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ICHNOCARPUS FRUTESCENS: A VALUABLE MEDICINAL PLANT

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Abstract

Ichnocarpus frutescens R. Br (Family: Apocyanaceae) is an evergreen medicinal herb found almost throughout Asia and other regions. The whole part of Ichnocarpus was (root, flowers and leaves) reported to use for various medical illness such as, demulcent, syphilis, loss of sensation and hemiplegia, headaches fevers, wounds between fingers tonic, diaphoretic, diuretic, dyspepsia and skin troubles. It is mainly administered with milk for diabetes mellitus, excretion of the stone in the bladder and purification of blood. Phytochemical studies on the various parts of Ichnocarpus have revealed the presence of phenylpropanoids, phenolic acids, carbohydrates, saponins, proteins, aminoacids, coumarines, alkaloids, flavonoids, sterols and pentacyclic triterpenoids. Pharmacological investigations have demonstrated that Ichnocarpus possess antiinflammatory, analgesic, antipyretic, membrane stabilizer, wound healing, anticancer, hepatoprotective, antiurolithiatic, antimicrobial, antidiabetic, cardioprotective, antioxidant, antihyperlipidemic and cytoprotective activities. The major aim of this paper is to review the complete ethnoboanical, ethnomedical, ethnopharmacological, phytochemical, toxicological and pharmacological studies of various parts of Ichnocarpus frutescens.

Keywords: Ichnocarpus frutescens, pharmacognosy, ethnopharmacology, toxicology, pharmacology, phytochemicals, flavonoids,

Introduction

Ichnocarpus frutescens R. Br (Family: Apocyanaceae) is commonly known as 'black creeper'. It is an evergreen and climbing shrub (large much branched twining shrub; young branches are finely fulvous-tomentose) with slender branches, laticiferous, woody creeper with rusty red appearance. It is mainly distributed throughout India, Malaysia, Australia,China and Thailand in the plains and lower hills up to 4000 m. Leaves are opposite, elliptic-oblong to broadly lanceolate, entire, acute or acuminate, base usually rounded, base attenuate, glabrous above, pubescent beneath, lateral nerves 4-6 pairs, coriaceous, pubescent when young; flowers are fragrant, greenish white or purplish. Seeds are long, linear, black, not beaked, coma as long as the seed, scanty and white. Three species occur in Asian regions. The root was reported to be medicinally useful and they are used in medicine as a substitute for Indian *sarsaparilla* and often are mixed with the later, though neither their therapeutic properties for their suitability for use as a sarsaparilla substitute have been already established. Probably, because of the rust colored stems, this climber earned the name as "black creeper".

Botanical description and scientific classification

Kingdom: *Plantae*
Binomial name*: Ichnocarpus frutescens* R. Br.
Botanical name: *Ichnocarpus frutescens*
Family: *Apocynaceae (Oleander family)*
Genus: *Ichnocarpus*
Order: *Gentianales*
Common name: *Black Creeper*
Synonyms: *Apocynum frutescens, Echites frutescens, Quirivelia frutescens*

Ethno-medical uses

The complete ethno-medical uses of *Ichnocarpus* have been summarized in Table 1. Leaves are boiled in oil and applied to headaches, fevers and wounds between the fingers [1-3]. The seeds are used for the treatment of rheumatism. The stem and leaves are used for acute urticaria. The roots are sweet, refrigerant, febrifuge, aphrodisiac, diaphoretics, diuretic, depurative, demulcent and tonic in anorexia, leucorrhoea. They are useful in different conditions of pitta, burning sensation, hyperdipsia, leucorrhoea, syphilis, fever, seminal weakness, nephrolithiasis, skin diseases, leprosy, pruritus, dyspepsia, vomiting, diabetes, cephalagia and general weakness [4]. Various parts of *Ichnocarpus* are used in night blindness, bleeding of gums, enlargement of spleen, rheumatism, asthma, cholera, fever, atrophy, smallpox, ulcer, dysentery, snake bite, dysentery, hematuria, cough, asthma, abdominal and glandular tumors [5,6]. The root portion of this plant was much more used in traditional as well as in the modern era. *Ichnocarpus* have been used as folk medicine and as an ingredient in Ayurvedic and Unani preparations against various diseases. A decoction of the roots of *Colocynth*, *Anantamul*, *Sariva* and *Hedyotis biflora* prepared in the usual way is administered with the addition of powdered long pepper and bdellium in chronic skin diseases, syphilis, loss of sensation and hemiplegia [7].

Pharmacognosy

Pharmacognostical studies and determination of different phytochemical parameters are very much essential for the standardization of drug and establishing its pharmacological efficacy. For the purpose of quality control, assessment of purity and identification of any sample, standardization is very much essential [8]. Therefore, it has become extremely important to make an effort towards quality control and standardization of the plant material to be used as medicine. Another study was investigated the transverse section of the mature root shows thick walled cork cells with reddish content followed by secondary cortex [9]. Microscopical evaluation of root powder showed yellowish brown color with fragmented vessels, trachieds and lignified fibers. Fibers were shown with tapering ends, vessels with simple pits on their walls. Numerous starch grains, cork cells with reddish brown content and a few bundles of acicular crystals also observed. The total ash value, acid insoluble ash value and water soluble ash value were found to be 4%, 1 % and 0.6%, respectively. Cortex cells were simple and few of them contain latex like substance. Secondary phloem is narrow zone and also contains laticiferous cells and phloem fibers. Secondary xylem was a wide zone made up of xylem parenchyma, isolated vessels and uniseriate medullary rays (Fig 1). Further *Ichnocarpus* was investigated to gather information for the systematic identification, authentication and pharmacognostic standardization of the aerial parts (stem and leaves) as per WHO guideline [10]. The result obtained in the present investigation could be useful for the industry to identify, authenticate and quality analysis of commercial samples received from various herbal suppliers. The data of the study will be used for making monograph on this plant for different pharmacopoeias and official books. Since the whole

