quantities in fruits.[17] Gas chromatography-mass spectrometry analysis of methanolic extract of the whole plant of TT revealed the presence of α-Amyrin as the major constituent and seven minor constituents, which are 3,7,11,15-tetramethyl-2-hexadecen-1-ol, *n*-hexadecadienoic acid, hexadecadienoic acid ethyl ester, phytol, 9,12-octadecadienoic acid, 9,12,15-octadecatrienoic acid, and 1,2-benzenedicarboxylic acid disoctyl ester. Sterols such as β-sitosterols and stigmasterols were also found to be present.[18]

TRADITIONAL USES

TT is used in folk medicines as a tonic, aphrodisiac, palliative, astringent, stomachic, antihypertensive, diuretic, lithotriptic, and urinary disinfectant. The dried fruit of the herb is very effective in most of the genitourinary tract disorders. It is a vital constituent of *Gokshuradi Guggul*, a potent Ayurvedic medicine used to support proper functioning of the genitourinary tract and to remove the urinary stones. TT has been used for centuries in Ayurveda to treat impotence, venereal diseases, and sexual debility. In Bulgaria, the plant is used as a folk medicine for treating impotence. In addition to all these applications, the Ayurvedic Pharmacopoeia of India attributes cardiotonic properties to the root and fruit. In traditional Chinese medicine, the fruits were used for treatment of eye trouble, edema, abdominal distension, emission, morbid leukorrhea, and sexual dysfunction. TT is described as a highly valuable drug in the

Shern-Nong Pharmacopoeia (the oldest known pharmacological work in China) in restoring the depressed liver, for treatment of fullness in the chest, mastitis, flatulence, acute conjunctivitis, headache, and vitiligo. In Unani medicine, TT is used as diuretic, mild laxative, and general tonic.[19]

PHARMACOLOGICAL ACTIVITIES

Diuretic activity

The diuretic properties of TT are due to large quantities of nitrates and essential oil present in its fruits and seeds. The diuretic activity can also be attributed to the presence of potassium salts in high concentration. Ali *et al.* tested the aqueous extract of TT prepared from its fruit and leaves in rat diuretic model and strips of isolated Guinea pig ileum were used for the contractility test. The aqueous extract of TT, in oral dose of 5 g/kg, elicited a positive diuresis, which was slightly more than that of furosemide. Sodium and chloride concentrations in the urine were increased. The increased tonicity of the smooth muscles, which was produced by TT extract, together with its diuretic activity helped in the propulsion of stones along the urinary tract.[20] Saurabh *et al.* evaluated the different extracts of TT fruits, viz. aqueous, methanolic, *Kwatha*-high strength, *Kwatha*-low strength, and *Ghana* powder, for diuretic activity in rats. *Kwatha*-high strength showed diuretic effect comparable to that of the reference standard frusemide and also exhibited additional advantage of potassium-sparing effect.[21] The diuretic action of TT makes it useful as an anti-hypertensive agent.

Aphrodisiac activity

Adaikan *et al.* reported that the TT extract exhibited a pro-erectile effect on rabbit corpus cavernosum smooth muscle *ex vivo* after oral treatment at doses of 2.5, 5, and 10 mg/kg body weight for 8 weeks. A significant relaxation of 24% was observed with nitroglycerine in the corpus cavernosum smooth muscle tissue. Similarly, 10% relaxation was observed with both acetylcholine and electrical field stimulation, respectively, following the above treatment with TT in rabbits. The enhanced relaxant effect observed is due to increase in the release of nitric oxide from the endothelium and nitrergic nerve endings, which may account for its claims as an aphrodisiac.[22] Singh *et al.* evaluated the acute and repeated dose administration of lyophilized aqueous extract of the dried fruits of TT (LAET) at doses of 50 and 100 mg/kg of body weight as a sexual enhancer in the management of sexual dysfunction in male rat. A dose-dependent improvement in sexual behavior was observed with the LAET treatment, which was more prominent on chronic administration of LAET. A significant increase in serum testosterone levels too was observed. These findings confirm the traditional use of TT as a sexual enhancer in the management of sexual dysfunction in males.[23] Ethanolic extract of TT exhibited protective effect against cadmium-induced testicular damage. The protective effect appears to be mediated directly either through inhibition of testicular tissue peroxidation by antioxidant and metal chelating activity or by stimulating the testosterone production from Leydig cells.[24] TT extract (100-300 mg/l) treatment to a fish colony was found to be effective in increasing the proportion of males in the population. It was found that testes of fish treated with TT extract showed all stages of spermatogenesis with improved growth performance in *Poeciliata reticulata* fish species.[25] The two main components of the saponin fraction from TT, namely protodioscin and protogracillin, are responsible for the observed biological aphrodisiac activity.[26] It is suggested that protodioscin works by increasing the conversion of testosterone into the potent dehydrotestosterone, which stimulates not only increase in the sex drive but also the production of red cells from bone marrow along with muscular developments contributing to improvement of blood circulation and the oxygen transport systems, leading to optimal health.

Antiurolithic activity

An ethanolic extract of TT fruits was tested in urolithiasis induced by glass bead implantation in albino rats by Anand *et al.* It exhibited significant dose-dependent protection against deposition of calculogenic material around the glass bead, leukocytosis, and elevation in serum urea levels. Subsequent fractionation of the ethanol extract led to decrease in activity.[27] Various other biochemical parameters in urine, serum, and the histopathology of urinary bladder were restored in a dose-dependent manner. A novel antilithic protein having cytoprotective potency and of molecular weight ~ 60 kDa was purified from TT.[28] Aggarwal tested the activity of TT on the nucleation and growth of calcium oxalate (CaOx) crystals as well as on oxalate-induced cell injury of NRK 52E renal epithelial cells. The experiments revealed that TT extract not only has a potential to inhibit nucleation and growth of the CaOx crystals but also has a cytoprotective role.[28] TT was found to inhibit stone formation in various models of urolithiasis using sodium glycolate and ethylene glycol.[29]

Glycolate oxidase (GOX) is one of the principal enzymes involved in the pathway of oxalate synthesis converting glycolate to glyoxylate by oxidation and finally to oxalate. The antiurolithic activity of TT is attributed to its GOX inhibition. Quercetin and kaempherol, the active components of TT, were found to be non-competitive and competitive inhibitors of GOX, respectively.[30]

Immunomodulatory activity

Saponins isolated from the fruits of TT demonstrated dose-dependent increase in phagocytosis, indicating stimulation of nonspecific immune response. An alcoholic extract of the whole plant of TT exhibited a significant dose-dependent increase in humoral antibody titre and delayed type hypersensitivity response, indicating increased specific immune response.[31]

Antidiabetic activity

Saponin from TT possesses hypoglycemic properties.[32] TT significantly reduced the level of serum glucose, serum triglyceride, and serum cholesterol, while serum superoxide dismutase (SOD) activity was found to be increased in alloxan-induced diabetic mice. The decoction of TT showed

inhibition of gluconeogenesis in mice.[33,34] TT ethanolic extract at 2 g/kg body weight produced protective effect in streptozotocin-induced diabetic rats by inhibiting oxidative stress. Ethanolic extract of TT exhibited 70% inhibition of α-glucosidase at 500 μg/ml using maltose as the substrate and 100% inhibition of aldose reductase at a dose of 30 μg/ml using dl-glyceraldehyde as the substrate.[35] A significant decrease in the postprandial blood glucose level of rats was found after administration of saponin from TT. TT produced dilation of coronary artery and improved the coronary circulation. It is therefore recommended in Ayurveda for the treatment of angina pectoris and other cardiac complications of diabetes. Thus, TT could be beneficial in the treatment of diabetes by lowering blood glucose, lipid levels, and by its antioxidant mechanism.

Absorption enhancer

Ethanolic extract of TT enhanced the absorption of metformin hydrochloride, a Biopharmaceutics Classification System (BCS) class III drug, in everted sac technique using goat intestine, due to the presence of saponins in the extract.[36]

Hypolipidemic activity

The aqueous extract of the fruits of TT was evaluated for their hypolipidemic activity in Wistar albino rats. A dose of 580 mg/kg of the extract was found to decrease cholesterol-induced hyperlipidemia, with a decrease in cholesterol, triglycerides, low density lipoprotein (LDL), very low density lipoprotein (VLDL), and atherogenic index (AI), and an increase in high density lipoprotein (HDL) levels in the blood. Hypolipidemic activity may be due to the presence of phenolic compounds leading to increased lipoprotein lipases in the muscles and decreased activity in the adipose tissues, thus indicating that plasma triglycerides are utilized for energy production by the muscle and not for energy storage by the adipose tissue.[37] The pleotropic effect of TT at 5 mg/kg/day dose for 8 weeks on the lipid profile and vascular endothelium of the abdominal aorta in New Zealand rabbits fed on a cholesterol-rich diet was studied. It was found that dietary intake of the herb significantly lowered the serum lipid profile, decreased endothelial cellular surface damage as well as ruptures, and partially repaired the endothelial dysfunction resulting from hyperlipidemia.[38]

Saponins from TT were studied on diet-induced hyperlipidemia in mice for its preventive and therapeutic effect. The preventive effect was demonstrated by decrease in the levels of serum total cholesterol (TC) and LDL-cholesterol. It also reduced the liver TC and triglycerides and increased the activity of SOD in the liver. It showed therapeutic effect by significantly reducing the serum TC and liver TC.[39]

Activity in cardiac disorders

TT showed significant effect in the treatment of various cardiac diseases including coronary disease, myocardial infarction, cerebral arteriosclerosis, and the sequelae of cerebral thrombosis. Zhang *et al.* evaluated the protective effect of tribulosin from TT against cardiac ischemia/reperfusion injury to study the underlying mechanism in rats. Tribulosin protected myocardium against ischemia/reperfusion injury through protein kinase C epsilon activation.[40] Tribulosin treatment resulted in a significant reduction of malondialdehyde, aspartate transaminases, creatine kinase, lactate dehydrogenase activity, and myocardial apoptosis rate. It increased the activity of SOD. Crude saponin fraction of this plant has shown significant effects in the treatment of various cardiac diseases including hypertension, coronary heart disease, myocardial infarction, cerebral arteriosclerosis, and thrombosis. It also has been shown that the aqueous extract of TT fruits has significant acetylcholinesterase (ACE) inhibitory effects *in vitro*. Methanolic and aqueous extracts of TT are shown to possess significant antihypertensive activity by direct arterial smooth muscle relaxation and membrane hyperpolarization in spontaneously hypertensive rats.[41] TT also appears to protect the heart cells and may even improve the heart function following a heart attack.[42]

Central nervous system (CNS) activity

Swiss Albino mice demonstrated antidepressant and anxiolytic activity on administration of 260 mg/kg dose of *Rasayana Ghana* tablet comprising three potent well-established rejuvenator herbs, viz. *Tinospora cordifolia* (stem), *Emblica officinalis* (fruit), and TT (fruit and root), present in equal quantities in the tablet. It was suggested that harmine, a β-carboline alkaloid present in TT, is one of the main active constituents that contributes to the above-mentioned activities. Harmine is an inhibitor of monoamine oxidase which helps to increase level of dopamine in the brain.[43]

