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Review Article

PHARMACOLOGICAL AND THERAPEUTIC PROFILE OF *ANANTAMULA* (*HEMIDESMUS INDICUS* (L.) R. BR.): A COMPREHENSIVE REVIEW

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ABSTRACT

The vast field of Ayurvedic science is gaining more importance and popularity throughout the world because of its amazing therapeutic value. Since the beginning of human civilization, medicinal plants have been used by mankind for its therapeutic value. The World Health Organization estimated that 80% of people worldwide rely on herbal medicines for some aspect of their primary healthcare. *Hemidesmus indicus* is a widely used shrub in Indian folk medicine and considered as magical spiritual dream herb in Ayurvedic medication. It is used as a vital herb for healing many ailments and to treat diversified diseases. Following a large number of claims on the wide range of traditional medicinal properties of the plants, considerable effort have been made to verify its efficacy as a curative agent through pharmacological investigations. Different pharmacological experiments *in vitro* and *in vivo* models convincingly demonstrated the ability of *Anantamula* to exhibit analgesic, anti-inflammatory, antipyretic, antiarthritic, antioxidant, hepatoprotective, nephroprotective, antiepileptic, anticonvulsant, antileprotic, antiacne, antipsychotic, nootropic, antinociceptive, antidiarrhoeal, antigenotoxic, antiangiogenic, wound healing, antiulcer, larvicidal, antivenom, antithrombotic, antihyperlipaedaemic, antimicrobial and anticarcinogenic activities due to its remarkable biological activity and bioactive constituents. This plant is a good source of different bioactive chemical compound like Hemidesmin-1 and Hemidesmin-2, α-amyrin, β-amyrin, lupeol acetate, β-sitosterol, hemidesmol and hemidesterol which were responsible for many of the pharmacological activities. This review aims at providing an up-to-date overview of comprehensive account of the phytochemical investigation, therapeutic potential and pharmacological studies of *Hemidesmus indicus*.

KEYWORDS: *Indian Sarsaparilla*, *Hemidesmus indicus*, Ayurvedic, Pharmacology.

INTRODUCTION

Hemidesmus indicus (L.) R. Br. commonly known as Indian Sarsaparilla/*Anantamul* belongs to family Asclepiadaceae. It is perennial, diffusely twinning or prostrate semi erect shrub with a woody root stock having numerous slender wiry laticiferous branches with purplish brown bark. This plant is found throughout India growing under mesophytic to semi dry conditions in the plains and upto an altitude of 600 m. It is quite common in open scrub jungles, hedges, uncultivated soil. It is found in India, Sri Lanka, Pakistan, Iran, Bangladesh and Molusccas[1-4]. Though almost all of its parts are used in traditional systems of medicines, leaves, stem and roots are the most important parts which are used medicinally. It is a well known traditional medicinal plant widely used in Ayurveda, Siddha and Unani systems of medicine to treat a variety of diseases such as dysentery, diarhhoea, syphilis, dyspepsia, leucoderma, diuretic, blood purifier, burning of body, chronic fever and asthma, liver diseases, venereal diseases, leprosy, urinary tract infection, asthma, arthritis, bronchitis, epileptic seizures, high blood pressure, skin diseases (eczema and psoriasis), rheumatism, chronic nervous diseases, impotence and immune disorders. The use of herbal drugs is increasing worldwide as they have fewer or no side effects as compared with synthetic drugs. Ayurveda claims therapeutic potentials of this plant and a lot of pharmacological research work has been carried out and therefore the present review compile available information in a comprehensive manner.