plant of *Ichnocarpus* has therapeutic qualities, the present investigation has laid down a set of anatomical features of the root and stem which can be employed for its botanical diagnosis. The stem has a thin, superficial, continuous periderm, and parenchymatous showed narrow zone of the cortex. The vascular cylinder consists of outer continuous cylinder of normal secondary phloem and inner discrete strands of medullary phloem or intra-xylary phloem. Secondary xylem is characteristic in that it consists of four or five concentric rings of wide vessels. Each ring representing a growth ring. Abundant tannin content, starch grains and prismatic calcium oxalate crystals are the cell inclusions found in the parenchyma cells [11].

Phytochemistry

Preliminary phytochemical examination of various extracts of *Ichnocarpus* revealed presence of polyphenols, terpenoids, alkaloids, phytosterols, carbohydrates, coumarins, glycosides, flavonoids, while, saponins, anthroquinones and steroids were absent [12, 13]. Additional exploration on the stem part of *Ichnocarpus* has demonstrated presence five compounds and identified as n-butyl oleate (1), n-octyl tetracontane (2), tetratriacontadiene (3), n-nonadecanyl benzoate (4), and benzocosanyl arachidate (5) [14]. Earlier, research on *Ichnocarpus* led to the isolation *of* α-L-sarbopyranoside (6), 6,8, 8, trimethylpentacosan-7-one (7), α-L-rhamnopyranosyl-(1→4)-β-D-glucopyranosyl-(1→3)-α-amyrin (8), α-amyrin (9) and its acetates (10), lupeol and its acetates (11, 12), friedelin (13), epi-friedelinol (14), oleanolic acid (15) and β-sitosterol (16) from its stems[15-17]. Its leaf mainly contain simple phenolic acid flavones and glycoflavones such as sinapic acid (17), protocatechuic acid (18), ferulic acid (19), caffeic acid (20), apigenin (21), vanillic acid (22), syringic acid (23), luteolin (24), ursolic acid and its acetate (25, 26), kaemferol (27), kaemferol-3-galactoside (trifolin) (28) and mannitol (29) and its flowers contain quercetin (30) and quercetin-3-O-β-D-glucopyranoside (31) [5, 18-19]. Systematic fractionation of an ethyl acetate portion of the methanol extract of defatted roots of *Ichnocarpus* led to the isolation of triterpene acid, ursolic acid (25). *Ichnocarpus* has been already reviewed for some aspects of ethnomedical, pharmacological and other flavonoid constitents of *Ichnocarpus* vitexin (32), isovitexin (33) and proanthocyanidin (34) [20-24].

Elemental analysis

The leaves, stems and roots of *Ichnocarpus* were investigated for the metal and mineral content by using energy dispersive X-Ray spectroscopy (EDX). The sample for EDX experiment was prepared by fixing *Ichnocarpus* powder on copper specimen stubs, sticky carbon tape followed by coating with gold sputter coater. Elemental analysis was performed on eleven elements (C, O, Mg, Al, Si, Cl, K, Ca, Fe, Cu, and Zn).The analysis of EDX showed that root possesses all the tested elements. However, leaf was found deficient in Fe and Al and stem deficient in Mg. The percentage of essential element was higher in root as compared to leaf and stem [25].

Pharmacology

Antimicrobial activity

The rising incidence of multidrug resistance amongst pathogenic microbes has further necessitated the need to search for newer antibiotic sources [26-27]. Another study on chloroform and aqueous extracts of *Ichnocarpus* roots were carried out to evaluate their antimicrobial activity. The chloroform extract showed highest antimicrobial and antifungal activities against *Eschericia coli* and *Aspergillus falvus* respectively. With the increasing concentration of the extract a corresponding increase in diameter of inhibition zone was observed [28].

Wound healing activity

Cutaneous injury is characterised by fibroplasia, angiogenesis and re-epithelisation and involves the migration and proliferation of cells such as fibroblasts, endothelial cells and epithelial cells, deposition of connective tissue and contraction of the wound [29]. The methanol extract of *Ichnocarpus* roots was investigated for wound healing activity in different experimental models of wounds in rats [30]. The methanol extract in the form of an ointment with two different concentrations (1 % and 2 % w/w ointment of root extract in a simple ointment base) was evaluated for wound healing potential in an excision wound and incision wound mode. The ointment formulations showed significant responses in both types of experimental wounds. The significant wound healing effect was produced by formulations, in terms of wound contracting ability, wound closure time, regeneration of tissues at wound site, tensile strength of the wound and histopathological characteristics were comparable to framycetin sulphate cream.

