International Journal of Research in Pharmacy and Pharmaceutical Sciences
www.pharmacyjournal.in
ISSN: 2455-698X
Received: 13-05-2021, Accepted: 28-05-2021, Published: 12-06-2021
Volume 6, Issue 3, 2021, Page No. 13-17

Morphological, phytochemical and pharmacological study of *Helicteres isora* (Marorphali)

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Abstract
Medicinal plants are worth to nature. The bioactive compounds present in medicinal plants have various pharmaceutical importance. *Helicteres isora* commonly known as the Indian screw tree (Marorphali), has been reviewed for its phytochemical and pharmacological significance. The fruit, leaf, bark, root, and seed mainly contains carbohydrates, saponin, tannin, proteins, steroids, anthraquinon glycosides, cardiac glycosides, phenolic compounds, terpenoides, alkaloid salts, free alkaloids, flavonoid glucuronides, α-tocopherol, reduced glutathione, and sapogenin. The plant has therapeutical importance and mainly shows antidiabetic, antioxidant, anticancer, antinociceptive, antimicrobial, antispasmodic, anti-inflammatory activities. The plant has been used in the traditional system of medicine to treat stomach-related disorders like stomachache, diarrhea, wormicide, and snakebite.

Keywords: *Helicteres isora*, phytochemical, pharmacological, traditional medicine

Introduction
The plants containing health-related constituents have been used by human civilization since prehistoric times. Human knowledge of medicinal plants dates back 5000-3000 BC, written by Sumerians on clay tablets [1]. Presently, 88% of WHO member countries rely on herbal plants as traditional and complementary medicines [2]. The medicinal plants have been studied for their bioactive compounds for a long time [3-6]. The introduction of modern techniques like multivariate analysis software enables to test of the quality and suitability of plant compounds for clinical trials [7]. Earlier various medicinal plants have been evaluated for their phytochemical and pharmacological investigation [8-12]. The present comprehensive review is mainly based on plant profile, phytochemical analysis, and pharmacological investigation of *Helicteres isora*

Plant profile
Helicteres isora L., local name “Marorphali”, sanskrit name “Avartani”, english name “Indian screw tree”, is a small tree or large shrub belonging to the family Malvaceae. The plant mainly prefers deciduous vegetation [13] dry grasslands on slopes; and generally found below 100-600 m [14]. In India, the plant is mainly used to treat stomachache, rickets dysentery, pain, sores, and carbuncles [15]. India is a major exporter of the fruits and exports to 19 countries, leading being Indonesia, where the fruit extracts are mainly used in the cosmetic industry and to prepare "Tolak Angin", the most popular commercial "jamu" herbal medicines [16].
The plant is large shrubs or small trees 5-8 m in height. The leaves are obovate or suborbicular, with cordate base, irregular margin, and are crenate or serrate, the apex is acute. The leaf contains 3-5-nerves at the base and is scabrous above and the lower portion is stellately tomentose. Leaf petioles are 1.2 cm long. The bark is pale greyish and finely wrinkled having young stellate-tomentose shoots. Flowers are axillary, solitary, or in cymes; containing 2-3 mm long bracts which are linear containing two brown glands in the axil. The pedicel is 6 mm long. Flower calyx is slightly yellow, tubular, and persistent, with 5 irregular lobes. The tube is 1.5-2 cm long and is dense, stellate, and hairy. Petals are unequal and 5 in numbers, 2-2.5 cm long, clawed, obovate, Crimson to pale blue in colour. The staminal column is 3-3.5 cm long and cylindrical, stamens are 10 in number with 5 staminodes. The ovaries are 2-2.5 mm long and present at the tip of the gynophore, pentalobed and 5-celled. The ovules are many with 5 styles and subulate stigma subulate. The follicles are 4-6 cm long and 5 in number and are spirally twisted, stellate-tomentose, and beaked. The seeds are 2-3 mm long, black in colour, angular and wrinkled.

Fig1: *Helicteres isora*-flowers and fruit

Phytochemical composition
The phytochemical studies of the plant are an important step to identify the bioactive compounds present in the medicinal plants. These compounds have various use in medicinal industries to prepare novel drugs [17]. Phytochemical screening of crude extract and chloroform extract of the plant shows the presence of carbohydrates, saponin tannin, proteins, steroids, anthraquinon glycosides, cardiac glycosides, phenolic compounds, terpenoides, alkaloid salts, and free alkaloids [18, 19]. The subcritical extract of the plant (prepared at 10 bar pressure, 160oc, 1:30 sample-to-solvent ratio, and 30 minutes) shows the presence of Octadecnoic