Fig. 1. Leaves of *Anantamula*

Fig.2. Flower of *Anantamula*

Fig.3. Root of *Anantamula*

PHYTOCHEMISTRY

Phytoconstituents reported from different parts of *Hemidesmus indicus* [5-6].

i. Roots: Pregnane glycoside viz. Hemindicusin. Coumarinolignoids viz. Hemidesmin-1 and Hemidesmin-2. Others–β-amyrin acetate, α-amyrin, β-amyrin, lupeol acetate, β-sitosterol, hexadecanoic acid, hexatriacontane, lupeol octasonate. Oil contains 80% crystalline matter, glucose, hemidesmol, hemidesterol, 2-hydroxy-4-methoxy benzaldehyde, resin acid, glucoside, α-amyrin triterpene, β-amyrin triterpene, and benzaldehyde.

ii. Stem: Glycosides such as Indicine and Hemidine. Pregnane glycoside such as Hemidescine and Emidine. Pregnane oligoglycosides viz. demicunine and heminine. Desinine, Indicusin, Medidesmine, Hemisine and Demicine. Steroidal compounds viz. Calogenin-3-o-β-D-digitoxopyranosteroid, desminine steroid, hemisine steroid. Triterpenoids viz. 3-keto-lup-12-ene-21->28 olide triterpene, lup-12-ene-3- β –ol-acetate triterpene.

iii. Leaves: Coumarin olignoids viz. hemidesminine, hemidesmin-1, hemidesmin-2. Flavonoids viz. hyperoside and rutin, 2.50% tannins.

iv. Flowers: Flavanoid glycosides viz. Hyperoside, Isoquercetin and Rutin.

Phamacological Studies

Analgesic activity

The hydro-alcoholic extract of *Hemidesmus indicus* at different doses (100,200 and 300 mg/kg, p.o.) in Swiss albino mice significantly inhibits writhing response, decrease the licking response in acetic acid–induced writhing response and Eddy's hot plate method. A maximal effect was observed at 300 mg/kg which was comparable to10 mg of piroxicam per kg body weight (b.w.), i.p.[7]. Hydroalcoholic extracts of 100, 200 and 300 mg/kg b.w in adult Wistar rats showed significantly reduces the licking response in Eddy's hot plate method (55-56ºC). The analgesic effect of the extract may therefore be due to either its action on the inhibition of the production of algogenic substances or the inhibition at the central level of the transmission of painful message.[8]

Anti-pyretic activity

The anti-pyretic (brewer's yeast induced pyrexia) effect in Wistar albino rats (measured as % reduction in body temperature) was compared with paracetamol (100 mg/kg, orally). Hydro-alcoholic extract of *Hemisdesmus indicus* at the dose of 300 mg/kg caused significant decrease in body temperature of rats[9]. Standard drug paracetamol 100 mg/kg b.w and *Hemidesmus indicus* extract at a dose of 100, 200 and 400 mg/kg BW reduced the yeast elevated rectal temperature compared to control group[10]. A traditional medicine *Jwarhar mahakashayan* an Ayurvedic preparation of the roots of *Hemidesmus indicus* has been used to cure antipyretic-analgesic effect. Aqueous extract of above preparation showed antipyretic-analgesic property with very low ulcerogenicity and toxicity in animal model[11].

Anti-inflammatory activity

The ethylacetate extract of roots of *Hemisdesmus indicus* exhibited significant inhibition of inflammation in both acute and sub acute inflammation induced by carrageenan, bradykinin, S-hydroxy tryptamine, but less active in granuloma pouch and cotton pellet implantation and ineffective in dextran induced inflammation methods in rats[12]. The treatment with the hydroalcoholic root extract of *Hemisdesmus indicus* at different doses (100, 200 and 300 mg/kg b.w., p.o.) significantly prevented increase in volume of paw edema and formation of granulation tissue in dose dependent manner and maximal effect was observed at 300 mg/kg b.w which was comparable to phenylbutazone 100 mg/kg b.w., i.p.**[13]**. In carragenan induced paw oedema, methanolic roots extract also exhibited significant reduction in volume between 2-4 h after treatment[14]. A saponin from the *Hemisdesmus indicus* is found to have anti inflammatory activity against formalin induced edema[15].