Hepatoprotective activity

Liver diseases, such as jaundice, cirrhosis and fatty

liver have become one of the major causes of morbidity and mortality worldwide [31]. It has been reported that 160 phytoconstituents from 101 plants have hepatoprotective activity [32]. The hepatoprotective effect of chloroform extract of whole plant was investigated against by paracetamol (750 mg/kg) induced liver damage in Wistar rats [33]. The degree of protection was measured by using biochemical parameters such as serum glutamate oxalate transaminase and serum glutamate pyruvate transaminase, alkaline phosphatase, bilirubin and total protein. Both extracts at 250 and 500 mg/kg were produced significant ($P<0.05$) hepatoprotection by decreasing the activity of serum enzymes and bilirubin, in a dose dependent manner. Subsequently, another study was investigated prophylactic and curative hepatoprotective effect of *Ichnocarpus* against carbon tetrachloride and tamoxifen induced liver damage in rats. Carbon tetrachloride and tamoxifen caused liver damage in rats caused by a significant rise in serum enzyme levels. Both treatments with polyphenol extract generally resulted in a good liver protection against carbon tetrachloride and tamoxifen intoxicated rats. The extract also inhibited CYP450 monoxygenases aminopyrine-N-demethylase and aniline hydroxylase, suggesting a plausible hepatoprotective mechanism. The normalization of phenobarbitone induced sleeping time suggests the restoration of liver CYP450 enzymes [34].

Anti-inflammatory, analgesic and antipyretic activities

Plants have yielded many widely used drugs and the current treatment of inflammatory conditions as well as infectious diseases relies heavily on natural products [35]. It is believed that current non-steroidal anti-inflammatory drugs are not useful in all cases, because of side effects. As a result, a search for other alternatives seems necessary and beneficial. The study of plants that have been traditionally used for inflammation is still fruitful and logical research strategy in the source of new anti-inflammatory drugs. The hydro-alcoholic extract of the leaves were investigated in various *in vivo* (carrageenan, dextran induced paw edema, cotton pellet granuloma assay) and *in vitro* (inhibition of protein denaturation and protease activity) anti-inflammatory models. Hydro-alcoholic extract showed dose dependent anti-inflammatory activity with maximum of 33.10 %, 30.13 % and 39.85 % in carrageenan, dextran induced paw edema and cotton pellet granuloma in rats, at 300 mg/kg body wt. Different concentrations of hydro-alcoholic extract (50-250 µg/ml) also showed ability to inhibit protease activity and denaturation of proteins [36].

Anti-inflammatory activity of 70% alcohol extract of leaf, stem and roots was analyzed by carageenan-induced paw edema. Anti-inflammatory activity of ethanol extract of stem at 500 mg/kg showed higher percentage of inhibition (29%) at 180 min when compared to leaf and root extract (24% and 25%, respectively). Further, anti-inflammatory activity of methanol extract of root was assessed by carrageenan and cotton pellet induced granuloma tests to determine its effects on acute and chronic phase of inflammation models in rats, respectively. The maximum inhibition (54.63 %) was obtained at the dose of 100 mg/kg after 3 hours of drug treatment in carrageenan induced acute rat paw edema model. In the chronic model, 300 mg/kg of methanol extract decreased formation of granuloma tissue by 22.64 %. These results were clearly indicated its strong antiinflammatory property [37].

More studies were undertaken to evaluate the topical preparation of methanol extracts of root for its analgesic and anti-inflammatory activities. Four different concentrations of the root extract were made into a topical preparation i.e. IF 1%, IF 2%, IF 4% and IF 6% with the help of a cream base containing cetyl alcohol, white petrolatum, mineral oil, carbapol, tween 80, water and propylene glycol. All the four formulations along with cream base were screened for their analgesic and anti-inflammatory activities using formalin induced paw licking test and carrageenan induce paw edema models, respectively. In analgesic activity, the IF 6 % has shown a significant analgesic effect by decreasing the number of paw lickings in formalin induced rat paw licking test. In anti-inflammatory activity of IF 1%, IF 2% have shown slight inhibition and IF 4%, IF 6% have shown significant inhibition of carrageenan induced rat paw edema [37-39]. In addition, the methanol extract was evaluated for its anti-pyretic potential on normal body temperature and yeast-induced pyrexia in albino rats. Yeast suspension (10 ml/kg body wt, sc) increased the rectal temperature after 19 hrs injection. The methanol extract, at 100, 200, and 300 mg/kg body wt (po), produced significant reduction in normal body temperature and yeast-provoked elevated temperature in a dose dependent manner. It was identified that antipyretic activity of root extract may be due to the presence of β-sitosterol and other triterpenoids present in *Ichnocarpus* [40].

Anti-urolithiatic activity

Urinary stone disease is a common disorder estimated to occur in approximately 12% of the population, with a recurrence rate of 70-81% in males, and 47-60% in females. The anti-urolithiatic effect of ethyl acetate root extract was performed in nephrolithiasis induced rats by feeding with ethylene glycol water (0.75%) for 28 days. Ethylene glycol feeding resulted in hyperoxaluria as well as increased renal excretion of calcium and phosphate. Supplementation with ethylacetate extract significantly reduced the elevated urinary oxalate, showing a regulatory action on endogenous oxalate synthesis. The increased deposition of stone forming constituents in the kidneys of calculogenic rats was also significantly lowered by the extract treated groups. Treatment of *Ichnocarpus* restores phosphate level, thus reducing the risk of stone formation [41].