Hepatoprotective activity

The TT extract (250 mg/kg) showed a remarkable hepatoprotective activity against acetaminophen-induced hepatotoxicity in *Oreochromis mossambicus* fish. The elevated biochemical parameters and decreased level of reduced glutathione enzymes were normalized by treatment with TT extract (250 mg/kg) for acetaminophen-induced toxicity in freshwater fish.[44]

Antiinflammatory activity

The ethanolic extract of TT inhibited the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) in lipopolysaccharide-stimulated RAW264.7 cells. It also suppressed the expression of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-4 in macrophage cell line. Thus, the ethanolic extract of TT inhibits the expression of mediators related to inflammation and expression of inflammatory cytokines, which has a beneficial effect on various inflammatory conditions.[45] The methanolic extract of TT showed a dose-dependent inhibition of rat paw volume in carrageenan-induced inflammation in rats.[46]

Analgesic activity

Analgesic activities of TT were studied in male mice using formalin and tail flick test. The study indicated that the methanolic extract of TT at a dose of 100 mg/kg produced analgesic effect. This analgesic effect of the TT extract may be mediated centrally and/or peripherally. Effect of the extract was

lower than morphine and higher than acetylsalicylic acid (aspirin) in both tests. Pretreatment of animals with opioid receptor antagonist, naloxone, did not change the analgesic effect of the extract in both tests; therefore, the involvement of opioid receptors in the analgesic effect of TT is excluded. However, the other mechanisms responsible for the analgesic effect of TT remain to be investigated. The results of ulcerogenic studies indicate that the gastric ulcerogenecity of TT is lower than indomethacin in the rat's stomach.[47]

Antispasmodic activity

The lyophilized saponin mixture of the plant exhibited a significant decrease in peristaltic movements of rabbit jejunum preparation in a dose-dependent manner. These results showed that the saponin mixture may be useful for smooth muscle spasms or colic pains.[48]

Anticancer activity

Chemopreventive potential of the aqueous extract of the root and fruit of TT at 800 mg/kg on 7,12-dimethylbenz (a) anthracene (DMBA) and croton oil induced papillomagenesis in Swiss albino male mice depicted significant reduction in tumor incidence, tumor burden, and cumulative number of papillomas, along with a significant increase in the average latent period in mice treated orally with TT suspension continuously at pre-, peri-, and post-initiation stages of papillomagenesis, as compared to the control group treated with DMBA and croton oil alone. The root extract of TT exhibited better chemopreventive potential than the fruit extract at the same concentration (800 mg/kg body weight) in skin papillomagenesis in mice.[49] The aqueous extract of TT blocked proliferation in HepG2 cells and could also induce apoptosis through the inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling. Thus, TT has clinical therapeutic effects against liver cancer cells.[50] The aqueous root extract of TT produced significant radioprotection when given orally (800 mg/kg) for seven consecutive days prior to gamma irradiation. TT extract pretreatment protected against radiation damage by inhibiting radiation-induced glutathione depletion and decreasing lipoperoxidation level in the liver of mice.[51]

Saponins isolated from the aerial parts of TT were studied for their cytostatic/cytototoxic activity on human fibroblasts. The effects were determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) analysis and ^{3H}thymidine incorporation to assess cell viability and proliferation, respectively. Saponins showed a dose-dependent decrease in ^{3H}thymidine incorporation into the DNA, indicating decreased proliferation. Similarly, they were found to be less toxic for normal human skin fibroblasts. The mechanism of action involves up- and down regulation of polyamines' homeostasis, suppression of proliferation, and induction of apoptosis.[52]

Antibacterial activity

All parts (fruits, stems, leaves, and roots) of Turkish and Iranian TT showed antibacterial activity against *Enterococcus faecalis*, *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*, in contrast to the aerial parts of Yemeni TT which had no detectable antibacterial activity against these bacteria, while only the fruits and leaves of Indian TT were active exclusively against *E. coli* and *S. aureus*. These different results relating to the antibacterial activity of TT may be due to using different geographic sources of the plant, types of strains, and assay methods. The methanolic extract of fruits of TT was found to be most active against gram-positive and gram-negative bacteria, while moderate activity was observed in its petroleum ether extract and chloroform extract.[53,54]

Anthelmintic activity

The methanolic extract of TT was found to be more effective than the petroleum ether, chloroform, and water extracts for *in vitro* anthelmintic activity on the nematode *Caenorhabditis elegans*. Further bioactivity-guided fractionation confirmed tribulosin and β-sitosterol-d-glucoside to be the active components with ED_{50} of 76.25 and 82.50 μg/ml, respectively.[55,56]

Larvicidal activity

The petroleum ether extract of the leaves of TT exhibited better larvicidal activity against the third instar larvae and adults of the mosquito, *Aedes aegypti*, which is the vector of dengue fever, with LC_{50} of 64.6 ppm as compared to the crude ethanol and

Figure 1: Whole plant of *tribulus terrestris*

Figure 2: Fruit of *tribulus terrestris* plant

acetone extracts.[57,58]

Anticariogenic activity

The ethanolic extract of fruits of TT (0.1-0.5 mg/ml) possesses significant anticariogenic activity against *Streptococcus mutans*, the pathogen responsible for dental caries. The growth, acid production, adhesion, and water-insoluble glucan synthesis of *S. mutans* were significantly inhibited in the presence of the ethanol extract of TT. Further studies are necessary to elucidate the active constituents of TT responsible for such activities.[59]

Recommended dose of TT in Ayurveda

- Fruit: 3-6 g of the drug in powder form; 20-30 g of the drug for decoction
- Root: 20-30 g of the drug for decoction[60].

Important formulations

Gokshuradi Guggulu, Trikantak Ghruta, Drakshadi Choorna, Rasayana Choorna, Gokshuradi Kwatha, Dashamoola Kwatha[60]

CONCLUSION

TT, a commonly available weed, is of significant value in the traditional systems of medicine, viz. Ayurveda, Chinese, Siddha, and Unani. TT is also a reputed herb in the folk medicine of many countries for a number of diseases. The whole plant of TT has been explored exhaustively for its phytochemical and pharmacological activities such as diuretic, aphrodisiac, antiurolithic, immunomodulatory, antihypertensive, antihyperlipidemic, antidiabetic, hepatoprotective, anticancer, anthelmintic, antibacterial, analgesic, and anti-inflammatory. Considering the available literature on TT, the plant could have a potential as a herbal medicine for effective blood pressure control due to its diuretic activity (potassium sparing), antihyperlipidemic activity, and cardioprotective activity. Though TT has been used extensively over the centuries and currently scientific evidence with respect to its pharmacological activities is also being generated, more studies at the molecular level are needed to further understand the mechanism by which it modifies the disease condition. The pharmacological experiments performed on the plant must be extended to the next level of clinical trials to generate novel drugs. This will help TT in achieving a status of medicine or to be prescribed as a dietary supplement in various disease conditions.

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Plants used to treat skin diseases

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ABSTRACT

Skin diseases are numerous and a frequently occurring health problem affecting all ages from the neonates to the elderly and cause harm in number of ways. Maintaining healthy skin is important for a healthy body. Many people may develop skin diseases that affect the skin, including cancer, herpes and cellulitis. Some wild plants and their parts are frequently used to treat these diseases. The use of plants is as old as the mankind. Natural treatment is cheap and claimed to be safe. It is also suitable raw material for production of new synthetic agents. A review of some plants for the treatment of skin diseases is provided that summarizes the recent technical advancements that have taken place in this area during the past 17 years.

Key words: Ethnomedicine, herbs, medicinal plants, skin diseases

INTRODUCTION

Human skin, the outer covering of the body, is the largest organ in the body. It also constitutes the first line of defense. Skin contains many specialized cells and structures. It is divided into three main layers viz. epidermis, dermis and hypodermis. Each layer provides a distinct role in the overall function of the skin. Epidermis, the outer most layer of the skin, varies in thickness in different regions of the body. It is the thinnest on the eyelids (0.05 mm) and the thickest on the palms and soles (1.5 mm). The dermis also varies in thickness depending on the location of the skin. It is 0.3 mm on the eyelid and 3.0 mm on the back of the body. The dermis is attached to an underlying hypodermis or subcutaneous connective tissue. The subcutaneous tissue is a layer of fat and connective tissue that houses larger blood vessels and nerves. This layer is important in the regulation of temperature of the skin itself and the body. The size of this layer varies throughout the body and from person-to-person. Hair follicles, sweat glands and sebaceous glands are the main skin appendages.

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The skin guards the underlying muscles, bones, ligaments and internal organs. There are two general types of skin, hairy and glabrous skin.[1] However, the skin can be dry, sensitive, pale, sagging or tired. People deficient in essential nutrients such as beta-carotene, the B complex vitamins and vitamins C and E often suffer from the drying of the skin.

FUNCTIONS OF SKIN

Because it interfaces with the environment, skin plays a key role in protecting (the body) against pathogens.[2,3] and excessive water loss.[3] Its other functions are insulation, temperature regulation, sensation, storage and synthesis of vitamin D by action of ultraviolet (UV) and the protection of vitamin B folates, absorption of oxygen and drugs[4] and water resistance.[5] Severely damaged skin will try to heal by forming scar tissue. This is often discolored and depigmented.

COMMON SKIN PROBLEMS

Skin disease is a common ailment and it affects all ages from the neonate to the elderly and cause harm in number of ways.[1] There are more than a thousand conditions that may affect the skin but most skin diseases can be categorized into nine common types.[6]

Rashes

A rash is an area of red, inflamed skin or a group of individual spots. These can be caused by irritation, allergy, infection, an underlying disease, as well as by structural defects for example, blocked pores or malfunctioning oil glands. Examples of rashes include acne, dermatitis, eczema, hives, pityriasis rosea and psorasis.

Viral infections

These occur when a virus penetrates the stratum corneum and infects the inner layers of the skin. Examples of viral skin infections include herpes simplex, shingles (herpes zoster) and warts. Some systemic viral infections, such as chicken pox and measles, may also affect the skin. Viral infections cannot be cured with antibiotics.

Bacterial infections

Such infections are caused by a variety of bacteria, the most common types being staphylococci and streptococci. Bacteria may infect the topmost layers of skin, the follicles, or the deeper layers of skin. If not treated correctly, these infections may spread throughout the body. Examples include impel folliculitis, cellulitis and lyme disease. Bacterial infections are better treated with antibiotics.

Fungal infections

Harmless fungi are always present on surface of the skin. Infection occurs when these organisms enter into the body. These infections are usually superficial, affecting the skin, hair, nails and include athlete's foot, lock itch and ringworm. However, in people with suppressed immune system or who have been taking antibiotics for long period -, the fungi may spread to deep within the body, causing more serious disease.

Parasitic infections

These infections occur after exposure to parasites such as lice and scabies.

Pigmentation disorders

The amount of pigment in the skin is determined by the amount of melanin being produced by the body. Loss of pigment (hypo pigmentation) can be caused by absence of melanocytes, malfunctioning cells, exposure to cold or chemicals, or some types of infection. An increase in pigment (hyperpigmentation) may be caused by skin irritation, hormonal changes, aging, a metabolic disorder, or any other underlying problem. Age spots, freckles and melasma are examples of hyper pigmentation. Vitiligo is an example of hypo pigmentation.