Antioxidant activity

The aqueous extract of whole plant of *Hemidesmus indicus* showed significant free radical scavenging activity which indicates that the plants extract has a potential source of antioxidants and thus could prevent many radical diseases[16]. Methanolic extract of *Hemidesmus indicus* roots showed a

concentration dose dependent inhibition of 1, 1-diphenyl-2-picryl hydrazyl (DPPH) radical, superoxide radicals and moderate nitric oxide scavenging activity due to the presence of polar components. Lipid peroxidation induced by Ferric-ADP and ascorbate in rat liver homogenate was also inhibited. Haemolysis of erythrocytes by phenylhydrazine was also effectively inhibited[17]. Similar effects were reported by Mohana and coworkers by using 50% aqueous ethanolic extract of *Hemidesmus indicus* along with hepatoprotective effect**[18]**. Topical application of ethanolic extract of *Hemidesmus indicus* prior to application of cumene hydroperoxide showed significant inhibition of cutaneous oxidative stress and increased level of antioxidant enzymes by an unknown mechanism[19]. Ethanolic extract of *Hemidesmus indicus* showed potent antioxidant effect and provided protection against free radical mediated oxidative stress in kidney in ethanol induce nephrotoxicity in rats[20]. Administration of *Hemidesmus indicus* extract 500 mg/kg/day for 30 days of experiment significantly reduced the level of serum-urea, uric acid, creatinine and kidney-thiobarbituric acid reacting substances (TBARS), lipid peroxides and conjugated dienes. The extract also increased level of kidney superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and reduced glutathione (GSH)[21]. Terpenoidal fraction obtained from successive extraction of *Hemidesmus indicus* roots possess potent free radical scavenging activity[22]. In streptozotocin induced diabetic rats, administration of aqueous extract of *Hemidesmus indicus* roots (500mg /kg/day) for a period of 12 weeks decreased lipid peroxidation index which is attributed to its antioxidant action[23].

Hepatoprotective activity

Methanolic root extract of *Hemidesmus indicus* (500 mg/kg, p.o.) showed a remarkable hepato-protective activity against paracetamol induced hepatotoxicity[24]. Methanolic root extract of *Hemidesmus indicus* showed hepatoprotective activity against paracetamol and carbontetrachloride induced liver toxicity in rats[25]. Ethanolic extract of *Hemidesmus indicus* roots showed protective effect against Rifampicin and Isoniazid (INH) induced liver toxicity. Extract (100mg/kg b.w./day, for 15 days) prevented alteration in activities of isocitrate dehydrogenase, α-ketoglutarate dehydrogenase, succinate dehydrogenase, malate dehydrogenase, cytochrome C oxidase and NADH dehydrogenase. These effects probably might be due to the presence of coumarino lignoids viz. hemidesmin-I and hemidesmin-II which has free radical scavenging activity[26]. 50% aqueous ethanolic extract of *Hemidesmus indicus* (400mg/kg, per orally) showed similar hepatoprotective activity against carbon tetrachloride (CCl4) induced liver damage. These effects were attributed to its free radical scavenging and anti-lipid peroxidative activities[27]. Methanolic extract of roots of *Hemidesmus indicus* showed hepatoprotective effect against carbon tetrachloride (CCl4) and paracetamol induced liver damage. The extract decreased elevated level of serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), alkaline phosphatase (ALP), total and direct bilirubin in rats with hepatic damage[28]. The ethanolic extract of *Hemidesmus indicus* also showed protective effect against ethanol induced liver injury. The extract significantly decreased level of liver collagen and hydroxyproline content, lipid peroxidation and increases solubility of liver collagen and ascorbic acid level. The extract also decreased activities of matrix metalloproteinase-2 and matrix metalloproteinase-9 which are implicated in extracellular matrix degradation during ethanol intoxication.[29]