Anti-tumor activity

The polyphenol extract of leaves was evaluated for antitumor activity *in vivo* using murine Ehrlich ascites carcinoma (EAC) model. The *in vitro* cytotoxicity was also determined *in* U-937 monocytoid leukemia and K-562 erythroleukemia cell lines. A significant decrease in tumor volume, viable tumor cell count and a significant increase of life span in the polyphenol extract treated group compared to untreated one: the life span of polyphenol extract treated animals also increased by 53.41% (50 mg/kg) and 73.95% (100 mg/kg). Hematological studies have revealed that at 100 m/kg has restored WBC differential count, Hb and RBC content close to normal levels. Polyphenol extract (5, 10 and 20 µg/ml) effectively inhibited *in vitro* proliferation of U-937 and K-562 cell lines. The study revealed that polyphenol extract displayed strong anti-tumor activity on both *in vitro* and *in vivo* models [42]. The chloroform and methanol extracts of whole plant were further explored experimentally for the possible antitumor activity in the mice transplanted with EAC. Both extracts were administered at 150 and 300 mg/kg body wt (ip) for 7 days after 24 h of tumor inoculation in mice. Treatment with chloroform extract at 150 and 300 mg/kg remarkably decreased the tumor volume, packed cell volume, viable cell count and increased the nonviable cell count of EAC tumor bearing mice when compared with the same dose of methanol extract [43].

In another experiment, the *in vitro* anticancer activity was performed by MTT assay using various human cancer cell lines such as, MCF-7 (Human breast cancer cell line), BEL-7402 (Human hepatocellular carcinoma cell line), SPC-A-1 (Human lung cancer cell line) and SGC-7901 (Human gastric cancer cell line). The methanol extract of roots of *Ichnocarpus* showed significant anticancer activity on four cancer cell lines with IC_{50} values 163.5±3.58, 156.3±2.95, 142.6±2.60 and 112.4±1.85, respectively. The IC_{50} of ursolic acid and α-amyrin were approximately of a similar order to their concentration in the methanol extract. These results indicated that the anticancer activity of the methanol extract may be due to the presence of these ursolic acid and α-amyrin triterpenes. In addition, these authors have already been reviewed the literature data on the phytochemical and biological properties of *Ichnocarpus* till 2011 [44].

Acute toxicity study

Acute oral toxicity study was performed as per the OECD guidelines on albino rats of either sex. The animals were administered with *Ichnocarpus* at 5 mg/kg body wt by (po) and continuously observed for 14 days. After administration of polyphenol extract, the rats were immediately observed for 2 h for behavioral, neurological and autonomic profiles for any changes or lethality for the next 48 h. The results from the study revealed the non-toxic nature of the polyphenol extract followed by clinical observation. There was no lethality or any toxic reactions were found at any of the doses selected until the end of the study period. According to the OECD guidelines for acute oral toxicity, an LD50 at a dose of 2000 mg/kg and above was characterized as unclassified and hence *Ichnocarpus* was found to be safe [45]. On subsequent studies, the purified ethylacetate extract was subjected for the acute toxicity study to determine the therapeutic dose using albino mice in a controlled environment. No deviation from normal behavior pattern was observed. But only a few animals showed mild behavioral changes like dyspnoea and mild writhing in higher doses. Observation was done continuously for 14 days and no mortality was observed in any of the dose treated. Hence, *Ichnocarpus* was practically nontoxic in normal mice and fall under the category of class V drug [46].

Androgenic and cytoprotective activities

Oral administration of *Ichnocarpus* (10 mg/kg) to male Wistar rats resulted a significant changes in testicular function was confirmed with the deviations in the levels of reproductive hormones and semen parameters. The reproductive hormones studied were testosterone, FSH and LH, while the semen

parameters were sperm count, sperm motility, sperm morphology, sperm debris and primordial sperm count. The increase in sperm density and motility in cauda epididymis is of importance with regard to fertilization. Therefore, the aqueous extracts of root and rhizome were causing an androgen stimulatory effect on the testes, beneficial alterations in the motility, morphology and metabolism of the spermatozoa in male rats. The increase in the cauda epididymal sperm motility might be due to an alteration in the microenvironment in the cauda epididymis of the treated rats may be as a result of the androgen-stimulatory effect with increased level of testosterone production. The mechanism of cytoprotective activity of aqueous extract may involve the inhibition of free radical production along with enhancement of the body defense system [47].

Antidiabetic effects

Effect on oral and intraperitoneal glucose tolerance tests

The total polyphenol extract of the leaf was tested for its oral glucose tolerance test. At 60 min after glucose load serum glucose levels were gradually increased and reached a peak at 120 min, two doses of polyphenol extract produced significant reduction in blood glucose levels as compared to the vehicle. In the OGTT test, at 60 min the maximum decrease of blood glucose was observed with 200 mg/kg. In IPGTT test, a significant decrease in blood glucose levels was noted at 180 min after glucose loading in Wistar albino rats fed with polyphenol extract [45].

Effect on alloxan induced diabetes

Another experimental study was carried out to evaluate the antidiabetic and antihyperlipidemic effects of the polyphenol extract in alloxan induced diabetic rats. Diabetes was induced by single injection of alloxan (150 mg/kg body wt, ip) and polyphenol extract to diabetic rats at 150 and 300 mg/kg body wt resulted in a significant reduction of fasting blood glucose (FBG) levels. Based upon the data reported from the study that the polyphenol fraction may have a significant antidiabetic effect [44].

