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Possible therapeutic potential of *Helicteres isora* (L.) and it's mechanism of action in diseases

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Abstract
Many indigenous medicinal plants possess promising therapeutic properties, but experimental demonstration of specific active compound is lacking. Recent research findings suggest that bioactive fractions derived from a reverberated medicinal plant, namely, *Helicteres isora* (L.) possesses many therapeutic properties. Different plant extracts are known to cure diarrhea, diabetes, snakebite, weakness and various skin ailments. The present review is an attempt to briefly provide a scientific rationale for indigenously claimed therapeutic potential of bioactive fractions derived after extraction from *H. isora* against various diseases. Reports have shown that the extracts from bark, fruits and root possess antioxidant, anti-dysenteric, anti-diabetic and antimicrobial properties. The fruit extract of *H. isora* have been reported to exhibit free radical scavenging activities, ability to induce toxicity in tumor cells and protection to normal cells. However, most of the reports are limited to *in vitro* systems. Therefore, comprehensive laboratory studies and clinical trials are warranted to ratify the indigenous medicinal claims on *H. isora* plant. This paper is aimed to contribute to better understanding and in establishing a base for the development of *H. isora* related herbal formulation(s) that may enable us fight against many diseases including cancer.

Keywords: *Helicteres isora,* Antioxidants, Free radical scavenging, Extracts, Toxicity.

1. Introduction
Medicinal plants of Indian origin possess a plethora of therapeutic compounds useful for treating various diseases. Most of these compounds are highly nutritious and rich source of antioxidants. Many plants and herbs contain an excellent composite of nutritive and medicinal properties which are easily available, cost effective and safe for long term use. Considering these facts and taking into account a broad spectrum of their usage, focus of research has been to find lead molecules in herbal resources. Extensive experimental and clinical studies from our laboratory as well as that from other researchers have provided convincing evidences of association between bioactive compounds and reduced risk of cancer and other disorders [1-5]. Our research group has previously demonstrated that herbal formulation, Triphala, caused remarkable cytotoxicity to cancer cells but protected normal cells involving reactive oxygen species (ROS) in their action [1]. Further studies by our research group in this context showed that ellagic acid and alcoholic extract of *Nigella sativa* (L.) enhanced toxicity to tumor cells, but protected normal cells against ionizing radiation [3, 6].

Among several indigenous medicinal plants, *Helicteres isora* is an important medicinal plant possessing remarkable nutritional and therapeutic activities. It is a tropical south-east Asian shrub cultivated throughout India. Different parts of the plant are traditionally used in Indian System of Medicine (ISM) to cure various ailments. Furthermore, recent research results have suggested that *H. isora* was a rich source of bioactive compounds such as polyphenols, tannins and alkaloids that exhibit therapeutic effects. Moreover, *H. isora* is reported to be a good source of carbohydrate, proteins, fiber, calcium, phosphorus and iron [7]. Another report based on extraction and characterization studies has shown the presence of some antioxidant compounds such as ascorbic acid, flavonoids and phenolics (cucurbitacin B and isocucurbitacin B) [8, 9]. It is also reported that extracts of *H. isora* possess antibacterial, anti-diabetic and anticancer activities.

In view of the wide spectrum of therapeutic uses of *H. isora*, it was considered important to briefly outline present progress and point to future prospects of therapeutic applications of its bioactive fractions for treatment of diseases including cancer. The main aim of this review is to give an account of the outcome of experimental studies concerning therapeutic uses of extracts from different sources of *H. isora.* In addition, an attempt has been made to identify existing

research gaps with a view to prompt further research relevant to effective management and treatment of diseases.

2. Plant Profile of *Helicteres Isora*

H. isora is a large shrub or small tree having hairy, ovate shaped leaves with serrate margins (Fig.1a). It belongs to the Sterculiaceae family. The fruits are compound pod, twisted like screw with pointed end (Fig.1b, c), hence gratifying the name Indian Screw Tree.

Fig 1: Pictures showing (a) Shade dried leaves, (b) Fresh fruit, (c) Shade dried fruits of *Helicteres isora* with seeds (on a centimeter scale). All the images are from our own collection.

Flowers are orange-red in color. The plant is found throughout India; from Punjab to Bengal, Jammu to South India. Usually, the shrub/tree grows in dry deciduous forests of central and western India up to 1500 m on the hill slopes. It is widely found flora of Central and Western India. It is also found in Malay Peninsula, Java, Australia. In Indonesia it is called "Buah Kayu Ules or Ulet-Ulet" on Java island [15, 16].

It is to be noted that different parts of the plant contain a profile of important antioxidants like polyphenols, tannins and are good sources of nutrients [7]. These antioxidants and nutrients are well documented for their nutritional and medicinal values. Due to its nutritive and medicinal values different plant parts are used in herbal preparations like Gandharva Churna, and Siddha Praneshwar Ras [11, 12].