Antimicrobial activity

Aqueous root extract of *Hemidesmus indicus* along with barks of *Ficus bengalensis* and *Pterocarpus marspium roxb* showed antimicrobial activity against *Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae*[30]. Methanolic and ethanolic root extract of *Hemidesmus indicus* showed maximum zone of inhibition against *Escherichia coli* and *Vibrio cholerae* in agar well diffusion test[31]. Chloroform and 95% ethanolic extracts of *Hemidesmus indicus* roots showed antifungal activity against *Aspergillus niger*[32]. Das and coworkers reported potent *in vitro* antimicrobial activity of methanolic extract of *Hemidesmus indicus* roots against *Salmonella typhimurium*, *Escherichia coli* and *Shigella Flexneri*. The extract decreased colony forming unit (CFU)/ml in extract treated broth culture. Methanolic and chloroform extracts of *Hemidesmus indicus* inhibited growth in dose dependent manner showed most effective against *Shigella flexneri*, moderately effective against other strains and least effective against *Shigella dysenteries*. This anti-enterobacterial activity was attributed to the presence of antimicrobial trace elements such as copper and zinc**[33]**. Glycosides obtained from *Hemidesmus indicus* inhibited adherence of *Salmonella typhimurium* to host cell and hence reduced its pathological effect. Glycoside showed this action by mimicking host cell receptor saccharide and blocks bacterial ligands from binding to the host cell. Further, glycosides also reduced bacterial surface hydrophobicity[34]. Saponin fraction from the roots extract exhibited remarkable antimicrobial activity against *Staphylococcus aureus, Salmonella typhi, Klebsiella pneumoniae, Aspergillus flavus, Aspergillus fumigatus* and *Aspergillus niger*.[35]

Antileprotic activity

Aqueous extract of *Hemidesmus indicus* root orally administered at 2% concentration in mice infected with *Mycobacterium leprae* showed delayed in cutaneous hypersensitivity stimulation[36].

Antiacne activity

The roots extract of *Hemidesmus indicus* showed strong inhibitory effect on *Propionibacterium acne* and *Staphylococcus epidermis*. Minimum inhibitory

concentration for *Propionibacterium acne* and *Staphylococcus epidermis* was found to be 0.051mg/ml and 1.25mg/ml. But high concentrations were required to act as bactericidal agent[37]. Terpenoidal fraction obtained during successive extraction of *Hemidesmus indicus* showed potent antiacne activity and minimum inhibitory concentrations determined by broth dilution assay was found to be 38ug/ml for both *Propioni-bacterium acne* and *Staphylococcus epidermis* and minimum bactericidal concentrations were 38ug/ml and 46ug/ml respectively[38].

Anticarcinogenic activity

The roots decoction of *Hemidesmus indicus* showed cytotoxic on HepG2 cells[39]. The roots methanolic extract showed inhibition on colon adenocarcinoma cell line with IC50 60 µg/mL by MTT assay and this may be due to the presence of saponins, tannins and steroids[40]. Treatment of mouse skin with *Hemidesmus indicus* extract prior to application of cumene hydroxide prevented induction of ornithine decarboxylase activity and DNA synthesis which is considered to be a biochemical marker to evaluate tumor promoting potential of an agent. The extract showed inhibition of tumor growth in mouse skin and hence can be considered as a potent chemopreventive agent[41]. Decoction of *Hemidesmus indicus*, *Nigella sativa* and *Smilax glabra* for its effect on diethylnitrosamine (DEN)-induced hepatocarcino-genesis. Carcinogenic potential was scored by comparing number, area and staining intensity of glutathione S-transferase placental form (GST-P) positive foci and number of cell/cm2 of the positive foci in livers of rats. The decoction significantly inhibited DEN-mediated GST-P expression in rat liver and hence inhibited early DEN initiated phase of hepatocarcino-genesis. Mechanism of action of decoction was not clear but the authors hypothesized it to be either by detoxification of carcinogen, antioxidant activity, immunomodulatory action or cytotoxicity[42]. Long term treatment of rats with decoction of *Hemidesmus indicus* not only inhibited DEN induced GST-P expression but also the carcinogen mediated development of overt tumor and histopathological changes leading to tumor development. Also a marked reduction of angiogenesis was observed in rats treated with DEN and decoction, but mechanism by which decoction inhibit angiogenesis was not clear[43]. Chloroform fraction containing phytosterol and fatty acid obtain from crude methanolic extract of roots of *Hemidesmus indicus* showed protective effect against cytotoxicity induced by *Salmonella typhimurium* in human intestinal cell lines (Int 407). Int 407 cells infected with *Salmonella typhimurium* treated with 100ug/ml of chloroform fraction had 10 times less cytotoxicity compared to those cells which were infected by wild type bacteria. Adherence and invasive ability of *Salmonella typhimurium* when treated with chloroform fraction to Int 407 cells was decreased by 40 times and 10-15 times respectively. Further, Int 407 cells infected with chloroform fraction treated *Salmonella typhimurium* showed almost normal morphology with normal mitochondrial cristae. But few cells had one or two invaded bacteria and cells with altered morphology were rarely observed[44]. Extract of *Hemidesmus indicus* root protect microsomal membranes by reducing lipid peroxidation and also protect DNA from radiation induced strand breaks[45].

