Phytochemistry and pharmacology of *Ichnocarpus frutescens*

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[ABSTRACT] *Ichnocarpus frutescens* R. Br. (*Apocynaceae*), is a woody climbing shrub, found almost in all parts of India. In India, tribes used this plant as a substitute of Indian Sarsaparilla (*Hemidesmus indicus*) for the treatment of atrophy, convulsions, cough, delirium, dysentery, measles, splenomegaly, tuberculosis, tumor, diabetes as a lactogogue, antipyretic, demulcent, diaphoretic and in skin diseases. Phytochemical investigations indicate that 28 compounds reported from the plant belong to various chemical category viz. phytosterol, triterpenes, flavonoids and various other phenolic compounds. Pharmacological activities of different parts of the plant reported include antiurolithiatic, hepatoprotective, antioxidant, analgesic, antipyretic, anti-inflammatory, antidiabetic, antihyperlipidemic and antitumor activity. In the present review the literature data on the phytochemical and biological investigations on the *I. frutescens* are summarized up to March 2011.

[KEY WORDS] *Ichnocarpus frutescens*; Antitumor; Anti-inflammatory; Hepatoprotective

[1] Introduction

*Ichnocarpus frutescens* R. Br. (*Apocynaceae*), commonly known as Krishna Sariva, is a red woody climber, found almost in all parts of India, ascending to an altitude of 4 000 ft[1]. Leaves of the plant are characterized by 4.5–7.5 by 2.0–3.8 cm, elliptic–oblong, acute or acuminate, glabrous above, glabrous or slightly pubescent and pale beneath, base usually rounded, main nerve 5–7 pairs with finely reticulate venation, petiole 3–6 mm long. Flowers are greenish white, numerous, in axillary and terminal rusty-pubescent trichotomous pedunculate cymes, pedicles 3–4 mm long, often tree together, rusty pubescent. Calyx fulvous–hairy, divided 1/2-way down, lobes ovate, acute, without glands inside. Corolla-tube is 2.5–3.0 mm long with a narrow portion below about 0.85 mm long, the middle portion of the tube is much inflated (almost globular) over the stamens; the upper portion is constricted below the lobes, lobes 5 mm long pubescent on the upper side with white hairs, broad and oblong at the base, produced at the apex into a long falcate slender twisted acumen which is deflexed in bud and flower. Disks of 5 erect linear lobes, longer than the hairy ovary. Follicles 10–15 cm. by 4 mm, straight or slightly curved, very slender, cylindrical, rusty pubescent at first, afterwards glabrous. Seeds 1.3–2 cm long, linear, black, not beaked, coma as long as the seed, scanty and white[2].

2 Ethnopharmacology

Because of its good fragrance, it is known as Sugandha. This plant is used by tribes as a substitute of Indian Sarsaparilla (*Hemidesmus indicus*), for the treatment of atrophy, convulsions, cough, delirium, dysentery, measles, splenomegaly and tuberculosis. It is also used in the abdominal and glandular tumors and its roots are used as alterative, antidysentric, antipyretic, demulcent, diaphoretic and hypoglycemic[3-5]. Four different plant materials viz. *Decalepis hamiltonii*, *Cryptolepis buchananii*, *Ichnocarpus frutescens* and *Hemidesmus indicus* are indiscriminately sold in the local crude drug market under the name Sariva. Sariva is traditionally being given to pregnant women who have a tendency of abortion as this help to secure their fetal growth with advantage. *I. frutescens* is used in the indigenous system of medicine in the treatment of fever, gout, rheumatism, arthritis, epilepsy, venereal diseases, herpes and skin diseases[6-7]. The roots of *I. frutescens* are given to treat rheumatic pain[8]. Decoction of roots is used as blood purifier[9]. The Gond tribes use the roots as remedy for jaundice[10]. The roots of *I. frutescens*...
frutescens along with roots of Cissampelos pareira, Bauhinia vahlii and Ardisia solanacea are processed together and given orally to cure stomach cancer[11]. Dried root powder of I. frutescens is used as lactogogue and is administered about 10 g twice a day with a glass of fresh water after the meals[12]. The leaf is given to treat fever[13] and root paste is applied in the rat bites and skin diseases[14]. The roots of the plant are used as diuretic and diaphoretic[15]. The stalks and leaves are used in the treatment of skin eruptions and fever[16]. The tribal’s of Madhya Pradesh and Siddis of Uttara Kannada district of Karnataka use the roots and flowers as a cure for diabetes[17-18]. Leaf of the plant is used by the tribes of Chitrakoot, Madhya Pradesh on cuts to stop bleeding[19].