Tumors and cancers

These growths arise when skin cells begin to multiply faster than normal. Not every skin growth is cancerous. Some tumors are harmless and will not spread. Skin cancer is the most common of all the cancers, affecting 800,000 Americans each year. It is caused, in 90% of cases, by sun exposure. The three types of skin cancers are basal cell cancer (the most curable), squamous cell cancer (which may grow and spread) and malignant melanoma (the most deadly form). Prevention involves protecting the skin against damaging ultraviolet rays. Early detection helps to improve the chances of a cure. Regular self-examinations are, therefore, recommended.

Trauma

Trauma describes an injury to the skin caused by a blow, a cut, or a burn. Whenever the surface of the skin is broken, the body becomes more susceptible to infection and disease.

Other conditions

Wrinkles, rosacea, spider veins and varicose veins are among those conditions that cannot be neatly categorized. Wrinkles are caused by a breakdown of the collagen and elastin within the dermis, which results in sagging skin. Rosacea is a chronic disorder in which the skin of the face becomes red and develops pimples, lesions and more rarely enlargement of the nose. Its cause is unknown. Spider veins and varicose veins become apparent when blood vessels enlarge and become visible through the surface of the skin.

CONVENTIONAL TREATMENT OF SKIN DISEASES

The common medications for topical use include[7]:

1. Antibacterials: These medicines, like bactroban or cleocin, are often used to treat or prevent infection
2. Anthralin (drithocreme, micanol and others): Although not often used, these help to reduce inflammation and can help treat psoriasis
3. Antifungal agents: Lamisil, lotrimin and nizoral are few examples of common topical antifungal drugs used to treat skin conditions such as ringworm and athlete's foot
4. Benzoyl peroxide: Creams and other products containing benzoyl peroxide are used to treat acne
5. Coal tar: This topical treatment is available with and without a prescription, in strengths ranging from 0.5% to 5%. Coal tar is used to treat conditions including seborrheic dermatitis (usually in shampoos) or psoriasis. Currently, coal tar is seldom used because it can be slow acting and can cause severe staining of personal clothing and bedding
6. Corticosteroids: These are used to treat skin conditions including eczema and come in many forms including foams, lotions, ointments and creams
7. Retinoids: These medications (such as retin-A and tazorac) are gels or creams derived from vitamin A and are used to treat conditions including acne
8. Salicylic acid: This medication is available in the form of lotions, gels, soaps, shampoos and patches. It should be used sparingly as putting too much on one's body at once can cause toxicity. Salicylic acid is the active ingredient in many skin care products for the treatment of acne and warts.

Oral treatments for skin conditions include:

1. Antibiotics: Oral antibiotics like erythromycin, tetracycline and dicloxacillin are used to treat many skin conditions
2. Antifungal agents: Common oral antifungal drugs such as ketoconaole and diflucan can be used to treat more severe fungal infections
3. Antiviral agents: Common antiviral agents include

valtrex, acyclovir and famavir. Antiviral treatments are used for skin conditions including those related to herpes

4. Corticosteroids: These medications, including prednisone can be helpful in treating skin conditions linked to autoimmune diseases including vasculitis and inflammatory diseases such as eczema and psoriasis. Dermatologists prefer topical steroids to avoid side-effects; however, short-term use of prednisone is sometimes necessary
5. Immunosuppressants: Immunosuppressants, such as azathioprine and methotrexate, can be used to treat conditions including severe cases of psoriasis and eczema
6. Biologics: These new therapies are the latest methods being utilized to treat psoriasis and other conditions. Examples of biologics include enbrel, humira, remicade, stelara and amevive.

HERBAL DRUGS FOR SKIN DISEASES

Natural drugs from the plants are gaining popularity because of several advantages such as often having fewer side-effects, better patient tolerance, being relatively less expensive and acceptable due to a long history of use. Besides herbal medicines provide rational means for the treatment of many diseases that are obstinate and incurable in other systems of medicine. For these reasons several plants have been investigated for treatment of skin diseases ranging from itching to skin cancer. So far 31 plants have been reported to be effective in various skin diseases during the past 17 years (1995-2012) of research work, which are mentioned below.

Achyranthes aspera (Common name: Prickly chaff flower, Devil's horsewhip; Family: Amaranthaceae)

Traditionally, the plant is used in boils, scabies and eruptions of skin and other skin diseases. The MeOH extract, alkaloid, non-alkaloid and saponin fractions obtained from the leaves of *A. aspera* exhibited significant inhibitory effects (concentration 100 μg) on the Epstein-Barr virus early antigen (EBV-EA) activation induced by the tumor promotor 12-O-tetradecanoylphorbol-13-acetate (TPA) in Raji cells. In this *in vitro* assay the non-alkaloid fraction containing mainly non-polar compounds showed the most significant inhibitory activity (96.9%; 60% viability). In the *in vivo* two-stage mouse skin carcinogenesis test the total methanolic extract possessed a pronounced ant carcinogenic effect (76%). The results revealed that leaf extract and the non-alkaloid fraction are valuable antitumor promotors in carcinogenesis.[8]

Allium cepa (Common name: Onion; Family: Liliacea)

A study undertaken in patients with seborrheic keratoses to evaluate the ability of onion extract gel to improve the appearance of scars following excision, has shown that this extract gel improved scar softness, redness, texture and global appearance at the excision site at study weeks 4, 6 and 10 as assessed by the blinded investigator.[9]

In another study, the antifungal activity of aqueous extracts prepared from *A. cepa* (onion; AOE) and *Allium sativum* (garlic; AGE) were evaluated against *Malassezia furfur* (25 strains), *Candida albicans* (18 strains), other *Candida* sp. (12 strains) as well as 35 strains of various dermatophyte species. The results indicated that onion and garlic might be promising in treatment of fungal-associated diseases from important pathogenic genera like *Candida, Malassezia* and the dermatophytes.[10]

A. sativum (Common name: Garlic; Family: Liliaceae)

In a study conducted on Swiss albino mice in whom cancer was induced by 7,12-dimethylbenz(a)anthracene (DMBA) revealed that best chemo preventive action of garlic was observed in mice in which garlic treatment was performed before and after the induction of skin carcinogenesis. Garlic ingestion delayed formation of skin papillomas in animals and simultaneously decreased the size and number of papillomas, which was also reflected in the skin histology of the treated mice. The protective effect against skin cancer elicited by garlic in mice is believed to be due at least in part to the induction of cellular defense systems.[11]

Aloe vera (Common name: Barbados aloe; Family: Xanthorrhoeaceae)

Aloe vera has shown very good results in skin diseases and it is often taken as health drink. It is also found effective in treating wrinkles, stretch marks and pigmentations. It also seems to be able to speed wound healing by improving blood circulation through the area and preventing cell death around a wound. One of the studies conducted on mice to investigate the effects of *Scutellariae radix* and *Aloe vera* gel (AV), in spontaneous atopic dermatitis (AD)-like skin lesions revealed that the group receiving only AV in a dose of 0.8 mg/kg p.o provided relief in AD due to reduction of interleukin (IL)-5 and IL-10 levels.[12]

The gel has properties that are harmful to certain types of bacteria and fungi. A cream containing 0.5% aloe for 4 weeks reduced the skin "plaques" associated with psoriasis.[13] Application of gel helped in the improvement of partial thickness burns.[14] When applied to the skin, the gel seems to help skin survive frostbite injury.[15] It might delay the appearance of skin damage during and after radiation treatment.[16]

Azadirachta indica (Common name: Neem; Family: Meliaceae)

Leaf extract is applied externally on boils and blisters.[17] In one study, skin tumors were induced in mice by topical application of DMBA (500 nmol/100 μl for 2 weeks) followed by TPA (1.7 nmol/100 μl of acetone, twice weekly) as a promoter. The test group received aqueous *Azadirachta indica* leaf extract (AAILE) orally at a dose level of 300 mg/kg body weight three times a week for 20 weeks. The results of this study revealed the chemopreventive potential of *A. indica* against murine skin carcinogenesis.[18]

Study designed to determine the modulatory effect of aqueous AAILE on cell cycle-associated proteins during two-stage skin carcinogenesis in mice in which skin tumors were induced by topical application of DMBA as a carcinogen followed by the repetitive application of TPA as a promoter. Skin tumors obtained in the DMBA/TPA group exhibited enhanced expression of proliferating cell nuclear antigen (PCNA, index of proliferation), p21 and cyclin D1, with no alterations in p53 expression in comparison to the control group. Tumors in AAILE + DMBA/TPA group exhibited low PCNA and cyclin D1 expression and enhanced expression of p53 and p21 in comparison to the DMBA/TPA group. The skin tumors obtained in the AAILE + DMBA/TPA group exhibited high lipid peroxidation levels in comparison to the tumors obtained in the DMBA/TPA group. The observations of the study suggested that AAILE behaves as a pro-oxidant in the tumors, thereby rendering them susceptible to damage, which eventually culminates into its anti-neoplastic action. Also, cell cycle regulatory proteins may be modulated by AAILE and could affect the progression of cells through the cell cycle.[19]

Another study, conducted on an anti-acne moisturizer formulated from herbal crude extracts and investigated for the physico-chemical parameters as well as antibacterial activity of the formulation, revealed that ethanol extract of *Andrographis paniculata, Glycyrrhiza glabra, Ocimum sanctum, A. indica* and Green tea possessed the potential for inhibiting acne. It was observed that the optimal formula of anti-acne moisturizer was satisfactorily effective to control acne inducing bacteria i.e., *Staphylococcus epidermis* and *Propionibacterium*.[20]

Bauhinia variegata (Common name: Kachanar, Orchid tree, Camel's Foot Tree, Mountain Ebony; Family: Fabaceae)

The bark is internally administered for treating skin diseases, asthma, sore throat, diarrhea and abdominal discomfort and also applied externally for skin ulcers. In the skin papilloma model, significant prevention, with delayed appearance and reduction in the cumulative number of papillomas was observed in the DMBA + Kachanar + croton oil treated group as compared to the DMBA + croton oil group. C57 Bl mice which received a 50% methanolic extract of Kachanar extract at the doses of 500 and 1000 mg/kg body weight for 30 days showed increase in life span and tumor size was significantly reduced as compared to controls. In anti-mutagenic studies, a single application of Kachanar extract at doses of 300, 600 and 900 mg/kg dry weight, 24 h prior the i.p. administration of cyclophosphamide (at 50 mg/kg) significantly prevented micronucleus formation and chromosomal aberrations in bone marrow cells of mice, in a dose dependent manner.[21]

Beta vulgaris (Common name: Beetroot; Family: Brassicaceae)

The *in vitro* inhibitory effect of beet root extract on EBV-EA induction using Raji cells revealed a high order of activity compared to capsanthin, cranberry, red onion skin and short and long red bell peppers. An *in vivo* anti-tumor promoting activity evaluation against the mice skin and lung bioassays also revealed a significant tumor inhibitory effect. The combined findings suggest that beet-root ingestion can be one of the useful means to prevent cancer.[22]

Brassica oleraceae (Common name: Red Cabbage; Family: Brassicaceae)

Significant reduction of tumors was observed in mice in whom skin cancer was induced by a single topical application of 200 nmol of the initiator DMBA to their backs, followed 1 week later by promotion with 10 nmol of TPA twice weekly for 30 weeks followed by 0.1 g/L of aqueous extract of *B. oleraceae* 1 week after administration of initiator.[23]

Calendula officinalis (Common name: Marigold; Family: Asteraceae)