Antithrombotic activity

Methanolic extract of *Hemidesmus indicus* roots inhibit platelet aggregation. Intravenous administration of root extract delayed the plasma recalcification time. Further, the extract of increased release and activation of enzymes which results in metabolic degradation of lipids[46]. Antiatherogenic effect of a polyherbal formulation called Caps HT2 having *Hemidesmus indicus* as one of the ingredient showed inhibition of platelet aggregation, delaying plasma recalcification time in rabbits and enhancing lipoprotein lipase activity[47].

Antihyperlipidaemic activity

Cell culture extract of *Hemidesmus indicus* (CCH) administered at a dose of 16mg/kg showed decreased low density lipoproteins (LDL) and very low density lipoproteins (VLDL), Cholesterol and significantly increased high density lipoproteins (HDL): cholesterol ratio. In hypercholesterolemic rats, CCH administered at a dose of 2, 4 and 16 mg/kg showed significant reduction in total cholesterol, triglycerides, LDL cholesterol and phospholipids. The possible mechanism of action for the above effect can be an increase in liver LDL receptor activity with a concomitant decrease in hepatic triglyceride (TG) synthesis. Also faecal excretion of cholesterol and phospholipids were increased in hypercholesterolemic rats after administration of CCH (4 and 16 mg/kg) [48]. As mentioned above the polyherbal formulation Caps HT2 was also found to possess hypolipidemic activity as it raised HDL cholesterol level in hyperlipidemic rats[49]. In another invivo study in rats, 2-hydroxy-4-methoxy benzoic acid (HMBA) present in *Hemidesmus indicus* may be responsible for its antihyperlipidemic action. Administration of HMBA 200ug/kg/day for 30days after oral administration of ethanol for 30days to rats decreased plasma total cholesterol, TG, lipoproteins, phospholipids, free fatty acids and increased plasma lipoprotein lipase concentration[50].

Anti nociceptive activity

Oral administration of *Hemidesmus indicus* extract in mice showed dose-dependent antinociceptive effect in all the mice models for antinociception and it blocked both the neurogenic and inflammatory pain[51].

Wound healing activity

The alcoholic extract of *Hemidesmus indicus* leaves (5% and 10% ointment) increased rate of wound contraction and period of epithelization in rats[52]. A clinical study was conducted in 30 patients of chronic

wounds of either sex, the patients were kept on observation. Depending upon the progress of epithelialization on complete cure and it was observed that *Hemidesmus indicus* root extract as applied in paste form to wounds showed wound healing activity[53]. A 5% (w/w) methanolic extract of *Hemidesmus indicus* root showed significant wound healing activity in Wistar rats[54].

Renoprotective activity

The ethanolic extract of *Hemidesmus indicus* roots at different dose levels of 250 and 500 mg/kg showed dose-dependent reduction in the elevated blood urea, serum creatinine and increase in the GSH and GST enzyme level in Cisplatin induced renal injury in rats. The extract also showed inhibition of Cisplatin induced lipid peroxidation. The results suggest that the alcoholic extract of the roots possesses significant nephro protective activity[55]. Efficacy of *Hemidesmus indicus* root extract evaluated against gentamicin induced hepatotoxicity in Wistar albino rats at 5 gm/kg single dose, p.o. for 6 days of treatment reduced renal impairment induced by gentamicin in rats[56].