3 Phytochemistry

Phytochemical investigation on I. frutescens led to the isolation of α-L-sarbopyranoside (1)[20], α-L-rhamnopyranosyl-(1→4)-β-D-glucopyranosyl-(1→3)-α-amyrin (2)[21], 6, 8, 8, trimethylpentacosan-7-one (3), α-amyrin (4a) and its acetates (4b), lupeol (5a) and its acetates (5b), friedelin (6), epi-friedelinol (7) β-sitosterol (8)[22], n-octyl tetracotane (10), tetratriacontadiene (11), n-nonadecanyl benzoate (12) and benzocosanyl arachidate (13) from its stem[23].

Leaves of the plant reported to contain apigenin (14), luteolin (14b), vanillic acid, syringic acid, protocatechuic acid, sinapic acid, ursolic acid acetate (15a), kaempferol (16a), kaempferol-3-galactoside (17) and mannitol (19). Flowers of I. frutescens contain quercetin (16b) and quercetin-3-O-β-D-glucopyranoside (18)[26]. Only one compound ursolic acid (15b) reported from the roots of the plants[27].

4 Pharmacology

4.1 Antiurolithiatic activity

The inhibitory effect of the ethyl acetate extract of the roots of I. frutescens on nephrolithiasis induced in the rats was investigated. Nephrolithiasis in the rats were induced by the administration of aqueous solution of ethylene glycol (0.75%) for 28 d. Ethylene glycol feeding resulted in hyper-
standard drugs, whereas excretion level of phosphate was
levels of oxalate and calcium significantly as compared to
duced hepatotoxicity in rats was examined. Carbon tetra-
ethyl acetate extract of 
rats, the levels of uric acid, blood urea nitrogen and creatinine 
creased in calculi-induced rats [(1.650 ± 0.06), (5.216 ± 0.14) and (3.74 ± 0.10) mg·dL\(^{-1}\), respectively] as compared to normal (Saline) rats [(0.191 ± 0.02), (4.783 ± 0.38) and (2.35 ± 0.03) mg·dL\(^{-1}\), respectively]. The deposition levels of oxalate, calcium and phosphate were significantly decreased [(0.500 ± 0.05), (3.633 ± 0.15) and (2.52 ± 0.07) mg·dL\(^{-1}\), respectively] in standard group. Administration of 250 mg·kg\(^{-1}\) p.o. of ethyl acetate extract of 
significantly lowered the deposition of oxalate, calcium and phosphate [(0.233 ± 0.03), (2.588 ± 0.23) and (2.08 ± 0.10), respectively]. Serum uric acid and blood urea nitrogen remarkably increased in calculi-induced rats [(7.866 ± 0.25) and (25.09 ± 0.24)], while serum creatinine is slightly elevated in calculi-induced rats (0.855 ± 0.01). When standard drug (Cystone 750 mg·kg\(^{-1}\) p.o.) was used in calculi-induced rats, the levels of uric acid, blood urea nitrogen and creatinine were significantly decreased [(5.033 ± 0.08), (21.398 ± 0.39) and (0.981 ± 0.006) mg·dL\(^{-1}\), respectively]. Administration of ethyl acetate extract of 
at 250 mg·kg\(^{-1}\) p.o. significantly lowered the levels of uric acid, blood urea nitrogen and creatinine [(1.533 ± 0.14), (33.431 ± 0.73) and (1.146 ± 0.01) mg·dL\(^{-1}\), respectively][28].