3. Ethno-Medicinal Properties of *Helicteres Isora*

Relative to random approach, prior information on the folk medicinal use of the plant substantially increases possibility of finding a herb/drug of marked therapeutic value.

Therefore, we attempted to find local medicinal uses of various parts of the plant by talking to native people and gathering some secondary ethnomedical data [10, 13, 17].

Leaf paste is claimed to be effective against various skin ailments such as eczema and scabies. **Fruit pod extracts** are found to be anti-dysenteric, vermifuge (colic). It is also used in flatulence, stomach ache, gout and as astringent [10]. Fruits are fried in mustard oil and used to apply on the body of new born babies to relieve pain. The fruit powder mixed with some other herbs and spices is given to new mothers as laddoo (Indian sweet dish) in order to cope up with post-delivery health weakness.

Roots and Bark: The root decoction/juice and the paste are reported to be traditionally used in ISM against diabetes, diarrhea, emphysema, stomach afflictions and asthma [13, 14, 17, 18]. It is also claimed to be used as expectorant, astringent, antigalactagogue, to reduce gripping and a cure for snakebite [12, 17, 18]. The extract from the root and bark possess insulin uptake sensitizing properties, Hypolipidemic activity and has the potential for use in the treatment of type-2 diabetes [19].

According to literature, the extract is used as anthelmintic; for treatment of gastro-spasm on Java Island; and as an antispasmodic, antipyretic, anti-diarrheic and anti-dysenteric in Saudi Arabia. Authors have also reported its use as a tonic compound after childbirth in the Malay Islands [15, 16].

4. Bioactive Compounds and Their Therapeutic Efficacy

The therapeutic value of the medicinal plant/herb lies in bioactive compounds they possess and their specific physiological action on the human body. Preliminary qualitative studies on various extracts suggested presence of phenolics, flavonoids, glycosides, tannins, carotenoids, ascorbic acid and saponins in different parts of *H. isora* [7, 20-23]; concentrations may vary according to season or part studied. The brief accounts of bioactive compounds derived from *H. isora* are enlisted in Table 1.

Among various identified bioactive compounds /antioxidants of *H. isora*, cucurbitacin, rosmarinic acid, gallic acid and kaempferol are notable antioxidants. They are already established anticancer agents with free radical scavenging activity, when isolated from other different herbs [1, 9, 28-30]. In addition, our previous research finding confirmed that the herbal formulation-Triphala contains a major polyphenolic fraction of gallic acid (50%) [1]. in our recent investigations, it was found that gallic acid is one of the antioxidant present in *H. isora* [results unpublished]. Moreover, the chemical composition of various parts of *H. isora* with regard to its major constituents matches the criteria of a good antioxidant reservoir [23].

Table 1: Major bioactive compounds isolated from *H. isora*

S. No.	Plant Part	Bioactive Compound	Class	Ref.
1.	Root	cucurbitacin b, isocucurbitacin b β-sitosterol, betulic acid, oleanolic acid, daucosterol, isorin, 3 β27diacetoxylup20(29)en-28-oic methyl ester Catechol, Gallic acid	Steroid Polyphenols	[8] [24] [23]
2.	Bark/stem	β-sitosterol; 10-methyl, 4-isopropenyl and dodecahydro- ethanophenanthrene	Phytosterols (plant sterols) ; terpene	[25]
3.	Leaves	Gallic acid, Caffeic acid, vanillin, p-Coumaric acid	Polyphenols	[23]
4.	Fruits	Rosmarinic acid and their derivatives; isoscutellarein and their derivatives; D-glucopyranosyl isorinic acid with rosmarinic acid; Helisterculins A and B, Helisorin Gallic acid, Caffeic acid, vanillin, p-Coumaric acid	Lactic acid Neolignans Polyphenols	[15,26] [27] [23]

4.1. Experimental evidences for biological activities

Although therapeutic importance of the *H. isora* was noticed earlier but significant experimental evidences appeared recently. Various reported pharmacological activities are not old than a decade. Different extracts are reported to display pharmacological properties such as antimicrobial, anti-diabetic, anti-cancer, anti-diarrheal and antioxidant; hence there is a great need to determine the presence of relative bioactive compounds in the concerned extracts and their target in the human body.

Antimicrobial activity

Some researchers have demonstrated antimicrobial activity from aqueous and alcoholic of fruits of *H. isora* against a number of bacterial strains [20, 31, 32]. Venkatesh *et al*. (2007) showed antimicrobial effects from butanol extract of roots of isora against a number of microbes [31].