The flowers of marigold have long been employed in folk therapy and more than 35 properties have been attributed to decoctions and tinctures from the flowers. The main uses are as remedies for burns (including sunburns), bruises and cutaneous and internal inflammatory diseases of several origins. Topical formulations containing marigold extract (ME), evaluated in hairless mice against UV-B irradiation-induced photo damage, revealed that application of ME in gel formulation, containing 0.21 μg/cm of narcissin and as 0.07 μg/cm of the rutin in the viable epidermis, were associated with a possible improvement in the collagen synthesis in the sub epidermal connective tissue.[24]

One of the experiments carried out in 34 patients with venous leg ulcers to determine the therapeutic efficacy of ME on the epithelialization of lower leg venous ulcers revealed significant acceleration of wound healing by producing epithelialization.[25] Research conducted on cream preparations containing seven different types of marigold and rosemary extracts, revealed that such creams are effective in experimentally induced irritant contact dermatitis when tested on healthy human volunteers.[26]

Camellia sinensis (Common name: Green tea, Chaay; Family: Theaceae)

Green tea comes from the tea plant *C. sinensis* and may play a beneficial role in treatment of skin tumours and cancer. It contains polyphenols, which act as antioxidants in the body. A specific polyphenol in Green tea called epigallocatechin gallate, according to the National Center for Complementary and Alternative Medicine, has been reported to prevent the onset of further growth of skin tumor in the body. It can rejuvenate old skin cells to start reproducing again, keeping the skin younger looking.[27]

Cannabis sativus (Common name: Charas, Ganja; Family: Cannabinaceae)

The powder of the leaves serves as a dressing for wounds and sores. Ganja is externally applied to relieve pain in itchy skin diseases. Hemp seed oil is useful for treatment of eczema and host of other skin diseases like dermatitis, seborrhoeic

dermatitis/cradle cap, varicose eczema, psoriasis, lichen planus and acne roseacea. By using hemp seed oil, the skin is strengthened and made better able to resist bacterial, viral and fungal infections. Crushed leaves are rubbed on the affected areas to control scabies.[16]

Crocus sativus (Common name: Saffron; Family: Iridaceae)

Saffron is a naturally derived plant product that acts as an antispasmodic, diaphoretic, carminative, emmenagogic and sedative. The chemopreventive effect of aqueous saffron on chemically induced skin carcinogenesis using a histopathological approach was studied. Its ingestion inhibited the formation of skin papillomas in animals and simultaneously reduced their size. Saffron inhibited DMBA-induced skin carcinoma in mice when treated early. This may be due, at least in part, to the induction of cellular defense systems.[28] It has also been found useful in treatment of psoriasis.[29]

Curcuma longa (Common name: Turmeric; Family: Zingiberaceae)

A study conducted on male Swiss albino mice in whom skin cancer was induced by topical application of DMBA, revealed a significant reduction in number of tumors per mouse in the group receiving 1% curcumin obtained from rhizomes of *C. longa*.[30]

Daucus carota (Common name: Carrot; Family: Apiaceae)

A study, conducted to investigate the chemopreventive effects of oil extract of *D. carota* umbels on DMBA-induced skin cancer in mice for 20 weeks, revealed significant reduction in tumor incidence following administration via intraperitonial (0.3 ml of 2% oil) and topical (0.2 ml of 5, 50 and 100% oil) but least with gavage (0.02 ml of 100% oil).[31]

Echinacea angustifolia, Echinacea purpurea (Common name: Purple cone flower; Family: Asteraceae)

Echinacea has been applied to and used to treat skin problems such as skin boils, wounds, ulcers, burns, herpes, hemorrhoids and psoriasis. Forms of *Echinacea* include tablets, juice and tea.[27] A study conducted on patients to determine the effect of oral supplementation with a nutraceutical, containing methionine, *Echinacea*, zinc, probiotics and other antioxidant and immunostimulating compounds, on the response of cutaneous warts revealed a significant reduction of warts in such patients.[32]

The herbal extract of *E. purpurea* (Echinaforce®), readily killed a standard laboratory strain of *Propionibacterium acnes* (main cause of acne) and several clinical isolates. In cell culture models of human bronchial epithelial cells and skin fibroblasts, *P. acne* induced the secretion of substantial amounts of several pro-inflammatory cytokines, including IL-6 and IL-8 (CXCL8), as determined by means of cytokine-antibody arrays. However, the *E. purpurea* completely reversed this effect and brought the cytokine levels back to normal. Thus Echinaforce® could provide a safe two-fold benefit to acne individuals by inhibiting proliferation of the organism and reversing the bacterial-induced inflammation.[33]

Eucalyptus globulus (Common name: Blue gum, Camphor oil; Family: Myrtaceae)

In a study conducted on humans it was revealed that human facial demodicidosis when treated with freshly prepared camphor oil with or without glycerol dilutions gave complete cure with concentrations of 100%, 75% and 50% respectively.[34] Study conducted on humans revealed that camphor oil with or without glycerol dilutions completely cured zoonotic scabies with concentrations of 100%, 75% and 50% within 5-10 days.[35]

Euphorbia walachii, Euphorbia hirta, Euphorbia tirucalli (Common name: Wallich spurge; Fam. Euphorbiaceae)

Juice of *E. walachii* is used to treat warts and skin infections.[36] A study, conducted on various species of *Euphorbia, E. hirta,* exhibited best antioxidant activity. The plant extracts showed more activity against Gram-positive bacteria and fungi. The best antimicrobial activity was shown by *E. tirucalli*. The study supported the folkloric use of *E. hirta* and *E. tirucalli* against some skin diseases caused by oxidative stress or by microorganisms.[37]

Ficus carica, Ficus racemosa, Ficus bengaalensis (Common name: Fig; Family: Moraceae)

In some rural areas of Iran, a traditional method for the treatment of warts comprises the use of fig tree (*F. carica*) latex. A study conducted in patients with warts has revealed that this therapy of warts offers several beneficial effects including short-duration therapy, no reports of any side-effects, ease-of-use, patient compliance and a low recurrence rate. Although, exact mechanism of the antiwart activity of fig tree latex is unclear it is likely to be the result of the proteolytic activity of the latex enzymes.[38] *F. recemosa* L. bark powder is used externally in case of pimples, itches and scabies and *F. bengaalensis* L. bark powder is also used externally to cure scabies.[17]

Lavendula officinalis (Common name: Lavender; Family: Labiatae)

The effects of lavender oil (1:500, 1:100, 1:10, 1:1, 1:0) on mast cell-mediated immediate-type allergic reactions in mice and rats have been studied. It has been reported to inhibit concentration-dependently the histamine release from the peritoneal mast cells. It also inhibits immediate-type allergic reactions by inhibition of mast cell degranulation *in vivo* and *in vitro* when tested on mice and rats.[39]

Lawsonia inermis (Common name: Henna; Family: Lythraceae)

Henna is a traditionally used plant of Middle-East that is applied on hands and feet. In the traditional system of medicine, leaf paste is applied twice a day, on the affected parts to cure impetigo.[40] In a study, clinical improvement in the patients suffering from hand and foot disease due to use of capecitabine, an anti-cancer drug, with use of henna revealed anti-inflammatory, antipyretic and analgesic effects of henna.[41]

Lycopersicon esculentum (Common name: Tomato; Family: Solanaceae)

A study conducted on healthy human volunteers using tomato paste (40 g), providing approximately 16 mg/d of lycopene, ingested with 10 g of olive oil over a period of 10 weeks has revealed that it is feasible to achieve protection against UV light-induced erythema by ingestion of a commonly consumed dietary source of lycopene.[42]

Another study conducted in healthy human volunteers using 55 g of tomato paste containing 16 mg of lycopene ingested with olive oil, also revealed that tomato paste containing lycopene provides protection against acute and potentially longer-term aspects of photo damage.[43]

Mangifera indica (Common name: Mango; Family: Anacardiaceae)

The gum is used in dressings for cracked feet and for scabies. Latex is applied to cure ulcers.[17] Aqueous extract of stem-bark (MIE, 50-800 mg/kg i.p.) produced a dose-dependent and significant ($P < 0.05$-0.001) anti-inflammatory effect against fresh egg albumin-induced paw edema in rats.[44]

Matricaria chamomile, Matricaria recutita or Chamomilla recutita (Common name: Chamomile; Family: Asteraceae)

It aids in skin cell regeneration and acts as an antioxidant, fighting free radical damage on the skin. Free radicals are a dangerous oxygen by-product of cellular metabolism. There have been allergies reported and those with daisy allergies may find themselves allergic to chamomile.[27] A controlled study of 161 individuals found chamomile cream equally effective as 0.25% hydrocortisone cream for the treatment of eczema.[45] In a double-blind study, chamomile cream proved less effective for reducing inflammation of the skin than hydrocortisone cream or witch hazel cream.[46]

Finally, in a single-blind trial, 50 women receiving radiation therapy for breast cancer were treated with either chamomile or placebo. Chamomile failed to prove superior to placebo for preventing skin inflammation caused by the radiation therapy.[47]

Mirabilis jalapa (Common name: Four o'clock flower, Marvel of Peru; Family: Nctaginaceae)

M. jalapa is used traditionally in allergic skin disorders and asthma. A study, employing ethanol: acetone (1:1) extract of the roots of *M. jalapa,* revealed that the extract (0.5 mL of 100 mg mL[-1]) inhibited histamine-induced guinea pig tracheal chain contractions non-competitively. The extract (100 or 200 mg kg[-1] i.p.) inhibited milk-induced eosinophilia, albumin-induced paw edema and protected mast cells against clonidine-induced granulation justifying the folkloric use of *M. jalapa* in the treatment of allergic diseases and asthma.[48]

Momordica charantia (Common name: Bitter gourd; Family: Cucurbitaceae)

Topical application of the fruit extract of (100 µl/animal/day) during the peri-initiation stage (1 week before and 2 weeks after initiation) by DMBA and/or during the tumor promotion stage reduced the (i) tumor burden to 4.26, 3.72 and 3.11 (positive control value: 5.42); (ii) cumulative number of papillomas to 81, 67 and 53 (positive control value: 103); and (iii) percent incidence of mice bearing papillomas to 100, 94 and 94, respectively (positive control value: 100). In a comparison of the anticarcinogenic efficacy of *Momordica* peel, pulp, seed and whole fruit extract (100 µl/animal/day), after topical treatment during the peri-initiation and during the tumor promotion stage, revealed the modulation of the (i) tumor burden (tumors/mouse) to 3.06, 3.61, 3.17 and 3.11; (ii) cumulative number of papillomas to 49, 65, 54 and 53; and (iii) percent incidence of mice bearing papillomas to 84, 100, 94 and 94, respectively.[49]

Plumbago zeylanica (Common name: Doctor Bush; Family: Plumbaginaceae)

Whole plant is crushed with a pinch of salt and the paste is applied externally in case of ringworm.[17] A study conducted on plumbagin (5-hydroxy-2-methyl-1,4-napthoquinone), a medicinal plant-derived naphthoquinone, isolated from the roots of the *P. zeylanica* revealed that topical application of plumbagin in mice inhibited UV induced development of squamous cell carcinomas.[50]

Portulaca oleraceae (Common name: Purslane, Pigweed, Little Hogweed; Family: Portulacaceae)