4.2 Hepatoprotective activity

Protective and curative effect of polyphenolic extract of 
against carbon tetrachloride and tamoxifen-induced hepatotoxicity in rats was examined. Carbon tetrachloride (1 mL·kg\(^{-1}\)) and tamoxifen (45 mg·kg\(^{-1}\)) given through intraperitoneal route caused liver damage in rats manifested by significant rise in serum enzymes levels, declines in reduced glutathione level and elevations in malondialdehyde levels. The oral administration of polyphenolic extract of leaves of 
in a dose of 200 mg·kg\(^{-1}\) to carbon tetrachloride and tamoxifen-intoxicated rats produced significant increment in the reduced glutathione levels with significant decrement in malondialdehyde and lever transaminases levels. Histopathological changes of liver sections showed that prophylactic and curative treatments with polyphenolic extract resulted in a relatively good protection against both carbon tetrachloride and tamoxifen intoxicated rats. The extract inhibits CYP monooxygenase aminopyrine-N-demethylase and aniline hydroxylase, suggesting a plausible hepatoprotective mechanism. The normalization of phenobarbitone induced sleeping time suggests the restoration of liver CYP enzymes. The study shows that hepatoprotective effect of polyphenolic extract is by regulating the level of hepatic microsomal drug metabolizing enzymes[29].

In another experiment chloroform and methanol extract of entire part of 
were conducted for their hepatoprotective effect on paracetamol (750 mg·kg\(^{-1}\))-induced acute liver damage on Wistar albino rats. The degree of protection was measured using biochemical parameters such as serum glutamate oxalate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase (ALP), bilirubin and total protein. Chloroform and methanol extracts at a dose of 250 and 500 mg·kg\(^{-1}\) produce significant hepatoprotection by decreasing the activity of serum enzymes and bilirubin but methanol extract at the same dose showed better effect than chloroform extract. The effects of chloroform and methanol extract of the plant were comparable to those of standard drug silymarin[30].

4.3 Antioxidant activity

In vitro antioxidant activity of methanolic extract of roots of 
was performed. Methanolic extract of the plant exhibited strong scavenging effects on 2, 2-diphenyl-2-picryl hydroxyl (DPPH) free radicals, nitric oxide, super oxide anion, hydroxyl radicals and lipid peroxidation with IC\(_{50}\) were (17.4 ± 0.75), (172.8 ± 1.95), (37.4 ± 0.3), (49.2 ± 0.64) and (130.7 ± 2.50) µg·mL\(^{-1}\), respectively[31].

In vitro antioxidant activity of petroleum ether, chloroform, ethyl acetate and alcoholic extracts of flowers and flavanoid isolated from thin layer chromatography from the ethyl acetate extract of flowers of 
was performed. The percentage of free radical scavenging activity by DPPH assay and scavenging capacity for hydroxyl radicals of different extracts and isolated flavanoid were performed. Isolated flavanoid showed more free radicals and hydroxyl radicals scavenging activity with IC\(_{50}\) was 33.89 and 19.83 respectively than different extracts of the flowers of 
[32].

4.4 Analgesic activity

Analgesic effects of 70% alcoholic extract of leaves, stem and roots of 
were performed in Wistar rats of either sex by hot plate and tail immersion methods. Alco-
holic extract of stem at a dose of 500 mg kg\(^{-1}\) showed higher latency of percentage protection (hot plate, 154.12% and tail immersion 221.33%) in comparison with alcoholic extract of leaf (hot plate, 122.42% and tail immersion 195%) and root (hot plate, 138.66% and tail immersion 214.67%)[33].

4.5 Antipyretic activity

Methanolic extract of the roots of \textit{I. frutescens} R. Br. was evaluated for its antipyretic potential on normal body temperature and yeast-induced pyrexia in albino rats. Yeast suspension (10 mg kg\(^{-1}\)) increased rectal temperature 19 h after subcutaneous injection. Methanolic extract of the root of plant at doses of 100, 200 and 300 mg kg\(^{-1}\), p.o. produced significant reduction in normal temperature and yeast induced elevated temperature in a dose-dependent manner. The effect extended up to 5 h after the drug administration. The antipyretic effect of methanolic extract of root of \textit{I. frutescens} was found comparable to that of standard drug paracetamol (150 mg kg\(^{-1}\), p.o.)[34].