acid, hexadecanoic acid, and berberine [20]. The plant extract also shows presence of two cytotoxic components Cucurbitacin B and isocucurbitacin B [21]. The phytochemicals analysis of fruit shows the presence of alkaloids, tannins, saponins, flavonoids, glycosides, cardiac glycosides, and anthraquinones [22]. The fruit contains high amounts of polyphenols, ascorbic acid, carotenoids, and a high amount of phosphorus in form of nutrients [23]. The spectroscopic analysis of the fruit revealed the presence of four compounds rosmarinic acid(1) and three new compounds 4, 4'-O-di-β-D-glucopyranosyl rosmarinic acid (2), 4'-O-β-D-glucopyranosyl rosmarinic acid (3), and 4'-O-β-D-glucopyranosyl isorinic acid (4) [24]. Besides, the fruit also contains2-ethoxyphenethylamine, 2-hydroxy-5-methylbenzaldehyde, and 4-dihydroxy methyl ester Beneneпropanic acid [25]. The spectroscopic and hydrolysis analysis yielded five flavonoid glucuronides compounds from the fruits of the plant mainly isoscutellarein 4'-methyl ether 8-O-beta-D-glucuronide 2", 4"-disulfate, isoscutellarein 4'-methyl ether 8-O-beta-D-glucuronide 6"-n-butyl ester, and isoscutellarein 8-O-beta-D-glucuronide 2",4"-disulfate [26]. In silico docking of the fruits using Autodock 4 software produced 4 compounds, among these 3 compounds HS-1, HS-2 and HS-4 exhibited anti-diabetic activity against type-2 diabetes mellitus in AMP kinase cascade system [27]. The plant bark contains high amounts of tannins, flavonoids, α-tocopherol, and reduced glutathione. The bark contains a high quantity of nutrients like total carbohydrates, calcium, and iron [23]. The phytochemical screening of the roots shows the presence of carbohydrates, alkaloids, proteins, amino acids, cardiac glycosides, terpenoids, flavonoids, steroids, saponin, and tannins. The pharmacognostic analysis exhibited moisture content (0.18%), acid insoluble ash (1%), total ash (4%), and water-soluble ash (1.5%) in roots [28]. In-vitro raising of plants from the mature seeds using MS + 13.32 µM BAP + 2.32 µM Kin and Agrobacterium rhizogenes strain ATCC-15834 induced hairy root formation, yielded quality diosgenin, a bioactive steroidal sapogenin from the roots which was confirmed by PCR techniques [29]. A study reported that in-vitro culture cells are the most suitable candidates for producing a higher amount of diosgenin, compared to plant parts [30]. According to another report the PCR analysis of suspension culture treated with biotic elicitors E. coli yielded quality diosgenin with increased volume by inducing the expression levels of regulatory genes the cycloartenol synthase (CAS) and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) in diosgenin biosynthetic pathway [31].

Pharmacological Activity

Helicteres isora Linn. as a medicinal plant mainly used in folk medicine in treating diarrhea, constipation of newborn babies, and snakebite. The plant possesses hypolipidaemic, antioxidant, antibacterial, cardiac antioxidant, brain-antioxidation potency, antiperoxidative potency, hepatoprotective, antinociceptive, anticancer, anti-diarrheal, wormicidal, and antiplasmid activities [32].