Effect on streptozotocin-nicotinamide induced diabetes

Additional studies on hypoglycemic activity was confirmed in streptozotocin induced (n-STZ) neonatal diabetic rats for six weeks. Two day old neonatal (pups) rats were rendered diabetic by single injection of STZ (90 mg/kg body wt, ip). A marked rise was observed in the levels of FBG (230.33 mg/dL) in STZ treated diabetic rats. Oral administration of polyphenol extract (150 and 300 mg/kg body wt, po) decreased FBG levels significantly to 187.66 and 170.50 mg/dL, respectively in STZ treated diabetic rats. Finally, it was concluded that polyphenol extracts shown antihyperglycemic activity in STZ (n-STZ) induced experimental diabetes [48]. A similar study was performed to evaluate the antidiabetic activity of root aqueous extract in STZ-nicotinamide induced type-II diabetic rats. STZ-nicotinamide induced type-II diabetic rats were treated with two different doses of aqueous root extract for 15 days. The serum glucose levels were analyzed at 0, 30, 60, and 120 min after drug administration. The aqueous root extract exhibited significant reduction ($P < 0.05$) on fasting blood glucose levels in STZ-nicotinamide induced type-II diabetic rats on the 10th and 15th days. From the study it was reported that *Ichnocarpus* has significant antidiabetic activity as it lowers the FBG level in diabetic rats [49]. On following studies, oral administration of polyphenol extract in graded doses caused a significant reduction of FBG levels in type II diabetic rats. The effect of polyphenol extract on liver glycolytic enzymes showed a significant increase in their levels, whereas a significant decrease was observed in the levels of gluconeogenic enzymes. The investigation proposed that, antidiabetic effect on diabetic rats was mediated through modulation of hepatic carbohydrate metabolizing enzymes. It also clarified the basis for its traditional use by tribal community of southern India.

Insulin secretagogue effect

Various extracts of *Ichnocarpus* leaves were tested for its insulin secretagogue effect against STZ-induced diabetic rats. The treatment with the methanol extract showed significant plasma glucose lowering effect and it was further tested against different types of glycemia (normal, glucose-fed hyperglycemia and STZ-induced diabetic rats) for their potential to induce insulin secretion and cellular insulin responses. The hypoglycemic effect was observed at 100 and 200 mg/kg after 6 and 2 hour administration, respectively, in the glucose-fed hyperglycemic rats. Oral administration of methanol extract and n-hexane fraction to normal and STZ-induced diabetic rats was decreased plasma glucose levels without any significant hypoglycemic effect. The final results were suggested that *Ichnocarups* may provide new therapeutic avenues against

diabetes mellitus [50].

Effect on diabetic complications

Diabetic nephropathy is one of the major complications of diabetes. This particular study was performed to examine whether the prolonged oral administration of polyphenol extract could prevent the progress or improve the outcome of diabetic nephropathy in STZ diabetic rats. During the eight weeks of the experimental period, diabetic rats exhibited a wide range of neurotic symptoms, including loss of body weight, hyperglycemia, polyuria, proteinuria, renal enlargement, and total renal dysfunction. After eight weeks, polyphenol extract treated groups showed a lower level of blood glucose compared with non-treated STZ diabetic rats. The increases in urinary albumin and protein after eight weeks of treatment were significantly inhibited by prolonged treatment. It was also found that it effectively protects the eyes against aldose reductase activity and protein damage. This specific action might be due to its enriched polyphenol content. Polyphenol administrations in diabetic rats were clearly ameliorated diabetic complications induced by chronic STZ treatment [45].

α-glucosidase inhibitory activity

The hydro-alcohol extract was tested for its α-glucosidase inhibitory activity using crude rat intestinal α-glucosidase enzyme. Hydro-alcohol extract was exhibited significant *in vitro* rat intestinal α-glucosidase, sucrase, isomaltase, and maltase inhibitory activities. Sucrose was administered orally with or without extract to rats at 1000 mg/kg. The postprandial elevation of blood glucose level after the administration of sucrose with extract was significantly suppressed [51].

Anti-hyperlipidemic activity

Natural remedies from medicinal plants are considered to be effective and safe alternative treatments for diabetes mellitus. A preclinical experiment was designed to evaluate antihyperlipidemic effect of polyphenolic extract in alloxan induced diabetic rats. Diabetes was induced by single intraperitoneal injection of alloxan (150 mg/kg body wt). Polyphenol extract (300 mg/kg body wt for 21 days) administration showed significant decrease in hepatic HMG-CoA reductase activity. It also exhibited significant hypolipidemic effect as evident from the correction of hyperlipidemia indicators (such as, TC, TGs, VLDL, HDL and LDL). Oral ad-ministration at 100 mg/kg significantly enhanced the release of lipoprotein lipase enzyme. It also prevented ADP-induced platelet aggregation in vitro models. All the results were revealed the therapeutic potential of polyphenol extract against hyperlipidemia and atherosclerosis leading diabetic complications and cardiovascular risks [44]. The crude methanol extract and its fractions were further investigated for antihyperlipidemic effect using triton WR-1339 and high-fat diet induced obesity in rats. The methanol extract reduced the total cholesterol by 29.63% and triglyceride by 51.10% at 400 mg/kg in triton WR-1339-induced animals and reduced TC (27.81%) and TGs (37.03%) at 400 mg/kg significantly in high fat fed animals. The observed properties were apparently validating the folk medicinal use of this plant in amelioration of hyperlipidemia [52].