Shriram *et al.* (2010) reported that the acetone extract of the fruit is capable of removing antibiotic resistant R-plasmid of many strains of bacteria thus making them more sensitive towards low antibiotic doses [32]. Such plasmid loss reversed the multiple antibiotic resistances in cured derivatives making them sensitive to low concentrations of antibiotics. Henceforth, it was suggested that acetone extracts of *H. isora* may be a source to develop antiplasmid agents of natural origin; and a sensitizer of multidrug resistant genes of pathogenic bacteria [32].

Anti-diabetic activities

Cumulative research findings on root extract of *H. isora* showed insulin-sensitizing, anti-hyperglycemic and hypolipidemic activity; suggesting the potential use of the extract in the treatment of type-2 diabetes [18, 19, 33-36]. In their experimental investigations Kumar and Murugesan (2007) reported that administration of aqueous bark extract to diabetic rats resulted in an appreciable decrease in lipid peroxidation products with normalization of endogenous antioxidants levels in the heart [19]. Simultaneously, Kumar *et al.* (2007), demonstrated a significant increase in the activities of plasma insulin and endogenous enzymes such as SOD, CAT, GPX, GST, GSH in the brain of diabetic rats on treatment with the aqueous extract from bark of *H. isora* [37]. These results suggested a possible antiperoxidative role of aqueous extract from bark of *H. isora*, therefore display protective effect against lipid peroxidation–induced membrane damage in brain [37]. In addition, histological examination from the laboratory of Venkatesh *et al.* (2010) convincingly showed restoration of pancreatic islets, kidney glomeruli, and liver to its normal size after treatment with root extract of *H. isora* [34]. Bhavsar *et al.* (2009), showed that saponins from *H. isora* exerts antidiabetic effects with activation of PI3K/Akt pathway, leading to phosphorylation and inactivation of GSK-3α/β with subsequent stimulation of glycogen synthesis as well as increase of Glut4-dependent glucose transport across the cell membrane [36].

Hepatoprotective effects

Researchers have provided a scientific rationale for the traditional use of this plant in the management of liver diseases, suggesting hepatoprotective role of ethanolic extract from bark and root. Dhevi *et al.* (2008) showed that administration of ethanolic extract of *H. isora* bark to rats resulted in total reversal and recovery of all studied biochemical and antioxidant markers [38]. Furthermore, in the following year Chitra *et al.* (2009) showed significant reduced levels of serum markers and increased total protein in the blood samples of rats treated with ethanolic root extract of *H. isora* [39].

Antioxidant activity

Aqueous and alcoholic extracts from fruits and bark of *H. isora* are reported to display antioxidant activity such as free radical scavenging, toxicity to tumor cells and protection to normal cells. However, most of them are limited to initial analysis in cell free systems [21, 22, 40, 41]. Pradhan *et al.* (2008) suggested differential cellular response of methanolic fruits extract (50%) of *H. isora*. They showed that the extract displayed significant antitumor activity in melanoma cells, but in contrast protected normal human blood lymphocytes [40]. Raman *et al.* (2012) reported strong anticancer activity and presence of antioxidants in acetone fruit extract of *H. isora* [42]. The current research work from our lab was aimed to evaluate anticancer activity of various extracts from *H. isora*. Table 2 shows the possible mode of action of various bioactive fractions derived from *H. isora.*

Table 2: Ethnobotanical claims and their probable scientific explanations*

Plant parts	Disease	Ethno-medicinal use	Possible Scientific basis	Experimental evidences (ref.)
1. BARK	Diarrhea	Bark boiled with water taken orally thrice per day	Antimicrobial activity/ Antispasmodic action	[20,31,32] [42]
2. FRUITS	Diabetes	1 fresh fruits each taken orally	**Antioxidant activity/ Anti-hyperglycemic and hypolipidemic effects** Decreased level of glucose, glycosylated hemoglobin and plasma glycoproteins; Increase in levels of plasma insulin, hemoglobin	[21,22] [39,40] [18,19,33-35]
	Gastrointestinal problems	Approx. 5 g fruit powder with salt is to be taken thrice daily with water	Antioxidant activity/ Antimicrobial effects	[21,22, 39,40] [20,31,32]
	Weakness in new born baby	1) Fruit paste mixed with mustard oil and turmeric paste is used for massaging in new born baby to cure profound weakness. 2) Fruits are fried in mustard oil, used on new	Antioxidants activity / Antispasmodic action	[21,22, 39,40] [42]

