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

Renu Dayal, Amrita Singh, Rudra P. Ojha, K. P. Mishra

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 affictions 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,
sorcoric 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

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Plant Part</th>
<th>Bioactive Compound</th>
<th>Class</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Root</td>
<td>cucumberin b, isocucurbitacin b, β-sitosterol, betulic acid, oleanolic acid, daucosterol, isorin, 3β,27dihydroxylup20(29)en-28-oic methyl ester</td>
<td>Steroid</td>
<td>[8] [24]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Catechol, Gallic acid</td>
<td>Polyphenols</td>
<td>[23]</td>
</tr>
<tr>
<td>2.</td>
<td>Bark/stem</td>
<td>β-sitosterol; 10-methyl, 4-isopropenyl and hexodehydro-ethanophenanthrene</td>
<td>Phytosterols (plant sterols); terpene</td>
<td>[25]</td>
</tr>
<tr>
<td>3.</td>
<td>Leaves</td>
<td>Gallic acid, Caffeic acid, vanillin, p-Coumaric acid</td>
<td>Polyphenols</td>
<td>[23]</td>
</tr>
<tr>
<td>4.</td>
<td>Fruits</td>
<td>Rosmarinic acid and their derivatives; isoscuetellarein and their derivatives; D-glucopyranosyl isorinic acid with rosmarinic acid; Helisterculins A and B, Helisorin Gallic acid, Caffeic acid, vanillin, p-Coumaric acid</td>
<td>Lactic acid, Neolignans, Polyphenols</td>
<td>[15,26] [27] [23]</td>
</tr>
</tbody>
</table>
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 antioxidative 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*. 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**

<table>
<thead>
<tr>
<th>Plant parts</th>
<th>Disease</th>
<th>Ethno-medicinal use</th>
<th>Possible Scientific basis</th>
<th>Experimental evidences (ref.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. BARK</td>
<td>Diarrhea</td>
<td>Bark boiled with water taken orally thrice per day</td>
<td>Antimicrobial activity/ Antispasmodic action</td>
<td>[20,31,32] [42]</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>1 fresh fruits each taken orally</td>
<td>Antioxidant activity/ Anti-hyperglycemic and hypolipidemic effects</td>
<td>Decreased level of glucose, glycosylated hemoglobin and plasma glycoproteins; Increase in levels of plasma insulin, hemoglobin</td>
</tr>
<tr>
<td>2. FRUITS</td>
<td>Gastrointestinal problems</td>
<td>Approx. 5 g fruit powder with salt is to be taken thrice daily with water</td>
<td>Antioxidant activity/ Antimicrobial effects</td>
<td>[21,22, 39,40]</td>
</tr>
<tr>
<td></td>
<td>Weakness in new born baby</td>
<td>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</td>
<td>Antioxidants activity / Antispasmodic action</td>
<td>[21,22, 39,40]</td>
</tr>
</tbody>
</table>

~ 97 ~
proliferation of biological activity including inhibition of cancer cell effects on target cells without significantly affecting normal toxicity to tumor and protection to normal cells [39, 42]. The extracts from different parts of H. isora 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 [30, 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 herbas 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 manest 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.

### 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 [30, 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 herbas 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.

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9. References