4.6 Anti-inflammatory activity

The anti-inflammatory activity of the methanolic extract of the root of \textit{I. frutescens} was evaluated by carrageenan-induced paw edema and cotton pellet-induced granuloma tests to determine its effects on acute and chronic phase of inflammation models in rats. Methanolic extract of the root of \textit{I. frutescens} showed maximum inhibition (54.63%) at a dose of 100 mg kg\(^{-1}\) b.w. after 3 h of drug administration in carrageenan-induced paw edema, whereas indomethacin produced 57.65% of inhibition. In the chronic model 300 mg kg\(^{-1}\) b.w. of methanolic extract like indomethacin and dexamethasone standard drug decreased formation of granuloma tissue by 22.64%, 29.63% and 34.84% respectively[33]. Anti-inflammatory activities of 70% alcoholic extract of leaf, stem and roots of \textit{I. frutescens} were analyzed by carrageenan-induced paw edema. Anti-inflammatory activity of ethanolic extract of stem at a dose of 500 mg kg\(^{-1}\) showed higher percentage of inhibition (29%) at 180 min to reduce inflammation in comparison to leaf and root extract (24% and 25% respectively) at the same dose[33].

4.7 Antidiabetic activity

Antidiabetic activity of aqueous extract of roots of \textit{I. frutescens} was estimated in streptozotocin–nicotinamide-induced type-II diabetic rats. Type-II diabetic rats were administered aqueous root extract (250 and 500 mg kg\(^{-1}\), p.o.) of the plant drug or vehicle (gum acacia solution) or standard drug glibenclamide (0.25 mg kg\(^{-1}\)) for 15 d. Blood samples were collected by retro-orbital puncture and were analyzed for serum glucose level on days 0, 5, 10 and 15 using glucose oxidase-peroxidase reactive strips and glukometer. For oral glucose tolerance tests glucose (2 g kg\(^{-1}\), p.o.) was administered to nondiabetic control rats treated with glibenclamide (10 mg kg\(^{-1}\), p.o.) and aqueous root extract of \textit{I. frutescens}. The serum glucose levels were analyzed at 0, 30, 60 and 120 min. after drug administration. The aqueous root extract of \textit{I. frutescens} (250 and 500 mg kg\(^{-1}\), p.o.) induced significant reduction (\(P < 0.05\)) of fasting blood glucose levels in streptozotocin–nicotinamide-induced type-II diabetic rats on 10th and 15th days. In the oral glucose tolerance test, the extract increased the glucose tolerance[35].

\(\alpha\)-Glucosidase inhibitory activity of alcohol–water extract (AWE) of \textit{Ichnocarpus frutescens} leaves was studied in the rats. AWE exhibited the rat intestinal \(\alpha\)-glucosidase, sucrase, isomaltase, and maltase activities. Sucrose was administered orally with or without extract to rats at a dose of 1000 mg kg\(^{-1}\), p.o. The postprandial elevation in the blood glucose level after the administration of sucrose with the extract was significantly suppressed when compared with the control[36].

Insulin secretagogue effect of \textit{Ichnocarpus frutescens} leaves extract were performed in the glucose-fed diabetic rats and streptozotocin-induced diabetic rats. Methanolic extract of the leaf of \textit{I. frutescens} was tested against different types of glycemia (normal, glucose–fed hyperglycemic and streptozotocin-induced diabetic rats) for their potential to induce insulin secretion and cellular insulin responses. Fasting plasma glucose levels were determined at different doses and times following treatment with methanolic extract of the leaf of \textit{I. frutescens} or with vehicle in normal, glucose-fed hyperglycemic and diabetic rats. Oral administration of the methanolic extract of the leaf of \textit{I. frutescens} led to a significant blood glucose-lowering effect in glucose–fed hyperglycemic and diabetic rats. The hypoglycemic effect was observed at doses of 100 and 200 mg kg\(^{-1}\) after 2 and 6 h administration respectively in glucose–fed hyperglycemic rats. The maximum effect of the methanolic extract of the leaf of \textit{I. frutescens} was detected at 2 h with 200 mg kg\(^{-1}\) in diabetic animals and this profile was maintained for the next 6 h (37.23%) but increased after that at 24 h. Oral administration of the methanolic extract of the leaf of \textit{I. frutescens} daily for 45 d to diabetic rats significantly reduced the fasting plasma glucose (54.5%) to near normal. After 7 d of streptozotocin administration plasma insulin decreased in diabetic controls compared to normal controls. Treatment with the methanolic extract of the leaf of \textit{I. frutescens} significantly prevented the decrease in plasma insulin levels from day 0 to 45 in comparison to diabetic controls. Oral administration of \(n\)-hexane fraction led to a significant glucose-lowering effect in diabetic rats (54.50%). Histopathological examination showed that methanolic extract of the leaf of \textit{I. frutescens} extract protected the pancreatic tissue from streptozotocin-induced damage enormously. Oral administration of methanolic extract and \(n\)-hexane extract of the leaf of \textit{I. frutescens} to normal and streptozotocin-induced diabetic rats decreased plasma glucose levels without hypoglycemic effect[37].