Antidiabetic activities

The ethanolic root extract shows a significant reduction in plasma glucose, triglyceride and insulin levels in diabetic and insulin-resistant mice. In normal glycemic, mild hypertriglyceridemic, and high fat-fed conditions also the extract shows a remarkable reduction in plasma triglyceride, insulin, and plasma lipid levels, and thus can be effectively used in treating type-2 diabetes [33]. The butanol root extracts at a dose of 250 mg/kg exhibit remarkable antihyperglycemic activity when administered orally to glucose-loaded rats and found comparable to standard drug glibenclamide [34]. The butanol root extracts are also a good antidiabetic agent and its oral administration for 10 days helps in the restoration of degenerative changes in kidney glomeruli, pancreatic islets, and liver to their normal size in alloxan-induced diabetic rats [35]. The aqueous bark extract shows hypoglycaemic activity significantly reducing the blood glucose levels in normal, and in 21 days daily oral administration in streptozotocin (STZ)-induced diabetic rats [36]. It was also observed that the extract tested for hepatoprotective activity as oral administration to streptozotocin-induced diabetic rats, resulted in a significant increase in hepatic hexokinase activity, body weight, and remarkable decrease in serum acid phosphatase (ACP), hepatic glucose-6-phosphatase, lactate dehydrogenase (LDH), and alkaline phosphatase (ALP) [37]. The oral administration of aqueous bark extract at 200 mg/kgb.w. Dose for 21 days resulted in a significant reduction in serum, tissue cholesterol, triglycerides free fatty acids, phospholipids, and high-density lipoprotein (HDL) whereas a remarkable increase in low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) in streptozotocin (STZ)-induced diabetic rats [38]. The oral administration of aqueous bark extract for 30 days significantly increases the levels of glucose, hydroperoxide, TBARS, glycosylated hemoglobin, and vitamin E whereas it remarkably decreases the level of hemoglobin, insulin, antioxidants, membrane-bound total ATPase, Ca(2+)-ATPase, Na(+)/K(+)-ATPase, and Mg(2+)-ATPase in streptozotocin (STZ) induced diabetic rat models [39]. The aqueous bark extract significantly increases palmitic acid, stearic acid, and oleic acid in the liver, kidney, and brain, and remarkably decreases linolenic acid and arachidonic acid in streptozotocin (STZ) induced diabetic rats. The oral administration of the extract for 30 days increases linolenic and arachidonic acid and decreases fatty acids, like stearic, palmitic, and oleic acid [40]. It was also reported that the administration of bark extracts for 30 days shows a significant decrease in plasma glucose levels and increase in liver and kidney weight, renal glycogen content, and reduction in hepatic and skeletal muscle glycogen content in streptozotocin (STZ) induced diabetes rat model and found comparable with standard hypoglycemic drug Tolbutamide [41]. The hot water fruit extract helps in the elevation and upregulation of glucose uptake in mouse skeletal muscle cells (L-6 cells) and is a good antidiabetic agent comparable with insulin and metformin [42]. It was reported that the ethanol and the crude fruit extract helps in restoring the lipid levels to normal in Streptozotocin-induced diabetic rats and shows similar action like standard drug glibenclamide [43].

The methanol extract of the plant, saponins, and pioglitazone after treatment for 14 days shows a significant decrease in the serum lipid and glucose levels and a remarkable increase in the expression of adipsin, glucose transporter 4 (Glut4), and peroxisome proliferator-activated receptor gamma (PPARgamma), and reduction in expression of fatty acid binding protein 4 (FABP4) and glucose-6-phosphatase (G6Pase), without any effect on expression levels of acyl-co-enzyme A oxidase (ACOX),

phosphoenolpyruvate carboxykinase (PEPCK), glucose transporter 2 (Glut2), lipoprotein lipase (LPL), peroxisome proliferator-activated receptor alpha (PPARalpha), angiopoietin-like 3 (ANGPTL3), angiopoietin-like 4 (ANGPTL4), and adiponectin in mice model. Thus saponins present in the plants help in improving hyperlipidemia and hyperglycemia potential in diabetic mice increasing the gene expression of Glut4, adipsin, and PPARgamma and decreasing gene expression of the enzyme G6Pase and G6Pase [44]. Another study suggests that the incubation of saponins and sapogenin helps in inducing the phosphorylation of the phosphatidylinositol-3-kinase (PI3K), protein kinase B/Akt, and glycogen synthase kinase GSK-3 alpha/beta and also increases the abundance of protein in insulin-sensitive glucose transporter Glut4 in C2C12 mouse skeletal muscle cells [45].

Antioxidant activities

Various researchers have identified the anti-oxidant potential of the plant. The plant is an important scavenging agent effective against 1, 1-diphenyl-2-picrylhydrazyl (DPPH), hydroxyl (OH), and superoxide radical (SOR) [46, 47]. A Compound named 4, 4'-O-di-β-D-glucopyranosyl rosmarinic acid obtained from the fruits shows significant scavenging activity against superoxide anion produced with xanthine and xanthine oxidase (XOD) [24]. The phenolic extract of the fruit shows dose-dependent hydroxyl radical scavenging, DPPH radical scavenging, and peroxidation inhibiting activity [48]. The ethanolic fruit extract also exhibits remarkable antioxidant DPPH radical-scavenging activity and Ferric reducing antioxidant power (FRAP) and was found comparable with standard Trolox [49]. The ethanolic leaf extracts possess a significant DPPH and nitric oxide (NO) radical-scavenging activity and also exhibit remarkable reducing power [50]. The subcritical water extract of the plant prepared at 160°C, 10 bar pressure, 30 min time, with 1: 30 sample-to-solvent ratio, also shows a significant DPPH radical scavenging activity [20].

