Protective effect of *Helicteres isora* in paclitaxel induced neuropathic pain in experimental animals

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Abstract- **Any abnormality in your body or a part of it will make you feel pain, which is an unpleasant experience. Depending on where it originates from, pain can be either physical or mental. There are several basic medicines that demonstrate their pharmacological efficacy for nociceptive activity. Nociception is the process of learning and processing noxious stimuli, and it describes the intensity of discomfort in the abdomen, which can be acute or persistent. It is a new approach with a low analgesic success rate. Rosemerinic Acid, which is present in H. isora and has been shown to be effective in treating neuropathy illnesses. The Sterculiaceae family includes the large tropical tree and shrub genera Helicteresisora L. The plant has been demonstrated to possess anti-inflammatory, hepatoprotective, anticancer, antidiarrheal, antibacterial, antiviral, and analgesic effects.During phytochemical screening, steroids, proteins, tannin and phenolic compounds,anthraquinon glycosides, and carbohydrates were found. In several animal models, such as the hot plate, tail flick, tail clip, cold pain, filament pain, tail immersion technique, acetic acid induced writhing test, and formalin induced writhing test, a number of synthetic and plant-based analgesics are being examined for efficacy and potency. By merely evaluating plant extracts using any of the models stated, many plant extracts have been shown to be analgesic; however, the current study is based on the detailed functioning principle and constructional detail of all the many models typically available in pharmacology laboratories.**

Index Terms: **-H.isora, Nociceptive activity, Hot plate, Sterculiaceae.**

1. Introduction: -

Pain is unpleasant, yet it serves as one of our body's most vital protection systems, alerting us to irregularity. Acute or chronic pain is the two primary classifications of pain, depending on the degree and intensity of the threshold. Serotonin/epinephrine reuptake inhibitors must be used to treat neuropathic pain since it can be brought on by a variety of conditions, including anxiety, depression, mania, epilepsy, convulsions, and phobias. It is vital to use common pain relievers like non-steroidal anti-inflammatory medicines while experiencing common pain including body pains, joint pain, inflammatory pain, or traumatic pain. Opioids are the analgesics of choice since they are the most often utilized analgesics worldwide. In order to create endogenous peptide neurotransmitter-like effects like endorphins, enkephalins, and dynorphin, the method involves binding to opioid receptors in the central nervous system (CNS). With numerous plants being utilized by tribal populations for a variety of diseases, almost 80% of the population relies on traditional remedies for their basic medical requirements. Due to the high prices and probable adverse effects of current medications, research into herbal treatments is expanding. Finding efficient, affordable, and Trustworthy traditional therapies is essential since herbal medication is frequently more affordable and has no adverse effects.

Biological source: It consists of dried fruit of *Helicteres isora*

Figure 1: - Helicteres isora

Family: *Sterculiacea*
English –Indian screw tree
Sanskrit – Mriga –shinga
Marathi – Murudsheng
Hindi – Marodphali

Figure 2: - Helicteres isora dried

Helicteres isora is a gregarious species that can be found growing along highways, in evergreen forests, and in secondary rainforests. As far west as Jammu and Sri Lanka, it is a tall shrub or small tree that can be found in central and western India. It can also be found on the slopes of hills in places like Panchkula (Morni), Yamunagar (kalesar), and other locations. *Helicteresisora* linn inhabits habitats such as teak woods, brushwood, and roadsides and can be found all over India in generally dry areas up to 300 m in altitude. Beaked, cylindrical, 1 to 2 in (5–6.3 cm) long, greenish brown, and with carpels that are spirally twisted. The word "mrigashringa" is derived from the Sanskrit words "mriga," which means "deer," and "shringa," which means "horn". The fruit ripens in March. Both tropical Asia and America contain members of the Sterculiaceae plant family, including the genus Helicteres. According to Kubitzki and Bayer (2003), there are about 60 different types of helicteres. The members of this genus have been used for thousands of years in traditional medical systems. According to Venkatesh et al. (2007), Helicteresisora has been used in the treatment of stomach ulcers, intestinal infections, and diabetes. Helicteres ovata and Helicteressacarolha were used by Truiti et al. (2005) as depurants in the treatment of syphilis. According to Libman et al. (2006), helicteres root has been used to treat uterine discomfort. According to biological studies, the H. isora extract has antinociceptive, antidiabetic, hypolipidemic, and hypoglycemic properties. (Venkatesh et al., 2007-Bhavsar et al., 2009; Venkatesh et al., 2006; Chakrabarti et al., 2002). Fruits from Helicteres. isora have a short stem and ragged, twisted brown follicles. 15 to 28 brown cubical seeds per follicle are present. Numerous ethnic groups in various parts of India have used the fruit juice of the large shrub Helicteresisora Linn to treat stomach aches. A H. isora fruit ethanolic extract caused a significant decline. Colic, gas, and diarrhea is among the digestive issues that are treated