The herb possesses natural cooling properties that soothe the skin, relieving it of skin inflammations and rashes during scorching heat. Burns and skin eruptions like boils and carbuncles can be treated with an effective concoction of the leaves. Topical application of the aqueous extract on to the skin is effective as antibacterial and antifungal.[51] Externally it is used to treat burns, earache, insect stings, inflammations, skin sores, ulcers, pruritis (itching skin), eczema and abscesses which are usually treated with the fresh herb as a poultice or the expressed juice is used.[51] In Ghana, the leaves are ground, mixed with oil and tied on boils.[52] Sometimes in combination the leaves are also eaten with tiger nuts (*Cyperus esculentus*) as a remedy for skin diseases and chancres. Extract of this plant was also found to be effective in treatment of AD using hairless mice.[53]

Prunus persica (Common name: Peach; Family: Rosaceae)

Ethanolic extract of the flowers (Ku-35) (50-200 µg/ml) were found to inhibit UVB and UVC induced deoxyribonucleic acid (DNA) damage by the COMET assay in the skin fibroblast cell (NIH/3T3). In addition, Ku-35 inhibited UVB-or UVC-induced lipid peroxidation, especially against UVB-induced peroxidation at higher than 10 µg/ml.[54]

Rosmarinus officinalis (Common name: Rosemary; Family: Labiatae)

Rosemary is a common household plant grown in many parts of the world. It is used for flavoring food, a beverage drink, as well

as in cosmetics. The most important constituents of rosemary are caffeic acid and its derivatives such as rosmarinic acid. These compounds have antioxidant effect. Chronic UV exposure is responsible for long term clinical manifestations such as photo aging and photo-cancers. Aqueous extract of *R. officinalis* has been reported to be effective in preventing cutaneous photo damage induced by UV radiations.[55]

In another study, the antibacterial activity of rosemary essential oil against *P. acnes* was observed with atomic force microscopy (AFM). Significant changes in morphology and size of *P. acnes* were observed by AFM in response to essential oil treatment. Rosemary oil has also been seen to be effective against *P. acnes*, a bacterium causing acne.[56] Application of methanol extract of leaves of rosemary to mouse skin inhibited the covalent binding of benzo(a)pyrene [B(a)P] to epidermal DNA and inhibited tumor initiation by B(a)*P* and DMBA.[57]

Sarco asoca (Common name: Ashoka; Family: Caesalpinaceae)

Paste of the roots is useful in freckles and external inflammations, ulcers and skin diseases. It is used for itching in eczema, psoriasis, dermatitis and herpes-kushta/visarpa by rubbing the crushed flower on the skin. It is a favorite herb to relieve pruritis, scabies and *tinea pedis*. 50 g of the dried flowers of *S. asoca* and the leaves of *L. inermis* are boiled in coconut oil and the extract is externally applied twice a day to treat eczema and scabies. A study revealed that pretreatment with the flavanoid fraction of *S. asoca* caused significant reduction in the number of tumors per mouse and the percentage of tumor-bearing mice. Furthermore, the latency period for the appearance of the first tumor was delayed by *S. asoca* pretreatment. A significant reduction in the expression of ornithine decarboxylase, a key enzyme in the promotion stage of 2-stage skin cancer, in the plant-treated group was also observed suggesting the chemopreventive activity of flavonoids from *S. asoca* on 2-stage skin carcinogenesis.[58]

Thyme vulgaris (Common name: Thyme; Family: Lamiaceae)

It may relieve the symptoms of cellulitis, an infection of the skin caused by bacteria which can lead to pain, tenderness, edema, fever, chills and reddening of the skin. It may also offer anti-fungal and antibacterial benefits. However, the University of Maryland Medical Center cautions that thyme has not been proven to specifically benefit cellulitis. In addition, this herb may raise the risk of bleeding.[27]

CONCLUSION

Herbals have great potential to cure different kinds of skin diseases. More than 80% of people in India depend on traditional health care and use different plant based products for curing skin related problems. Compared with the conventional allopathic drugs, they have relatively low cost and can be of great benefit to the population of India in general and poor people in particular. Herbals are a rich source of active ingredients and can be safer and cost effective treatment for skin diseases ranging from rashes to dreadful skin cancer. More than 50% of plant species useful for treatment of skin diseases appear to be restricted to forests, so activities such as deforestation, habitat destruction, urbanization etc., may pose a serious threat to these species. Conservation of these plants with the help of local participation and carrying out of extensive research in this respect to broaden the prospects of herbal drugs in skin disease treatment is the need of the hour.

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Strychnos potatorum: Phytochemical and pharmacological review

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ABSTRACT

In traditional system of medicine, the seeds of *Strychnos potatorum* Linn. (family: Loganiaceae) are used in the treatment of gonorrhea, leukorrhea leukeorrhea, gastropathy, bronchitis, chronic diarrhea, dysentery, renal and vesicle calculi, diabetes, conjunctivitis, scleritis, ulcers and other eye disease. An attempt has been made to highlight this medicinal seeds through phytochemical and pharmacological study. The present review deals with the phytochemical and pharmacological screening of therapeutic importance from *Strychnos potatorum* L., an important medicinal plant. This study includes the collective information of different medicinal uses of *Strychnos potatorum*. The generated data has provided the basis for its wide use as the therapeutant both in the traditional and folk medicines.

Key words: Medicinal plant; phytochemical; *Strychnos potatorum*

INTRODUCTION

Medicinal plants are used as a source of drugs for the treatment of various human and livestock health disorders all over the world from ancient times to the present day. They are important natural wealth. They provide primary healthcare services to people from all walks of life. They serve as important therapeutic agents as well as important raw materials for the manufacture of traditional and modern medicines. A total of 250,000 species of flowering plants are referred to as medicinal plants. The World Health Organization (WHO) enlisted some 21,000 medicinal plant species. The present global herbal market is worth about US$ 62 billion per annum. The annual growth of herbal market is about 15%and the global herbal market by 2050 is expected to be about US$ 5 trillion. Plants are one of the most important sources of medicines. Today the large number of drugs in use is derived from plants, like morphine from *Papaver somniferum*, Aswagandha from *Withania somnifera*, ephedrine from *Ephedra vulgaris*, atropine from *Atropa belladonna*, Reserpine from *Rouwolfiaserpentina*, etc., The medicinal plants are rich in secondary metabolites (which are potential sources of drugs) and essential oils of therapeutic importance. The important advantages claimed for therapeutic uses of medicinal plants in various ailments are their safety besides being economical, effective and their easy availability.[1,2] The increased global demand for polyherbal formulations is a reflection of positive impact of consolidated efforts aimed at reviving science of phytopharmacy.[3] *Strychnos potatorum* Linn (family: Loganiaceae) is a moderate sized tree found in southern and central parts of India, Sri Lanka, and Burma[4] In traditional system of medicine, the seeds are used in the treatment of gonorrhea, leukeorrhea, gastropathy, bronchitis, chronic diarrhea, dysentery, renal and vesicle calculi, diabetes, conjunctivitis, scleritis, ulcers, and other eye disease. The ripe seeds are used for clearing muddy water. The clarification is due to the combined action of colloids and alkaloids in the seeds[5] Hence in view of immense medicinal importance of the plant this review is therefore an effort to compile all the information reported on its phytochemical and pharmacological activities, this information will be helpful to create interest towards the plant and may be useful in developing new formulations, which are more effective and have more therapeutic values.

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TAXONOMIC CLASSIFICATION

- Kingdom: Plantae
- Class: Angiosperms
- Subclass: Eudicots
- Superorder: Asterids
- Order: Gentianales

- Family: Loganiaceae
- Genus: Strychnos.

PLANT PROFILE

- Common vernacular name[5,6]
- Clearing nut tree: English.

- Ambuprasadanaphala, Ambuprasadani, Chakshushya, Chh edaniya, Guchhaphala, Kata, Kataka, Katakarenu, Kattha, Khataka, Lekhanatmaka, Payaprasadi, Ruchishya, Ruchya, Rushya, Shlakshna, Shodanatmaka, Tiktamaricha, Tiktaphala, Toyaprasadana: Sanskrit
- Neimal, Nelmal, Nirmali: Hindi
- Chilbing, Chilhara, Gajara, Nirwali: Marathi
- Nirmali: Bengal
- Katakam, Tetta, Tettamparap, Titramparala: Malayalam
- Niemali: Punjabi
- Akkolam, Ilalam, Kadali, Sillam, Tatta, Tettankottai, Teru: Tamil
- Nirmali: Urdu

MORPHOLOGICAL CHARACTERS

Strychnos potatorum is a medium-sized, glabrous tree of height 1213 m. Stem is fluted and covered with black, thick, square to rectangular scales. Bark is 1.32 cm thick, black or brownish-black, corky, with very deep and narrow vertical, thin ridges, which easily break off. Branches are swollen at nodes. Leaves are about 57.5 cm long, nearly sessile, subcoriaceous, ovate or elliptic, acute, glabrous and shining, spuriously three or five nerved, with lateral nerves springing from the lower part of the mid rib, nearly reaching the tip. The base rounded or acute, petioles 2.5 mm long flowers large for the genus, in short almost glabrous nearly sessile axillary cymes; peduncles 0.5 mm long; and pedicels very short. Caly ×2 mm long, fivelobed; lobes 2.5 mm long, oblong, acute with a tuft of hair inside towards the base of each lobe. Ovary ovoid, glabrous, tapering into a long glabrous style; and stigma obscurely twolobed. Fruit is a berry, black when ripe, globose, 12 cm in diameter, whitish, shining, with short addressed yellow silky hairs. Seeds are globose in shape. Population of nirmali is depleting fast due to self nongenerative mechanism in fruits. They are often decayed and are prone to fungal attack as soon as they fall. Flowering occurs in September-October, while fruiting occurs in December [Figures 1 and 2].[5-9]

PHYTOCHEMICAL INVESTIGATION

Phytochemical studies revealed the presence of diaboline (major alkaloid) and its acetate[10] brucine, loganin, mannose, sucrose, arachidonic, lignoceric, linoleic, oleic, palmitic, and stearic acids.[11] On saponification of the oil: β-sitosterol, stigmasterol (also in leaves and bark along with campesterol); oleanolic acid and its 3β acetate, saponins containing acid oleanic, galactose and mannose (seeds) and triterpenes and sterols mannogalactans[12]

The curative properties of medicinal plants are perhaps due to the presence of various secondary metabolites such as alkaloids, flavonoids, glycosides, phenols, saponins, sterols etc., The successive extracts of root, stem bark, and seeds of *Strychnos potatorum* have revealed the presence of alkaloids, flavonoids, glycosides, lignins, phenols, saponins, sterols, and tannins. The lignan glycosides vanprukoside, strychnoside, and glucopyranoside isolated from *Strychnos vanprukii* have shown significant antioxidant property. Among the five groups of phytochemicals determined from the root, stem bark, and seeds of *Strychnos potatorum* tannins were found to be the most abundant one followed by saponins and alkaloids. While phenols and flavonoids were low in concentration 20 quenching and fluorescing alkaloids were reported from the various parts of the plant. However, more number of alkaloids were found in the root and stem bark.[13] The interconversion of these compounds into other derivatives owing to the prolonged period of storage and method of processing in case of the market seed. The most abundant alkaloid diaboline is found in all samples of *Strychnos potatorum* and identified by matching with authentic sample.

Figure 1: Lorius - The biodiversity conservation society

Figure 2: Prelude medicinal plants database

Alkaloids are the lead molecules of therapeutic importance from Strychnos species[14] These are heterocyclic indole compounds which have proved to be having pharmacological properties such as hypotensive activity, anticonvulsant activity, antiprotozoal, antimicrobial and antimalarial activities.