Antioxidant activities

Effect on in vitro free radicals

The successive methanol extract of root exhibited strong free radical scavenging effect against DPPH, hydroxyl, nitric oxide, super oxide free radicals as well as inhibition of in vitro lipid peroxidation process. These results were clearly indicating the strong antioxidant properties of *Ichnocarpus* [53]. The total hydro-alcohol extract were also analyzed and compared with reference antioxidants (a-tocopherol and BHT) for its *in vitro* antioxidant property. It was found to be significantly effective in scavenging DPPH (IC_{50} 194.06 µg/ml) and hydroxyl radicals (163.13µg/ml). The antioxidant activity enhanced with increasing concentration of extracts (50-250 µg/ml). It showed different levels of free radical scavenging activities in various *in vitro* antioxidant models [35]. Literature survey revealed that various parts of *Ichnocarpus* were known for its different flavonoids content. Hence the various extracts, fractions and its isolated flavonoids were screened for the antioxidant property using standard DPPH and hydroxyl radicals scavenging assays. The ethylacetate fraction showed remarkable and concentration dependent antioxidant activity than other fractions and extracts [54]. Nevertheless, these extracts showed significant inhibitory activities in all *in vitro* reactive oxygen species, might be attributed due to the high level of polyphenols. These findings provided evidence that *Ichnocarpus* is a natural source of antioxidant against oxidative damage [55-56].

The methanol extract of *Ichnocarpus* was further studied for its *in vitro* antioxidant and membrane stabilizing properties using various in vitro models. The extract of *Ichnocarpus* at a concentration range

of 0.50-2.0 mg/ml significantly protected the rat erythrocyte membrane against lysis induced by hypotonic solution. The methlanol extract showed significant antioxidant activities in all the tested assays (DPPH, nitrix oxide, hydrogen peroxide, reducing power and total antioxidant assay) in a dose dependent manner. The extracts displayed notable activities in reactive oxygen species (ROS) scavenging which could be attributed due its high phenolic content of *Ichnocarpus*. Moreover, extract showed strong reducing power and suppressed lipid peroxidation process. From this study concluded that suppression of lipid peroxidation and free radical scavenging nature of *Ichnocarpus* would be the probable mechanism of the stabilization of the RBC membrane.

Effect on in vivo antioxidant systems

The chloroform and methanol extracts of whole plant were investigated for its antioxidant activity in mice transplanted with EAC. Both extracts were administered at 150 and 300 mg/kg, body wt (ip) for 7 days after 24 hr of tumor inoculation in Swiss albino mice. Further, the tumor mice treated with extracts were revealed significant decrease in the levels of lipidperoxidation and increase in the levels of antioxidant enzymes [32, 42]. In addition, the aqueous root extract was studied for antioxidant against cisplatin (10 mg/kg, po) induced testicular toxicity in rodents. Cisplatin administration increased the amount of free radicals and caused the decrease in endogenous antioxidant levels. The treatment with an aqueous root extract significantly reduced ($P<0.01$) the elevated levels of lipidperoxidation towards normal in a dose dependent manner. Similarly, catalase and GSH levels were significantly restored ($P<0.01$) in all the test drug treated groups to near normal. From this study it was established that *Ichnocarpus* shown cytoprotection might due to its effect against free radical production in testicular cells [42].

In another study, a significant increase was observed in the LPO levels of liver tissue after CCl4 administration. Oral prophylactic and curative treatment with polyphenol extract prevented the progression of CCl4 induced chronic liver injury and lipid peroxidation and level of reduced glutathione was also recouped at 200 mg/kg. Administration of tamoxifen (45 mg/kg body wt (ip) for 7 days) caused a significant increase of LPO with reduced GSH levels. Oral treatment with polyphenol extract significantly ($P<0.01$) prevented the elevated liver LPO levels and increased the GSH levels [34]. Subsequently, another study was carried out for its antioxidant effects on paracetamol (750 mg/kg) induced acute liver damage in Wistar albino rats. It showed significant ($P<0.05$) hepatoprotection by decreasing the LPO process, while they significantly increased the levels of *in vivo* antioxidants in a dose dependent manner. The author was concluded that *Ichnocarpus* possesses noteworthy antioxidant activity in paracetamol induced oxidative stress [32]. Streptozotocin caused diabetes by the rapid depletion of β-cells and thereby brings about a reduction in insulin release and leads to hyperglycemia. Hyperglycemia causes oxidative damage by the generation of reactive oxygen species and results in the development of diabetic complications. Another experiment on antioxidant effect was carried out in STZ induced (n-STZ) neonatal diabetic rats for six weeks with the special aim to study on oxidative stress in experimental diabetes. Polyphenol extract showed promising effects ($P <0.01$) on reducing tissue antioxidant levels, with extreme ($P<0.01$) reduction of elevated LPO levels. These results were suggested that polyphenol enriched extract could be potentially useful for oxidative stress management to correct the hyperglycemia and diabetic state [48].

Further study was investigated the cardioprotective effect of *Ichnocarpu*s against isoproterenol induced induced myocardial infarction [57]. Isoproterenol causes marked decrease in the levels of antioxidant enzymes and increase in the levels of cardiac marker enzymes and lipid peroxidation. Its ability to ameliorate the lipid peroxidation through the free radical scavenging activity, and also causes a decrease in the levels of cardiac marker enzymes and increase in anti-oxidant activity in a dose dependent manner. *Ichnocarpus* at a dose of 400 mg/kg produced significant decrease in cardiac marker enzymes such as, lactate dehydrogenase, creatinine kinase and an increase in antioxidant enzyme levels when compared to isoproterenol induced cardiotoxic rats. From the study, it was concluded that, the cardioprotective effect could be due to its free radical scavenging property of phenolic compounds and flavonoids.