with fruits. Over 130 years have passed since the first use of H. isora fruits as a traditional medicine in India. They are currently one of 178 herbal medicine species traded annuallyIndia, with a volume exceeding 100 tonnes. Studies demonstratingthe pharmacology, chemistry, antibacterial, anti-inflammatory, hypolipidemic, and anti-diabetic properties of H. isora fruits have been conducted in great detail. The H. isora fruit is among the most frequently stocked imported herbal medicines in all categories of herbal dealers in South African traditional medicine, where it has also been incorporated.A flagship "jamu" herbal product made by PT Sido Muncul, Tolak Angin, contains 10% H. isora fruit extracts as well. From 2014 to 2017, Tolak Angin was the top-ranking brand in the Indonesia Top Brand Index. The first quantitative analysis of the international trade in H. isora fruits coming from India has been conducted here. Fruits from H. isora are traded from private properties mostly through Buginese and Chinese-Indonesian trade networks as they are part of a "hidden economy" and are not traded in local markets. We classify Helicteresisora as belonging to this group since the isolation, structural characterization, and pharmacological activities produced by its secondary metabolites have provided scientific proof of the biological and pharmacological effects of some species used in traditional medicine.

1. Morphological Description: -

- **Leaves: -**Broadly ovate-oblong edge, simple, alternating, bifurioussubsessible, pubescent on both surfaces, often lobed. Alternating in two opposing rows, they are between 7.5 to 15.0 cm long.
- **Flowers: -** 1 to 2 long, single flowers with reflexed petals red that age to a pale blue color bloom from August to December.
- **Fruits: -**Greenish brown, cylindrical, beaked, and 1 to 2 in (5–6.3 cm) long, with carpels that are spirally coiled.Sanskrit refers to this object as mrigashringa, which is formed from the words "mriga" and "shringa," which both imply "horn" [10, 11]. March is when everything start to ripen. Fruits from Helicteresisora have short stalks and follicles that are rough and twisted in color. 15–28 brown cubical seeds form up each follicle.

Table 1: Major bioactive compounds isolated from H. isora

Sr .no	Plant Part	Bioactive Compound	Class
1.	Root	Cucurbitacin B, Isocucurbitacin B-Sitosterol, Oleanolic Acid, Betulic Acid, Daucosterol, Isorin, 3 Diacetoxylup20(29)en-28-oic Methyl Ester Catechol, Gallic Acid	Steroid Polyphenols
2.	Bark/stem	β-sitosterol; 10-methyl, 4-isopropenyl and dodecahydro- ethanophenanthrene	Phytosterols (plant sterols) ; terpene
3.	Leaves	Gallic acid, Caffeic acid, vanillin, p-Coumaric acid	Polyphenols
4.	Fruits	The following compounds are related to rosmarinic acid: isoscutellarein, its derivatives, D-glucopyranosyl isorinic acid, helisterculins A and B, helisorin gallic acid, caffeic acid, vanillin, and p-coumaric acid lactic.	Lactic acid Neolignans Polyphenols

2. Mechanism of action: - People experience pain because the nociceptive receptor is stimulated by the neurotransmitters. There has been evidence linking the kappa, mu,and delta receptors to the perception of pain. Prostaglandin I, prostaglandin II, or rarely both of them, are produced by them. Both non-selective and selective COX-II receptor inhibition is possible with analgesic medications. By increasing the spinal cord threshold and enabling a person to endure higher pain levels, opioids alleviate pain.