Anti venom activity

Lupeol acetate isolated from the root extract of *Hemidesmus indicus* could significantly neutralize lethality, haemorrhage, defibrinogenation, edema, PLA2 activity induced by the *Daboia russellii* venom. It also neutralized *Naja kaouthia* venom induced lethality, cardiotoxicity, neurotoxicity and respiratory changes in experimental animals[57]. The methanol root extract was explored for the first time for neutralization of snake venom (*Vipera russellii*) activity and the extract significantly neutralized the viper venom-induced lethality and hemorrhagic activity in albino rat and mouse[58].

Anti arthritic activity

Hydroalcoholic extract and ethyl acetate fraction of *Hemidesmus indicus* showed significantly higher anti-arthritic activity than chloroform and residual fraction. Histopathological analysis demonstrated that both of hydroalcoholic extract and its ethyl acetate fraction had comparable anti-arthritic activity with methotrexates[59]. The *in vitro* study by inhibition of protein denaturation method emphasizes the anti-arthritic effect of *Hemidesmus indicus* root extract to that of the standard drug diclofenac sodium. The anti-arthritic activity may be due the presence of chemical profile like flavonoids, phenols, polyphenols and steroids[60].

Anti-ulcer activity

The alcoholic extract of *Hemidesmus indicus* root showed significant reduction in ulcer index at concentration of 200mg/kg and 400mg/kg. The root extract at the concentration of 200mg/kg showed 73.59% ulcer protection and 400mg/kg showed 76.82% ulcer protection, whereas omeprazole 20mg/kg showed 78.91% ulcer protection in Wistar rats after gastric ulcer was induced by oral administration of indomethacin @20mg/kg. Significant antiulcer property of ethanolic extract of *Hemidesmus indicus* root could be either due to cytoprotective action of the drug or by strengthening of gastric mucosa and thus enhancing mucosal defense[61]. The combined ethanolic extracts of *Hemidesmus indicus* and *Ficus religiosa* at the doses of 100, 200, 400, 800 mg/kg body weight orally administrated in albino rats showed good anti ulcer activity in the pylorus ligation model but in aspirin induced ulcer model, the combined extract have shown less significant activity[62].

Larvicidal activity

Aqueous extracts of *Hemidesmus indicus* roots showed significant larvicidal activity against *Culex quinquefasciatus* larvae at the concentrations of 1,2,3,4 and 5% up to three days[63]. Aqueous extract of *Hemidesmus indicus* showed larvicidal effect against *Culex quinquefasciatus* mosquito larvae which was responsible for transmission of lymphatic filariasis caused by *Wuchereria bancrofti*. The extracts showed 100% mortality at concentration of 5% on 2nd day[64].

Anticonvulsant activity

Ethanolic extract of *Hemidesmus indicus* roots at different concentration (100mg/kg and 200mg/kg) showed significantly reduced the duration of tonic extensor phase and post ictal depression in Maximal Electro Shock method and also the duration of clonus in pentylenetetrazol method in adult albino rats by using the standard drug as phenobarbitone. Hence, the ethanolic extract possess antiepileptic activity**[65]**. Aqueous root extract of *Hemidesmus indicus* at different concentrations (100, 300 and 500 mg/kg b.w.) significantly reduced the time spent in hind limb extensor phase (MES method) and onset of convulsions (INH) in rats[66].

Anti-psychotic activity

Aqueous extract of *Hemidesmus indicus* roots reconstituted in 2% aqueous tragacanth was administered orally at a dose 0f 100 mg/kg, 300 mg/kg and 500 mg/kg in rats. In a single dose study, the parameters were assessed after oral administration of the single dose of the extract whereas in a multiple dose study, the animals daily received the suitable oral dose of the extract for a period of 30 days and the parameters were assessed on the 15th and 30th day. The antipsychotic activity was screened using apomorphine induced Stereotyped behavior and Haloperidol induced catalepsy models. The extract significantly inhibited the stereotyped behavior induced by apomorphine in rats and also potentiate the catalepsy induced by haloperidol, thereby the extract showed anti-psychotic activity in experimental rats[67].