Conclusion

Ichnocarpus frutescens has already been demonstrated as an effective ethno- medical option in a variety of medical conditions such as, diabetes mellitus, fever, inflammation, wounds, kidney stones, glandular tumors, snake bite and liver disorders. Pharmacological investigations have confirmed its anti-diabetic, hepatoprotective, anti-hyperlipidemic, anti-inflammatory, antipyretic, anti-microbial, wound

healing, antioxidant and anticancer activities. Various plant secondary metabolites such as flavonoids, polyphenols, phenolic acid, phenylpropanoids, flavonoid glycosides, saponins and terpenoids have been reported in different parts of *Ichnocarpus*, which are known to demonstrate different pharmacological activities due to a variety of structural features. Among those secondary metabolites, polyphenols and terpenoids are the most frequently occurring metabolites in *Ichnocarpus*. There is not enough scientific information either on the active secondary metabolites or the toxic nature of this plant; therefore extensive toxicological research is warranted to establish the toxicity of *Ichnocarpus*. The outcome of such future phytochemical, pharmacological and toxicological investigations reveal promising source of potent secondary metabolites that would have great value for pharmaceutical industries. Although we presented here an extensive literature survey on *Ichnocarpus*, this review has certain limitations such as the use of non-indexed scientific literature published online that lacks the scientific data authentication. In conclusion**,** further studies on the mechanism of action of *Ichnocarpus,* especially, the pathway specific target studies using novel *in vitro* h*igh-throughput screening,* cellular and molecular biology techniques, should be explored in order to establish the therapeutic claims. For exploring the full potential of *Ichnocarpus,* scientific research community should draw their attention in performing more investigation, *in vitro* or *in vivo* animal models that may eventually lead to clinical trials on human.

Conflict of interest statement

We declare that we have no conflict of interest.

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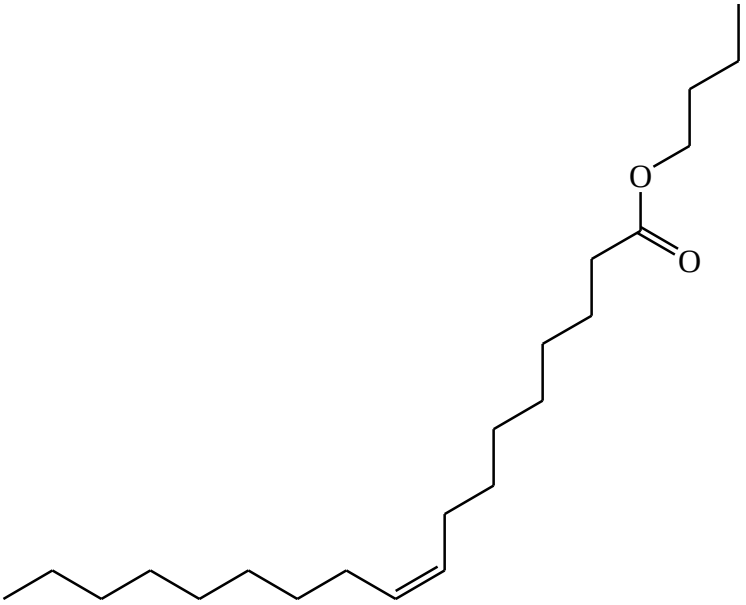
Table 1: Ethno-medical uses of different parts of *Ichnocarpus frutescens*

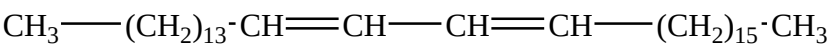
Parts used	Ethno-medical uses
Root	Root juice is used internally in the treatment of anemia and kidney stone [58].
Whole plant	Rheumatism, blood purifier,asthma, cough, bronchitis, bone fracture, cholera,constipation, dysentery, fever, nigh blindness, measles, ulcer, vomiting tonic, febrifuge, leucoderma [6].
oot and leaves	Root extract used for vomiting; leaves extract for stomach pain [59].
Root	Roots made into powder and taken with milk 2-3 times a day for diabetes mellitus [60, 61].
Root and Tuber	Root decoction is taken orally, twice a day for 2 days for body pain Tubor is mixed with other herbs as a remedy for body pain [62].
Root bark	Root bark extract mixed with root bark of Zizyphus rogosa with 1-2 spoonful sugar is given twice a day in case of urinary disorders [63].
Leaves	Paste with honey taken internally to treat ulcers [64].
Leaves	Leaf paste is applied on cuts to stop bleeding [65].
Leaves & stalks	Leaves are boiled in oil and applied for headaches and fevers and wounds between fingers, skin eruptions [1,66-67].
Roots	A decoction of the roots of Colocynth, Anantamul, Sariva (Sanskrit) and *Hedyotis biflora* prepared in the usual way is administered with the addition of powdered long pepper, bdellium in chronic skin diseases, syphilis, loss of sensation and hemiplegia [7].
Roots	The roots of *I. frutescens* along with roots of *Cissampelos pareira, Bauhinia vahlii* and*Ardisia solanacea* are processed together and given orally to cure stomach cancer (glandular tumor) [68].
Roots	Dried root powder of *I. frutescens* is used as lactagogue and is administered, a spoonful (ten grams) twice a day with a glass of fresh water after meals [69].
Roots	Root paste is applied in rat bites and skin diseases [70].
Roots	The root of *Ichnocarpus furtescens* is given to treat rheumatic pain [71].
Roots	Decoction of roots is used as blood purifier [72].
Roots	The Gond tribes use the roots as remedy for jaundice ad skin diseases [73].
Latex	Latex of the plant is applied topically on painful tumors to reduce pain and retard growth [74].
Flowers	Flowers of *Ichnocarpus frutescens* and the rhizome of *Hedychium coronarium* are together used in the treatment of diabetes mellitus[75].