3. Pharmacological Activity of Helicteres. isora Linn

- **Anti-nociseptive activity: -** Opioid peptides produced in the body act as neuromodulators that modify the actions of other neurotransmittersin the central nervous system. By alteringthe electrical properties of theirtarget neurons, therebymaking these neurons more difficult to excite, opioid peptides can influence the release of various neurotransmitters. As a result of this modulation, opioid peptides can among other functions inducepain relief and euphoria. Molecular biological approaches, such as recombinant DNA techniques, have demonstrated that these peptides fall into three categories--enkephalins, endorphins, and dynorphins. Three major categories of opioid receptors-mu, delta, and kappa-have been identified thatdiffer both intheir functions and in their binding characteristics. A givenopioid peptide caninteract with more than one type ofopioid receptor. The binding of opioid

peptides to thesereceptors initiates a series of biochemical events that culminatein various effects,including analgesia and euphoria.

- **Anti-inflammatory activity: -** More research was done to learn how proinflammatory mediators like PGE-2, COX2, and TNF- were altered by H. isora fruit extracts. Using ELISAs, it was determined how well H. isora fruit extracts inhibited THP1 cells' production of PGE-2 when LPS stimulated it. The findings demonstrated that, in comparison to celecoxib, which acts as a COX-2 inhibitor, hexane extract had the greatest impact on PGE-2 formation, with a 69.68 0.017% inhibition. The second-highest inhibition was seen in 80% ethanol extracts, at 57.17 0.021%. Additionally, the impact of H. isora fruit extracts on THP-1 cells' synthesis of COX-2 that is stimulated by LPS was investigated. Dichloromethane extracts exhibited the greatest COX-2 production reduction in compared to celecoxib, inhibiting it by 106.58 0.003%, followed by 80% ethanol extracts, which inhibited it by 56.58 0.003%. Further research on the anti-inflammatory effects of H. isora fruit extracts on TNF production in LPS-stimulated THP-1 cells was conducted. Dexamethasone, an anti-inflammatory medication, was shown to reduce TNF production more effectively than any crude extract from the H. isora fruit (51.61/0.79% inhibition at 100 g/mL).
- **Antioxidant activity:-** The antioxidant activities of H. isora fruit extracts were further investigated by reducing NO generation in LPS-stimulated human monocytic cells. The ethanol extract of this plant had a larger effect than dexamethasone, inhibiting NO production at a rate of 66.98 5.63% compared to hexane's 69.93 9.41%. Additionally, the DPPH radical scavenging experiment demonstrated that all crude extracts of H. isora fruit had varying degrees of free radical scavenging activity. With an IC50 value of 5.43 1.01 g/mL, 80% ethanol extracts were shown to have the highest activity, followed by dichloromethane extracts with an IC50 value of 33.52 2.63 g/mL. The reducing properties of the crude extracts of H. isora fruit were evaluated by FRAP assay. The greatest FRAP value was found in ethanol extracts, which was 22.83 0.13 mmol FeSO4/g sample. With a FRAP value of 10.84 0.04 mmol FeSO4/g sample, ethanol extracts had a higher FRAP value than Trolox.
- **Antibacterial Activity:-** H. isora's methanolic extract was tested against six test pathogens. It has antimicrobial properties and a 250 ug/ml minimum zone of inhibition. 500 ug/ml is the minimal zone of inhibition.
- **Antihelmintic activity:-** In their assessment of the antihelmintic action of fruit extract from Helicteresisora linn., D. Shah et al. looked at the shortest time needed for worm paralysis and death at two distinct doses (50 and 100 mg/ml). The antihelmintic efficacy of Helicteresisora L. bark extract against Pheretima Posthuma (adult Indian earthworm) was investigated by M. Manke et al. With the highest dose of extract being 50 mg/ml, the administration of several extracts at concentrations of 10, 20, and 50 mg/ml demonstrated increased efficiency in causing earthworm paralysis and death.
- **Antihyperlipidemic activity:-** The Antihyperlipidemic Activity of Helicteresisora Fruit Exract on Streptozotocin Induced Diabetic Male Wistar Rats was assessed by Raja et al. The amount of lipids, total cholesterol, triacyglycerol, and phospholipids significantly decreased in diabetic rats after 45 days of administration of the fruit extract of Helicteresisora. R. Sahane et al. looked into the flavonoid-rich fraction of Helicteresisora's anti-diabetic and anti-hyperlipidemic effects. On Steptozotocin-Induced Diabetic Rats, L Fruit. administering the flavonoid-rich portion of the H. isora fruit to Helicteres orally at a dosage of 400 mg/kg. Triacyglycerol, low density lipoprotein, and cholesterol were significantly reduced by isora dosage. It also had an impact on blood glucose levels, high density lipoprotein, serum albumine, serum triacyglycerol, serum creatinine, serum alkanine phosphatase, and serum total protein.