Anticancer activities

The ethanol extract of the plant exhibit a moderate cytotoxic activity against human cancer cell lines HeLa-B75 (34.21 ± 0.24%), HEP-3B (25.36 ± 1.78%), HL-60 (30.25 ± 1.36%), and PN-15 (29.21 ± 0.52%) [47]. The cell proliferation assay confirms the chemopreventive activity of hexane fruit extract reducing the formation of prostaglandin E2 (PGE-2), the levels of tumor necrosis factor-alpha (TNF-α), and nitric oxide (NO) in human acute monocytic leukemia (THP-1) cell lines [49].

Antinociceptive activity

The chloroform, petroleum ether, and aqueous ethanol root extracts at a dose of 250 mg/kg show antinociceptive activity on acetic acid-induced writhing test in mice [51].

Antimicrobial activities

The plant parts in form of crude and solvent extracts show significant antimicrobial activity. The butanol extract of the root possesses an effective antifungal activity against *Micrococcus luteus*, *Candida albicans*, and *Aspergillus niger* [52]. The aqueous fruit extract exhibit significant antibacterial activity against *Staphylococcus epidermidis*, *E. coli*, *Proteus vulgaris*, and *Salmonella typhimurium* [18]. The acetone fruit extract is good antiplasmid agent and their active fraction cures R-plasmid of *Escherichia coli*, *Enterococcus faecalis*, and *Bacillus cereus* [53]. The Silver nanoparticles (SNPs) biosynthesized from aqueous fruit extract exhibit antibacterial activity causing inhibition of drug-resistant (XDR) microbe *Pseudomonas aeruginosa* by inactivation of respiratory chain dehydrogenases, inducing lipid peroxidation, substantial leakage of reducing sugars, and eventually the cell death [54]. The oleanolic acid isolated from the chloroform fruit extract exhibit significant antibacterial activity against *E. coli*, *S. aureus*, *B. cereus*, *P. aeruginosa*, *B. cereus*, and *A. flavus* [55]. The Sabouraud's glucose broth media assay confirms the antifungal activity of methanol stem bark extract of the plant against *Cryptococcus neoformans*, *Microsporum furfure*, *Trychophyton rubrum*, *Candida tropicalis*, and *Epidermophyton floccosum* [56]. The chloroform stem extract shows the highest antibacterial activity against *Escherichia coli* and also helps in the inhibition of bacterial growth of *Staphylococcus aureus*, *Aspergillus*, *niger*, and *Candida albicans* [19]. The hydroalcoholic leaf extract exhibited dose-dependent antibacterial activity against human pathogens, *Staphylococcus aureus*, *Escherichia coli*, *Micrococcus luteus*, and *Pseudomonas aeruginosa*, and antifungal activity against *Candida albicans*, and found comparable with standard streptomycin and fluconazole for bacteria and fungi, respectively [50]. The subcritical water extract prepared at pressure 10 bar, 160°C temperature, with 1: 30 solid-to-water ratio, and 30 minutes timing, exhibits significant antibacterial activity against *B. cereus*, *S. saprophyticus*, *S. aureus*, and *B. subtilis* [20].

Anti-inflammatory activities

The ethanolic extract of the plant shows remarkable anti-inflammatory activity against cyclooxygenase-2 (COX-2), an important enzyme produced during inflammation [47]. The hexane fruit extract shows significant activity against the production of prostaglandin E2 (PGE-2) and tumor necrosis factor-alpha (TNF-α), whereas dichloromethane fruit extract shows a significant inhibitory activity on cyclooxygenase-2 (COX-2) in Human rectum adenocarcinoma cells (RCM-1) and Human monocytic leukemia cell line (THP-1 cells) [49]. The hydroalcoholic leaf extract- possess wound healing activity without any dermal toxicity and also helps in acceleration of cellular proliferation, increasing collagen synthesis and rapid formation of the well-keratinized epidermal layer, with the combination of dermal fibrous connective tissue in an animal model [50].

Antispasmodic activity

The plant fruits exhibit remarkable antispasmodic activity against spasmogens- histamine, acetylcholine, and barium chloride tested in-vitro in guinea-pig ileum and do not shows any acute toxicity when tested in-vivo for gastrointestinal motility in mice [57]. The polyherbal formulations prepared from the fruits of *Helicteres isora*, *Apium graveolens* seeds and *Mentha piperita* leaves possess good antispasmodic activity against stimulant effect induced by acetylcholine, nicotine, and histamine in guinea pig ileum, and when the same formulation was tested for gastrointestinal motility it does not show any effect in mice model [58].

Conclusion

In conclusion, *Helicteres isora* as a medicinal plant possesses various therapeutical activities. The chemical analysis suggests the presence of various bioactive compounds and their application in pharmacological activities. The fruit, bark, leaves, and seeds of the plant are of medicinal uses and there is a need to explore their pharmaceutical importance to develop drugs in curing various diseases.

Conflict of Interest

None

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