The effects of polyphenol extract of \textit{I. frutescens} in the progression of nephropathy due to oxidative stress in streptozotocin-induced diabetic rats were studied. Intraperitoneal...
glucose tolerance test revealed a significant decrease in blood glucose levels at 180 min after glucose loading in rats fed with polyphenol extract of *I. frutescens*. During the eight weeks of experimental period, diabetic rats exhibited wide range of symptoms, including loss of body weight, hyperglycemia, polyuria, proteinuria, renal enlargement, and total renal dysfunction. A significant increase in TBARS (Thio-Barbituric acid reactive substances) level was observed in diabetic kidney, which was accompanied by a significant decrease in enzymatic and non-enzymatic antioxidant levels.

After eight weeks, polyphenol extract of *I. frutescens* treated groups showed a lower level of blood glucose compared with non-treated streptozotocin-induced diabetic rats. The increases in urinary albumin and protein after eight weeks of treatment were significantly inhibited by prolonged treatment with polyphenol extract of *I. frutescens*. In addition, polyphenol extract of *I. frutescens* attenuates the adverse effects on hepatic biomarkers\[38\].

4.8 Antihyperlipidemic activity

Antihyperlipidemic effects of the polyphenolic extract of *I. frutescens* leaves was evaluated in alloxan-induced diabetic rats. Diabetes was induced by single intraperitoneal injection of alloxan (150 mg·kg\(^{-1}\)). Administration of polyphenolic extract of the plant (300 mg·kg\(^{-1}\) for 21 d) showed significant decrease in hepatic HMG-CoA reductase activity of alloxan diabetic rats. No significant effects were found in the normoglycemic rats. Polyphenolic extract exhibited significant hypolipidemic effect as evident from correction of hyperlipidemic indicators (TC, TGs, VLDL, HDL and LDL). Oral administration of polyphenolic extract (100 mg·kg\(^{-1}\)) significantly enhanced the release of lipoprotein lipase enzyme significantly. The histopathological studies of aorta in polyphenolic extract treated alloxan-rats revealed almost recovery with polyphenol extract of *I. frutescens*.

4.9 Antitumor activity

*In vivo* antitumor activity of polyphenolic extract of leaves of *I. frutescens* was evaluated on Murine Ehrlich Ascites Carcinoma (EAC) model. *In vitro* cytotoxicity study was performed in monocytes leukemia (U-937) and erythroleukemia (K-562) cell lines. *In vivo* study showed a significant decrease in tumor volume, viable tumor cell count and a significant increase in life span of the polyphenolic extract treated group compared to the untreated one. The life span of polyphenolic extract treated animals increased by 53.41% (50 mg·kg\(^{-1}\)) and 73.95% (100 mg·kg\(^{-1}\)). The result was found comparable with standard drug 5-fluorouracil (86.97%) at a dose of 20 mg·kg\(^{-1}\). *In vitro* study indicates that polyphenolic extract of the leaves of the plant at doses of 5, 10 and 20 µg·mL\(^{-1}\) effectively inhibits proliferation of U-937 and K-562 cell lines and result was found comparable with standard drug cytarabine arabinoside at a dose of 20 µg·mL\(^{-1}\)[39-41].

5 Conclusion

The phytochemical investigations of *I. frutescens* reveal the occurrence of 28 chemical compounds belong to phytosterol, triterpenes, flavonoids and other phenolics. Out of 28 compounds only one compound ursolic acid was reported from the root of the plant. Extracts and fractions of the plant possess antiurolithiatic, hepatoprotective, antioxidant, analgesic, antipyretic, anti-inflammatory, antidiabetic, antihyperlipidemic and antitumor activity. Pharmacological investigations of the plant reveal that no biological activity has been reported for isolated compound.

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References