		born baby to remove body pain.		
	Post-delivery weakness	Fruit powder along with other herbs and spice mixed sweet dish is given to women after child birth. It may be given to them during pregnancy.	Antioxidant activity/ Antispasmodic action	[21,22, 39,40] [42]
	Sores of ear	Fruits are made into liniment for sores of ear	Antioxidant activity/ Antimicrobial activity	[21,22, 39,40] [20,31,32]
2.1. SEEDS	Dysentery	5 g seed powder boil with water; taken twice a day	Antimicrobial activity for diarrhea and dysentery due to amoebiasis.	[42] [20,31,32]
3. ROOT	Diabetes	Fresh root juice taken twice a day	Anti-hyperglycemic activity	[18,19,33-35]
	Cut and wounds	Fresh root paste with turmeric paste is applied externally	Antioxidant activity/ Antimicrobial activity	[21,22] [39,40] [20,31,32]
	Diarrhea	Root decoction	Antioxidant activity/ Antimicrobial activity	[21,22,39,40] [20,31,32]
4. LEAVES	Scabies	Paste is applied externally twice per day till cure on infection area of scabies	Antimicrobial properties	[20,31,32]
	Skin infections	Fresh leaf paste applied thrice a day	Antioxidant activity/ Antimicrobial properties	[21,22,39,40]
	Snakebite	Fresh leaf paste applied on affected area	Free-radical scavenging activity might be playing an important role in inflammation.	[21,22,39,40]

* Most of the probable mode of actions of various bioactive fractions derived from *H.isora* is suggestive only; in-depth, comprehensive laboratory studies are warranted to confirm the indigenous medicinal claims.

5. Discussion

Table 2 summarizes the possible modes of action of various bioactive fractions derived from *H. isora.* However, most of the probable modes of action of various bioactive fractions derived from *H. isora* are suggestive since they lack systematic research based validation. Therefore, in-depth, comprehensive laboratory studies are warranted to confirm the indigenous medicinal claims and for establishment of *H. isora* based effective therapeutic modalities.

The mechanism of action demonstrated by researchers from different laboratories under stressed conditions involve the restoration or up-regulation of endogenous enzymes such as glutathione and catalase on administration of alcoholic extracts of bark [37, 38]. In addition, saponins derived from the extract are reported to be involved in the activation of PI3K/Akt pathway [36]. Fruit extract of *H. isora* is reported to induce toxicity to tumor and protection to normal cells [39, 42]. The major therapeutic effect of extract is attributed to free radical scavenging mechanism [21, 22]. These observations are in line with the reported mechanisms from our laboratory which showed herbals such as Triphala, Ellagic acid and *Nigella Sativa* increased tumor toxicity presumable by up-regulation of ROS level and spared normal cells after radiation exposure [1, 3, 6, 44, 45]. Taking clue from these reports, we tend to believe that extracts from different parts of *H. isora* may exert therapeutic effects on target cells without significantly affecting normal cells.

From the extraction and identification studies on *H. isora*, several bioactive compounds such as cucurbitacin, rosmarinic acid, gallic acid and kaempferol were found present which are known to possess strong anti-oxidant and anti-cancer properties when isolated from different herbal sources. For example, these compounds are reported to manifest a variety of biological activity including inhibition of cancer cell proliferation *in vitro* [29, 30, 46]. Reports have appeared showing that compound such as cucurbitacin B, kaempferol induce apoptosis by inhibition of JAK/STAT, MAPK pathways, potentiate anti-proliferative effects of gemcitabine and activation p53 in tumor cells [9, 29, 30]. Recent study conducted by Russell and coworkers (2011) reported that combined treatment of gallic acid with flutamide induced higher toxicity to prostate cancer cells than either of the compounds alone with simultaneous low toxicity to normal cells [46]. Comprehensive experimental studies on various extracts or isolated bioactive compounds from *H. isora* are warranted to identify potential drug targets and cellular responses.

It seems important to conduct further research on various extracts of *H. isora* plant at animal model followed by clinical evaluation to validate the local claims and explore newer therapeutic applications. Vast potential exists to identify the lead molecules from extracts of *H. isora* and determine their mechanisms of action on cellular targets in diverse pathological conditions.

6. Conclusion

Present paper gives a brief account of diverse medicinal uses of *Helicteres isora (L.)*. Both laboratory and epidemiologic studies have provided considerable evidence that each and every part of the plant *H. isora* possesses medicinal properties. Studies have suggested that alcoholic and acetone extracts of fruits showed strong antioxidant and free radical scavenging activities by the bioactive compounds. Reports also point to promising antitumor activity of fruits which may prove useful in chemoprevention as well as chemotherapy. It however, needs to be noted that most of these studies were limited to *in vitro* and cell free systems. Studies on animal models and clinical set up are lacking for evaluation of anti-inflammatory and anti-cancer effects. Extensive research is required to identify targets in cells for anti-cancer, anti-inflammatory, anti-diabetic and hepatoprotective effects. We strongly advocate that further detailed cohort studies are warranted both at laboratory and clinical level for the development of herbal formulation(s) containing *H .isora* alone or in combination with other herbals to fight against several diseases including cancer.

7. Acknowledgment

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8. Conflict Of Interest
None

9. References

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