4. Models for Analgesic Activity

- **Sciatic Nerve Surgery**

Male Wistar rats were anesthetized with sodium pentobarbital (40 mg/kg. ip, supplemented as necessary). The common sciatic nerve was exposed the level of the middle of the thigh by blunt dissection through biceps femoris. Proximal to the sciatics trifurcation about 7 mm of nerve was freed of adhering tissue and 4 ligatures (4.0 chromic gut) were tied loosely around with about 1 mm spacing. The length of nerve thus affected was 4-5 mm long. Great care as taken to tie the ligatures such that the diameter of the nerve was seen to be just barely Constricted when Viewed with 40X magnification. The desired degree of constriction retarded, but Aid not arest, circulation through the superficial epineurial Vasculatiure and a small, brief twitch in the muscle surrounding the exposure The ometmes produced incision Was elosed in layers , These animals were used to study effect of AERC on induced neuropatic pain in cold paclitaxel Iallodynia and hot plate method.

- **Cold Allodynia**

One day after sciatic nerve ligation animals received AERC00, 200 and 400 mg/kg. p.o) (17.5 mg/kg, i.p.).0One hour after administration of AERC and 30 minutes and Pentazocine after administration of Pentazocine, Paclitaxel was administered as an inducer. Number of licking was measured at 60, 120 and 180 min interval after paclitaxel by keeping the animal on the ice slab (Bennett GJ, Xie 1987).

- **Tail immersion method**

The distal 2-3 cm portion of mouse- tail was immersed in hot water maintained at 55 +-0.5'C (Turmer, 1971). The time taken by the animal to withdraw the tail from hot water was noted as reaction time at 60, 120 and 180 min. Pentazocine (17.5 mg/kg. ip.) which was administered 130 min prior was used as reference standard. AERC (100, 200, 400 mgkg p.o) was administered lhr prior to subjecting the animals in hot water. Paclitaxel was administered as an inducer at the time of the observation.

- **Cold Allodynia**

Acteone (0.1 ml of 2% v/v) in sub-plantar region of hind paw was injected once to mice one hour after oral administration of AERC (100 mgkg p.o), AERC (200 mg/kg p.o) and AERC (400 mg/kg) Pentazocine (17.5 mg/kg p.o) administered 30 min prior was used as reference standard. Number of paw licking was measured on 7. 10, 21 day. Paclitaxel was administered as an inducer at the time of the observation (Nieto and Entrena, 2008).

- **Hot Plate Method:**

The hot plate technique of analgesic evaluation is built on the theory of thermal stimuli. The animals used in this experiment were initially uncomfortable because their paws were heated. As a result, the rats will first feel discomfort before starting to lick their paws and momentarily attempting to balance on one leg before being administered the medicine or plan extract that will be evaluated. It is necessary to maintain a hot plate temperature of 55 °C continuously. The systematic procedure employed is:

Procedure: -

a) The mice or rats used in the experiment should be weighed and numbered.
b) Animals were divided into three groups: (1) Reference (2) Control (3) Experimental Groups.
c) When you put an animal on a hot plate, watch for how quickly it reacts by licking or jumping.
d) About 15 seconds will be the cutoff period in order to prevent needless suffering and harm.
e) Experimental animals are injected with the medicine (plant extract), which they must then absorb before being placed back on a heated plate to measure their baseline response time.
f) When inserting the drug, compare the reaction time before and after.
g) If an acceptable outcome or reaction is not received, repeat the procedure.

- **Statistical analysis:-** All the data was shown as mean t SEM. Statistical Analysis was performed with one-way ANOVA followed by Dunnett's test. Differences of "p<0.05 was considered statisticaily significant.

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