Three flavonoid were reported in the root. Collected and market seed samples show different color and Rf values. Whilein the stem bark four alkaloid were observed. Flavonoids are the phenolic substances and are the largest group of phenols. These generally occur as a C6-C3 unit linked to an aromatic ring. Three glycosides with similar color and Rf values were observed both in the root and stem bark whereas, four glycosides were observed in both seed samples.

The highest numbers of phenols were reported in the market seed. However, five phenolic with similar color and Rf values (6.67, 16.67, 44.0, 58.67, and 90.0) were found both in root and stem bark. Further, it is observed that five alkaloids were found to be common for root, stem bark, and collected seed. Plants have the limitless ability to synthesize phenols or their derivatives. The presence of phenols in all types of tissues is a characteristic feature of plants. The data of saponins of *Strychnos potatorum* by thin layer chromatography has revealed the presence of five yellow to intense yellow colored saponins in all parts of the plant. Saponins are glycosides of both triterpenes and sterols generally possessing five sugar units and gluconic unit as a component. The occurrence of saponins has been reported in over 70 families of higher plants.[14] The data of sterols of *Strychnos potatorum* by thin layer chromatography has revealed the presence of four sterols in the stem bark and seeds. While three sterols; which may be isomotiol, sitosterol, stigmasterol, or compesterol were found in the root. The high performance liquid chromatogram (HPLC) has shown 61 peaks. However, 18 peaks were prominent with significant percent area and height (>0.5%). The most abundant peak, which is probably diaboline, the prominent alkaloid of this plant as reported earlier. The total alkaloid fraction isolated from the seeds of *Strychnos potatorum* when administered in mice and rats at the doses of 70-100 mg/kg, intraperitoneally (i.p.) produced restlessness, irritability and tremorsfollowed by convulsions of tonic type all over the body and hypotensive action.[15,16] The methanolic extract of the dried seeds was found to have diuretic and antidiarrheal activities. The seed powder (SPP) was found to possess antidiabetic activity. Mannogalactans isolated from the seeds of *Strychnos potatorum* showed antihypercholesterolemic activity in experimental rats.[17]

Traditional uses

According to Ayurvedaseeds are acridalexipharmiclithotriptic and cures strangury, urinary discharges, head diseases etc., Roots cureleukeoderma whereas fruits are useful in eye diseases, thirst, poisoning, and hallucinations. The fruits are emetic, diaphoretic, alexiteric, etc., According to Unani system of medicine, seeds are bitter, astringent to bowels, aphrodisiac, tonic, diuretic and good for liver, kidney complaints, gonorrhea, colic, etc.

- Powdered stem bark mixed with lime juice given in cholera
- Leaves: As poultice over maggot infected ulcers
- Seed: Tonic stomachic demulcentemetic and used in acute diarrhea, diabetes, gonorrhoea, and eye diseases like conjunctivitis, lachrymation, or copious watery of eyes. The paste of seed is reported to be consumed internally along with little tender coconut milk in urinary disorder and retention of urine.[17]

Toxicological studies

The acute and chronic toxicity studies of aqueous extract (SPE) and of *Strychnos potatorum* Linn. were carried out on Wistar albino mice and rats. Both extracts did not produce any signs of toxicity and mortality up to the dose level of 2000mg/kg body weight orally in mice. The drug is categorized as unclassified. In chronic toxicity studies, both SPE and SPP at the dose of 100-200 mg/kg did not produce any significant changes in body weight from day 0 to 90 when compared with control group. Various parameters are taken into consideration like Red blood corpuscles white blood corpuscles hemoglobin erythrocyte sedimentation ratebiochemical parameters like blood glucose, urea, and serum creatinineenzyme parameters like alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and acid phosphatasewere studied.[18]

PHARMACOLOGICAL INVESTIGATION

Although many pharmacological studies have been performed on the basis of chemical constituents present, a lot more are still to be exploited, explored, and utilized. Important pharmacological findings are summarized below:

Anti-diabetic activity

Strychnos potatorum has antidiabetic activity. In Wistar albino rat, the diabetic state was induced by intraperitonial injection of alloxan at a dose of 100 mg/kg of body weight. Animals were grouped into normal rat (control), diabetic rat (alloxan), diabetic but extract treated rat, only extract treated rat, and diabetic but standard antidiabetic drug tolbutamide treated rat groups. Animals were screened for the parameters such as body weight, blood glucose level, total proteins, and cholesterol and enzyme levels such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) for deducing the antidiabetic activity of the test plant. The alloxan treated rat shows reduced body (26%) and liver (40%) weight. The blood glucose level falls by 53% with extract treatment, demonstrating the antidiabetic potential of the plant. The serum enzymes AST and ALT were increased from 24 and 18 IU/1 to 60 and 65 IU/1 respectively whereasALP was decreased to 5 IU/1 from 14 IU/1. The total serum protein level also increased up to 5 mg/ml in the extract treated animal. The insulin level also increased up to 61 μg/ml within 30 days of extract treatment compared to control with 51 μg/ml. The plant extract efficiently decreased the initial cholesterol 219 μg/ml level into 170 μg/ml.

In liver, the AST, ALT and ALP enzymes were decreased to 160, 60, and 140 IU/1 from 178, 79, and 156 IU/mlrespectively.[19]

Anti-inflammatory effect

The anti-inflammatory effect of SPP and SPE of *Strychnos potatorum* Linn. Seeds was studied in carrageenin-induced hind paw edema and cotton pellet granuloma models. Both SPP and SPE were found to normalize the increased alkaline, acid phosphatases, and lipid peroxide levels indicating their membrane stabilization and free radical scavenging properties, respectively. Both SPP and SPE exhibited dose dependent anti-inflammatory activity in acute and subacute inflammatory models, and its effect was also comparable with the standard drug diclofenac sodium.[20,21]

Antiulcerogenic potential

The antiulcerogenic potential of *Strychnos potatorum* Linn seeds on aspirin plus pyloric ligation (aspirin PL)-induced gastric ulcer model was studied. The SPP and SPE exhibitantiulcerogenic activity by both antisecretory and mucoprotective actions. The mucoprotective action of SPP and SPE may be due to the presence of polysaccharides in seeds. The antiulcerogenic potential of SPP and SPE was compared with the standard antiulcer drug, ranitidine. The antiulcerogenic potential was confirmed by the histopathological studies of stomach mucosa.[22]

Hepatoprotective and antioxidant activity

The SPP and SPE of *Strychnos potatorum* seeds possess hepatoprotective and antioxidant activities against CCl_4-induced acute hepatic injury. Hepatoprotective action is by reducing the serum marker enzymes like serum glutamate oxaloacetate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT). They also reduced the elevated levels of ALP and serum bilirubin. Reduced enzymic and nonenzymic antioxidant levels and elevated lipid peroxide levels were restored to normal by administration of SPP and SPE. Histopathological studies confirmed the hepatoprotective activity of SPP and SPE when compared with the CCl_4 treated control groups. The standard used for this study was silymarin.[23]

Antiarthritic activity

The effect of the SPE and the whole SPP of *Strychnos potatorum* Linn seeds on the Freund's complete adjuvant (FCA) induced arthritic rat paw edema, body weight changes and alterations in hematological and biochemical parameters in both developing and developed phases of arthritis was investigated in the laboratory on rats. Histopathology of proximal interphalangeal joints and radiology of hind legs were studied. Both SPP and SPE at the specified dose level showed reduction in rat paw edema volume and it could significantly normalize the hematological and biochemical abnormalities in adjuvant induced arthritic rats in both developing and developed phases of FCA induced arthritis. Further the histopathological and radiological studies confirmed the antiarthritic activity of SPP and SPE.[24]

Antinociceptive and antipyretic effect

The antinociceptive and antipyretic effect of SPP and SPE of *Strychnos potatorum* was evaluated in albino mice and rats respectively. The antinociceptive activity was studied in both chemical induced writing and thermal models of inducing nociception. SPP and SPE of *Strychnos potatorum* were found to exhibit antinociceptive activity in both chemical and thermal models indicating their central as well as peripheral mechanism in inhibiting the nociception respectively. Antipyretic activity is dose dependent.[25]

Antidiarrheal activity

The antidiarrheal activity of the methanol extract of the dried seeds of *Strychnos potatorum* (MESP) has been evaluated in rats using different models diarrhea (castor oil-induced), effects on gastrointestinal motility and on prostaglandin (PG) E2-induced gastric enteropooling. It significantly inhibited the frequency of defecation and reduced the wetness of fecal droppings in castor oil-induced diarrhea, decreased the propulsion of charcoal meal through the gastrointestinal tract, and also reduced the PGE2-induced enteropooling.[26]

Diuretic activity

(SPSE) was evaluated for its diuretic activity in Wistar albino rats. The parameters which were taken into account during the experimental on each rat were: Total urine volume (corrected for water intake during the test period), body weight before and after the experiment, and the concentration of sodium, potassium, and chloride ions in urine. The total urine volumes of the SPSE (600 mg/kg)-treated rats were evaluated nearly two and halffold then compared with the control (saline treated) group. Excretion of cations (sodium and potassium ions) and anions (chloride ions) also increased significantly with respect to the control group. The diuretic effect was comparable with that of the standard drug furosemide. The increase of cations in the urine on treatment with *Strychnos potatorum* seed extract (SPSE) was dose-dependent. This effect supports the use of the *Strychnos potatorum* seeds as a diuretic in folk remedies.[27]

Contraceptive efficacy

The 70% methanolic extract of *Strychnos potatorum* seeds shows contraceptive efficacy. The aqueous solution of extract was administered orally to male rats of proven fertility for 60 days. Sperm motility, sperm density, serum testosterone level, biochemical analysis and testicular cell population dynamics were carried out to assess the contraceptive effect of *Strychnos potatorum*. *Strychnos potatorum* seed possesses suppressive effects on male fertility and could be useful in development of male contraceptive agent.[28]

Surface active agents from the seed oil of Strychnos potatorum

The sodium soaps and sulfonated sodium surfactants prepared from the seed oil of *Strychnos potatorum* are found to be better critical micelle concentration (CMC), surface active matter and dispersive powers in comparison to the sodium and sulfonated sodium surfactants prepared from castor oil. *Strychnos potatorum*

detergents also exhibited a good inhibition activity on the growth of *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* that adds to their safe use.[29]

Clarification of turbid water

In developing countries, ground water, which is contaminated with domestic and industrial waste, is commonly used for drinking. Color, turbidity and microbial content affect quality of potable water. The seed of nirmali tree *Strychnos potatorum* Linn. shows coagulation properties in clarifying turbid water. This property was attributed to the presence of anionic polyelectrolytes having -COOH and free -OH surface groups that are present in the seed protein.[30]