Nootropic effect

Ethanolic extract of *Hemidesmus indicus* showed increased discrimination index in object recognition test and reaction time in hot plate test; potentiated the

haloperidol induced catalepsy and increased the duration of onset of death in sodium nitrite induced respiratory arrest in both acute and chronic studies in mice[68]. *n*-butanol fraction of ethanolic root extract of *Hemidesmus indicus* significantly improved learning power and memory in mice. Hence, the root extract proved to be a useful memory restorative agent in treatment of dementia seen in the Alzheimer's disease and other neurodegenerative disorders[69].

Antigenotoxic effect

Aqueous extract of *Hemidesmus indicus* roots showed potent antigenotoxic activity against cisplatin-induced cytogenetic damage and the extract protected the bone marrow cells in an inverse dose-dependent manner when administered in a split dose regime ((10, 20 and 40 mg/kg b.w./day) for five consecutive days by oral gavage in Swiss albino mice[70].

Anti-angiogenic activity

In vitro investigation of anti-angiogenic potential of *Hemidesmus indicus* (0.31–0.93 mg/mL) on human umbilical vein endothelial cells and delineate the main molecular mechanisms involved in its anti-angiogenic activity both in normoxia and hypoxia. Cell proliferation, apoptosis induction, and inhibition of endothelial cell migration and invasion were analyzed by flow cytometry. The endothelial tube formation assay was evaluated in matrix gel. The capillary tube branch points formed were counted using a Motic AE21 microscope and a VisiCam video camera. The regulation of key factors of the neovascularization process such as VEGF, HIF-1α and VEGFR-2 was explored at mRNA and protein level by real time PCR and flow cytometry, respectively. Decoction of *Hemidesmus indicus* showed significant inhibition of cell proliferation and tube formation in both normoxia and hypoxia. *Hemidesmus* differently regulated multiple molecular targets related to angiogenesis according to oxygen availability. In normoxia, the inhibition of VEGF was the main responsible for its anti-angiogenic effect; the angiogenesis inhibition induced in hypoxia was regulated by a more complex mechanism involving firstly HIF-1α inhibition, and then VEGF and VEGFR-2 down regulation. Additionally, the inhibition of endothelial cell migration and invasion by *Hemidesmus* was more pronounced in normoxia than in hypoxia, possibly due to the physiological enhanced induction of invasion characteristic of hypoxia.[71]

Antidiarrhoeal activity

Aqueous and ethanolic extract of *Hemidesmus indicus* roots significantly reduced the diarrheal effect by decreasing faecal droppings, intestinal transit and intestinal fluid secretion in rats. Ethanolic extract at 200mg/kg b.w. showed 75.5% protective effect in faecal score, 51.2% in intestinal dropping and 56.6% for intestinal fluid secretion[72]. The root powder or its water extract of *Hemidesmus indicus* can be incorporated in oral rehydrating salt solution (ORS) to increase its anti-diarrheal efficacy by increasing the absorption of water, Na+ and K+ (but not glucose) from the sac and intestinal motility was not affected[73]. Methanolic extract of *Hemidesmus indicus* roots showed significant antidiarrhoeal activity in albino rats. It was found that aqueous extract increase water absorption, Na+ and K+ from jejunum[74].

CONCLUSION

The phyto-chemistry and pharmacology of *Hemidesmus indicicus* has been widely investigated but the studies on toxicology of the extracts of the plant parts in different solvents are very few. Evidence from the above literature shows that the plant possess analgesic, anti-inflammatory, antipyretic, antiarthritic, antioxidant, hepatoprotective, nephroprotective, anti-epileptic, anticonvulsant, antileprotic, antiacne, antipsychotic, nootropic, antinociceptive, anti-diarrhoeal, antigenotoxic, antiangiogenic, wound healing, antiulcer, larvicidal, antivenom, antithrombotic, antihyperlipaedaemic, antimicrobial and anti-carcinogenic activities. Serious efforts for high quality studies is required to identify the novel clinical properties of the plant, the identification and isolation of the particular compound responsible for the specific activity. Further, the pharmacokinetics and bio-availability studies of this plant are very much urgent and necessary to fully understand the mode of action of the potential bioactive molecules for development of new drugs in future.

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