Metal binding properties

The metal binding property of these seeds is of recent interest where some bench scale experiments were conducted in order to establish the binding of metal ions from dilute HCl solutions. The seeds collected from the trees of *Strychnos potatorum* Linn. were ground to 0.5 mm size for experimentation purpose. The binding of different transition metals from aqueous solutions by these seeds was studied for Au (I), Ag (I), Cu (I), Cu (II), Co (II), Ni (II), Pb (II), Zn (II), Fe (II) and Fe (III) by shaking 1.0 g of the powdered seed in a 5% v/v HCl solution containing 50.0 and 1.0 ppm of the respective metal ion in a 50 ml solution for 5 min. The filtrate obtained after each experiment was analyzed for the respective metal ions and the results obtained are Au (I) = 40.80 ppm; Ag (I) = 41.10 ppm; Cu (I) = 38.00 ppm; Zn (II) = 41.70 ppm; Fe (II) = 42.10 ppm, and Fe (III) = 38.20 ppm. On an average the seed binds 0.5 mg of the respective metals per 1.0 g of the seed. These seeds were fractionated into three different fractions, namely, fractions A B, and C using solvent extraction, distillation, and centrifuging techniques in order to investigate what fraction of the seed is responsible in metal ion binding, and the weight percentages of each fraction were found to be 655, and 30%, respectively. Fraction A mostly comprises of carbohydrates and some protein, whereas, fraction C is pure protein. Fractions A and C are found to be equally responsible for the binding of metals.[31]

Antimicrobial properties

The alcoholic extracts of *Strychnos potatorum* showed antibacterial activity against pathogenic gram positive, gram negative, and acid-fast bacteria and fungi, *Staphylococcus aureus*, and *Escherichia coli*. These fractions have shown considerable antimicrobial activity against both bacteria and fungi at the tested concentrations (100 and 200 μg/ml). Further, the growth of *Proteus vulgaris*, *Staphylococcus aureus*, *Salmonella typhimurium, Vibrio cholerae, Mycobacterium tuberculosis, Aspergillus niger,* and *Candida albicans* were significantly inhibited.[32]

CONCLUSION

Strychnos potatorum, the versatile medicinal plant is the unique source of various types of compounds having diverse chemical structure. 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 utility to combat diseases. Although crude extracts from various parts of nirmali have medicinal applications from time immemorial, modern drugs can be developed after extensive investigation of its bioactivity, mechanism of action, pharmacotherapeutics, toxicity, and after proper standardization and clinical trials. As the global scenario is now changing towards the use of nontoxic plant products having traditional medicinal use, development of modern drugs from nirmali should be emphasized for the control of various diseases. Quite a significant amount of research has already been carried out during the past few decades in exploring the chemistry of different parts of nirmali. An extensive research and development work should be undertaken on nirmali and its products for their better economic and therapeutic utilization.

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A review on Insulin plant (*Costus igneus* Nak)

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ABSTRACT

Costus igneus Nak and *Costus pictus* D. Don, commonly known as Spiral flag, is a member of Costaceae and a newly introduced plant in India from South and Central America. It is a perennial, upright, spreading plant reaching about two feet tall, with spirally arranged leaves and attractive flowers. In southern India, it usually grows as an ornamental plant and its leaves are used as a dietary supplement in the treatment of diabetes mellitus. Recently, a number of researches have been carried out to evaluate the anti-diabetic potential of this plant. Besides, it has been proven to possess various pharmacological activities like hypolipidemic, diuretic, antioxidant, anti-microbial, anti-cancerous. Further, various phytochemical investigations reveal the presence of carbohydrates, triterpenoids, proteins, alkaloids, tannins, saponins, flavonoids, steroid, and appreciable amounts of trace elements. This work is an attempt to compile and explore the different pharmacological and phytochemical studies reported till date.

Key words: Anti-diabetic activity, *Costus igneus* Nak, *Costus pictus* D. Don, diabetes mellitus, insulin plant

INTRODUCTION

Costus igneus Nak (syn. *Costus pictus* D. Don, *Costus mexicanus* Liebm ex Petersen or *Costus congenitus* Rowle), commonly known as fiery costus, Step ladder or Spiral flag or Insulin plant, is native to South and Central America. This is a recent introduction to India from America as an herbal cure for diabetes and hence commonly called as 'insulin plant.'[1] It is widely grown in gardens as ornamental plant in South India and also run wild in many places.[2] It is used in India to control diabetes, and it is known that diabetic people eat one leaf daily to keep their blood glucose low.[3] Leaves of *C. igneus* were one among the plants known to be effectively used for treating diabetes by the tribal people of Kolli hills of Namakkal district, Tamilnadu.[4] In Mexican folk medicine, the aerial part of *C. pictus* D. Don is used as an infusion in the treatment of renal disorders.[5]

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The plant belongs to the family Costaceae. The Costaceae was first raised to the rank of family by Nakai on the basis of spirally arranged leaves and rhizomes being free from aromatic essential oils. Before the elevation to family status, Engler and Prantl recognized Costoideal as a subfamily under Zingiberaceae. Several anatomical and morphological features support this isolated position including well developed aerial shoot with distinct, rigid, and commonly branched stems. The leaves are inserted in a low spiral with divergences. The family Costaceae consists of four genera and approximately 200 species. The genus Costus is the largest in the family with about 150 species that are mainly tropical in distribution.[2,6] The present review deals with the recent research carried out in the area of phytochemistry, pharmacological, biological activities, and safety of *Costus igneus* Nak.

Taxonomy

Botanical name:[7]	*Costus igneus* N.E.Br
Domain:	Eukaryota
Kingdom:	Plantae
Subkingdom:	Viridaeplantae
Phylum:	Tracheophyta
Subphylum:	Euphyllophytina
Infraphylum:	Radiatopses
Class:	Liliopsida
Subclass:	Commelinidae
Superorder:	Zingiberanae
Order:	Zingiberales
Family:	Costaceae
Subfamily:	Asteroideae
Tribe:	Coreopsideae
Genus:	Costus
Specific epithet:	Igneus

Morphology

It is a perennial, upright, spreading plant reaching about two feet tall, with the tallest stems falling over and lying on the ground. Leaves are simple, alternate, entire, oblong, evergreen, 4-8 inches in length with parallel venation. The large, smooth, dark green leaves of this tropical evergreen have light purple undersides and are spirally arranged around stems, forming attractive, arching clumps arising from underground rootstocks. Beautiful, 1.5-inch diameter, orange flowers are produced in the warm months, appearing on cone-like heads at the tips of branches.[8] Fruits are inconspicuous, not showy, less than 0.5 inch, and green-colored [Figure 1].

Growth and propagation

Spiral flag grows in either full sun or partial shade. It needs fertile soil and ample moisture, and is often planted near water. Propagation is by division of the clumps, cuttings, or by separating the offsets or plantlets that form below the flower heads. Mites and nematodes can be a problem, especially on light, sandy soil. The plant has no diseases are of major concern.[8]

Phytochemical study

Sequential screening for phytochemicals of *C. igneus* leaves revealed that it is rich in protein, iron, and antioxidant components such as ascorbic acid, α-tocopherol, β-carotene, terpinoids, steroids, and flavonoids.[9,10] It was revealed in another study that methanolic extract was found to contain the highest number of phytochemicals such as carbohydrates, triterpenoids, proteins, alkaloids, tannins, saponins, and flavonoids.[11] Preliminary phytochemical evaluation of Insulin plant (*C. pictus*) revealed that the leaves contain 21.2% fibers. Successive extracts gave 5.2% extractives in petroleum ether, 1.06% in cyclohexane, 1.33% in acetone, and 2.95% in ethanol. Analysis of successive extracts showed presence of steroids in all extracts. The ethanol extract contained alkaloid also. The major component of the ether fraction was bis (2'-ethylhexyl)-1,2-benzenedicarboxylate (59.04%) apart from α-tocopherol and a steroid, ergastanol.[12] Stem showed the presence of a terpenoid compound lupeol and a steroid compound stigmasterol.[13] Bioactive compounds quercetin and diosgenin, a steroidal sapogenin, were isolated from *C. igneus* rhizome.[14] Trace elemental analysis showed that the leaves and rhizomes of *C. pictus* contains appreciable amounts of the elements K, Ca, Cr, Mn, Cu, and Zn.[15] Steam distillation of stems, leaves, and rhizomes of *C. pictus* D. Don yielded clear and yellowish essential oils. The major constituents identified[1] in the essential oil are enlisted in Table 1.

Major pharmacological activities

Anti-diabetic activity

Of late, a lot of research work has been conducted to evaluate the anti-diabetic effect of insulin plant.[3,11,14-30] The summary of the animal experimentations done are tabulated [Table 2]. In a cross- sectional clinical study, patients consuming either one fresh leaf or 1 teaspoon of shade-dried powder/day of *C. igneus* in conjunction with other modalities of treatment had effectively produced glycemic control in diabetics.[31]

However, an *in vitro* study of ethanolic extract of *C. pictus* leaf was analyzed to study GLUT4 translocation and glucose uptake activity, which showed no direct peripheral action at 300 μg/ml dose comparable with insulin and metformin.[32] A study evaluated the ability of a tea made from the leaves of *C. spicatus* to alter glucose homeostasis in C57BLKS/J (KS) *db/db* mice, a model of obesity-induced hyperglycemia, with progressive beta-cell depletion. Intraperitoneal (IP) insulin tolerance testing after the 10-week study period showed that *C. spicatus* tea consumption did not alter insulin sensitivity, which suggested that at the dose given, tea made from *C. spicatus* leaves had no efficacy in the treatment of obesity-induced hyperglycemia.[33]

Toxicity study

Acute toxicity studies were studied with different doses of aqueous extract of *C. pictus* from 5, 10, 20, and 40 g/kg body weight. None of the doses of this extract produced mortality or any behavioral disorders.[5] Acute toxicity studies revealed that the administration of aqueous extract 1 g/kg b.w/day for 30 days produced no effect on the general behavior and all the animals survived the test period.[30] Administration of ethanolic

Figure 1: Insulin plant

Table 1: Major constituents of essential oil

Stem oil (%)	Leaf oil (%)	Rhizome oil (%)
Hexadecanoic acid (28.3)	Hexadecanoic acid (24.51)	Hexadecanoic acid (25.26)
9,12-octadecadienoic acid (18.33)	2-pentanol (22.48)	9,12-octadecadienoic acid (7.74)
Dodecanoic acid (5.62)	Dodecanoic acid (3.96)	Dodecanoic acid (16.56)
Linalyl propanoate (6.03)	ß-ionone (8.69)	Tetradecanoic acid (10.20)
Tetradecanoic acid (4.82)	Farnesyl acetone (7.04)	Linalool (8.48)
A-eudesmol (3.55)	A- ionone (8.01)	α-terpineol (4.44)
γ-eudesmol (3.21)		
4-ethoxy phenol (3.06)		

Table 2: Studies carried out to evaluate anti-diabetic effect

Author, year	Model	Part/extract used	Results
S P Dhanabal, 2007	Normoglycemic rats and Hyperglycemic rats	200, 400 mg/kg b.w of ethanolic leaf extract	Both the doses did not significantly reduce the blood glucose levels in Normoglycemic rats. 400 mg/kg b.w of extract led to significant blood glucose-lowering effect in hyperglycemia rats
Nandhakumar Jothivel, 2007	Alloxan induced in Male Wistar Albino rats	120 mg/kg b.w of methanolic leaf extract, p.o, single dose/day for 21 days	The methanolic extract significantly decreased serum glucose level and increase in liver glycogen, which shows its anti-diabetic effect. It also showed increase in plasma insulin level and improvement in lipid profile (cholesterol, triglyceride, HDL, LDL, VLDL, and phosopholipids), which indicates it is useful in hyperlipidemia consequent upon diabetes mellitus
Gireesh 2007	STZ induced in Male Albino Wistar rats	250 mg/kg b.w of crude aqueous extract, orally for 14 days	*C. pictus* leaf extract significantly reduced the blood glucose to near the control in diabetic rats. *In vitro* studies showed *C. pictus* leaf extract induced glucose-stimulated insulin secretion in pancreatic islets. *C. pictus* extracts have a regulatory role in the secretion and glucose homeostasis through muscarinic receptors.
M A Jayasri, S Gunasekaran, 2008	STZ induced in Albino Wistar rats	2 gm/kg b.w of aqueous solution, orally for 28 days	It was evident that the aqueous solution of *C. pictus* leaves was effective in maintaining the blood glucose levels in normal and STZ-induced diabetic rats. Morphometric analysis of *C. pictus*-treated rat pancreatic islets showed a significant increase in the number and area of islets.
V Devi, Asna Urooj, 2008	STZ induced in Male Albino Wistar rats	500 mg/kg b.w of crude leaf powder, orally for 15 days	Preliminary data of this study indicates that leaf powder is effective in lowering blood glucose
Gireesh G, Santhosh K, 2009	STZ induced in Male Albino Wistar rats	250 mg/kg b.w of crude aqueous extract, orally for 14 days	It significantly increased the plasma insulin level to near control in diabetic rats. *In vitro* insulin secretion study using rat islet culture revealed that aqueous extract of *C. pictus* enhanced insulin secretion.
P P Sethumathui, J Nandakumar, 2009	Alloxan induced in Male albino Wistar rats	120 mg/kg and 180 mg/kg b.w of methanolic leaf extract, p.o, single dose/ day for 21 days	Extract at both doses produced significant reduction in blood glucose and lipid peroxidation (LPO)
Bhat Vishnu, Asuti Naveen, 2010	Alloxan induced in Male albino Wistar rats	500 mg ethanolic leaf extract, orally for 7 days	The extract significantly decreased glucose level in diabetic rats
Pangal Mani, 2010	Alloxan induced in Male Albino Wistar rats	50, 100, 200 mg/kg b.w of methanolic and aqueous leaf extract, intra peritoneally for 30 days	Among these extracts, methanolic extract at 200 mg/kg b.w was found to be almost significant as the standard drug (Glibenclamide-0.5 mg/kg) in lowering blood glucose level when compared to aqueous extracts
Altaf Al- Romaiyan, 2010	*In vitro* study in Mouse and Human Islets of Langerhans	Methanolic leaf extract	*In vitro* observations suggest that one mode of action of *C. pictus* is through stimulating insulin secretion, which may be mediated, in part, by the ability of the plant extract to increase [Ca^{2+}] levels through voltage-gated Ca^{2+}channel (VGCC)
Akhila J Shetty, 2010	Dexamethasone in Male Albino Wistar rats	100, 250, 500 mg/kg b.w leaf powder, orally for 7 days	250, 500 mg/kg leaf powder reduced the fasting and post-prandial blood sugar levels, bringing them to normal.
V Devi, Asna Urooj, 2011	STZ induced in Male Albino Wistar rats	500 mg/kg b.w of leaf powder for 45 days	Supplementation of *C. pictus* powder resulted in a consistent and gradual decrease in blood glucose levels
Kripa Krishnan, 2011	STZ induced in Male Albino Sprague- Dawley	100 mg/kg b.w of aqueous, methanolic, and ethanolic leaf extract, orally for 30 days	Of the three extracts, methanolic extract at 100 mg/kg b.w showed optimum benefits by eliciting pronounced hypoglycemia and antioxidant activities
Pazhanichamy Kalailingam, 2011	STZ induced in Albino Wistar rats	100, 200 mg/kg b.w of ethanol rhizome extract, orally for 30 days	Study showed that the extracts significantly reduced blood glucose levels in diabetic rats and also reversed levels of carbohydrate metabolic, hepatoproductive, and antioxidant enzymes
Stabitha T Issac, 2011	STZ induced in Male albino rats	500 mg/kg b.w of aqueous leaf extract of *C. pictus* and *C. pictus*, orally for 15 days	Both are highly effective in lowering the blood glucose levels; however, hypoglycemic activity of *C. pictus* was found to be higher than *C. pictus*
Pazhanichamy Kalailingam,	STZ induced in Albino Wistar	100, 200 mg/kg b.w of methanolic rhizome	Results showed that fasting blood glucose, lipid profile levels were significantly decreased, and hence *C. igneus*

Contd..

Table 2: contd...

Author, year	Model	Part/extract used	Results
2011	rats	extract, orally for 30 days	rhizome showed potent anti-diabetic and hypolipidemic effect
S Suganya, 2012	Alloxan induced in Female Albino Wistar rats	200 mg/kg b.w of aqueous extract, orally for 30 days	Significantly reduced the levels of blood glucose, lipid profile, lipid peroxidation, liver marker enzymes, liver marker enzymes, urea, creatinine and increased the antioxidant enzymes
M V Kumudhavalli, 2012	STZ induced in Male Albino Wistar rats	250, 500 mg/kg b.w each of aqueous and ethanolic leaf extract, orally for 15 days	500 mg/kg b.w of both aqueous and ethanolic extracts showed significant reduction in blood glucose level and lipid profile. However, anti-diabetic activity of 500 mg/kg b.w of ethanolic extract was more significant than the aqueous extract
R Remya, M Daniel, 2012	Alloxan induced in Male Sprague Dawley rats	200, 400 mg/kg b.w of fresh leaf extract, orally for 60 days	Results show significant decrease in blood glucose level and lipid profiles

extract of *C. igneus* leaves from 50 mg/kg b.w up to the dose of 5000 mg/kg b.w did not show significant toxicity signs during the first four hours and followed by daily observations for 14 days, and no mortality was also observed; the drug was found to be safe at the tested dose level of 5000 mg/kg b.wt.[20] However, in a study carried out on the methanolic extract of *C. igneus*, findings indicated toxicity at 250 mg/kg body weight.[25] Further, in another investigation, palmitic acid was found to be the major component in the stem, leaf, and rhizome oils of *C. pictus*. Palmitic acid is found to induce degeneration of myofibrils in healthy adult rat cardiomyocytes, enhance LDL to HDL cholesterol ratio, and it was found to be the important precursor for the development of coronary heart diseases. So, the constant use of *C. pictus* leaves for diabetic treatment may cause serious cardiac diseases, and it is not recommended for the treatment.[1]

Hypolipidemic activity

A study was carried out to comparatively evaluate the methanolic and aqueous extracts of *C. igneus* in diabetes-induced hyperlipidemia in rats. The study revealed that methanolic and aqueous extracts at a dose of 200 mg/kg body weight reversed the diabetes-induced hyperlipidemia.[21] Alcoholic extract of *C. igneus* at the dose of 400 mg/kg (p.o) had significantly decreased the levels of serum cholesterol, triglycerides, LDL in Triton-induced hyperlipidemic rats.[34]

Diuretic effect

A study was carried out to measure the diuretic effect of an aqueous extract of *C. pictus* D. Don at doses of 100 and 200 mg/kg body weight and to compare it with the one induced by furosemide at 4 mg/kg. The results revealed that *C. pictus* induced a natriuretic effect similar to furosemide. The aqueous extract induced an increment in sodium and potassium clearance similar to the one obtained with furosemide, suggesting that it represents significant diuresis.[5]

Antioxidant activity

An *in vitro* study of alcoholic extract of leaves of *C. mexicanus* showed moderate antioxidant activity.[16] The antioxidant activities of leaves and rhizomes in methanol, aqueous, ethanol, and ethyl acetate extracts were assessed using different models like DPPH, β-carotene, Deoxyribose, superoxide anion, reducing power, and metal chelating assay at different concentrations. Leaves and rhizomes of *C. pictus* showed good antioxidant activity of about 89.5% and 90.0% when compared with standard BHT (Butylated Hydroxy Toulene) (85%) at a concentration of 400 μg/ml. Results obtained revealed that methanolic extracts of both leaves and rhizomes of *C. pictus* possess higher antioxidant activity when compared with other extracts.[35] In another study, methanolic leaf extract of *C. pictus* D. Don caused significant increase in superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, vitamin A, vitamin C, vitamin E and reduced glutathione, and thus, could be effective in reducing oxidative stress and free radical-mediated diseases. The antioxidant property of this plant may be due to the presence of phenolic substances.[19] Methanolic extracts of flower and stem of *C. pictus* possess *in vitro* antioxidant activity against oxidative protein damage.[36] Among the extracts tested for, chloroform extract of *C. pictus* D. Don bark possessed high antioxidant activity.[37] Oral administration of ethanolic extract of *C. igneus* rhizome at 200 mg/kg body weight to diabetic rats for 30 days induced a significant antioxidant effect. The bioactive compound quercetin and diosgenin present in the plant exhibited antioxidant activity, which was sufficient to reverse oxidative stress in liver, pancreas, and kidney of diabetic rats as well as to stimulate glycolytic enzymes and control gluconeogenesis in diabetic animals.[14]

Ameliorative effect

A study was conducted to evaluate the ameliorative effect of ethanolic extract (50 mg/kg b.wt, orally) of rhizome on mitochondrial enzymes in alcohol-induced free radical toxicity in male albino rats. After 21 days of treatment, mitochondrial enzymes were restored to normal levels, which showed that *C. pictus* improved mitochondrial activities during alcohol-induced free radical stress.[38]

Anti-microbial activity

Methanolic extract of *C. igneus* showed maximum anti-bacterial activity against g*ram-positive Bacillus cerus, Bacillus megaterium, Micrococcus leuteus, Staphylococcusn aureus, Streptococcus lactis*, and

gram-negative strains *Pseudomonas aeruginosa*, *Escherichia coli*, *Enterobacter aerogenes, Klebsiella pneumoniae,* and *Salmonella typhimurium*.[39] The isolated compound from the ethanolic extract of *Costus igneus* showed moderate anti-bacterial and anti-fungal activity against *Staphylococcus aureus, Eschericia coli, and Candida albicans*.[40] Among the extracts of various parts of *C. pictus*, methanolic extracts of stem and flower exhibited maximum inhibitory activity on the growth of tested microbes, *viz*., *Shigella flexneri, Klebsiella pneumonia*, *Bacillus subtilis*, *Escherichia coli* at the concentration of 150 μg/ml.[36]

Anti-cancer effect

The ethanolic extract of leaves of *C. pictus* was found to have anti-proliferative and anti-cancer potential in *in-vitro* mammalian fibrosarcoma (HT-1080) cells.[41] All the extracts of bark had potent anti-cancer properties against HT 29 and A549 cells.[37]

Putative activity

Aqueous extract of *Costus* stem and isolated compounds lupeol, and stigmasterol had an inhibitory effect on calcium oxalate urolithiasis, and its putative activity was confirmed by the promotion of formation of calcium oxalate dehydrate (COD) crystals and may possibly treat urinary stones by inhibiting the formation of calcium oxalate monohydrate (COM) crystals.[13]

CONCLUSION

This review supports the therapeutic potential of the leaves in diabetes. However, these results have to be further evaluated and revalidated by clinical trials. The anti-diabetic effect of its leaves is currently been tested in diabetic patients. Studies reveal its role in various diseases, which opens up new clinical research areas. Furthermore, it paves new avenues to explore the compounds responsible for these therapeutic effects, and study the mechanism of its action.

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