Figure 1. *Ichnocarpus frutescens*

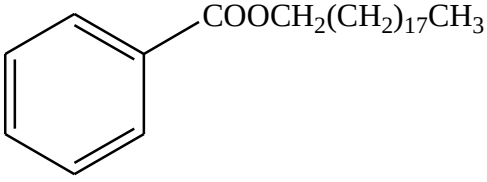


n-butyl oleate **(1)**

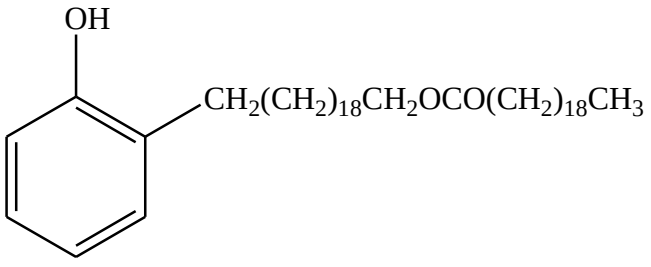
n-octyl tetracontane **(2)**



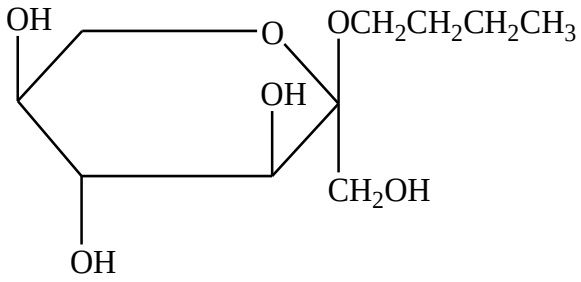
Tetratriacontadiene **(3)**



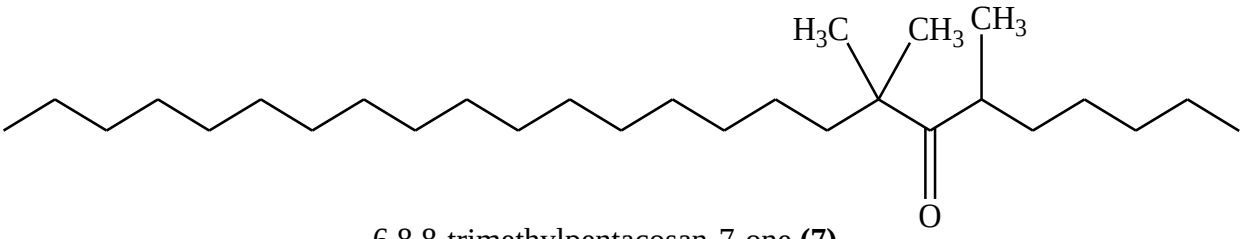
n-nonadecanyl benzoate **(4)**



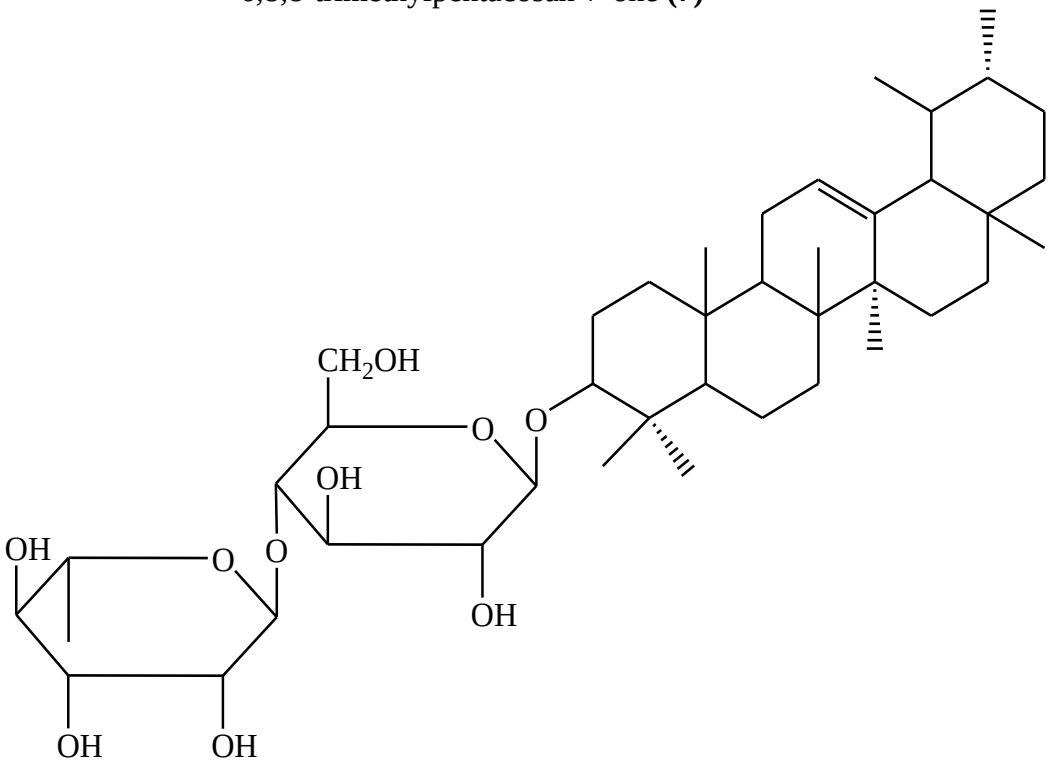
Benzocosanyl arachidate **(5)**



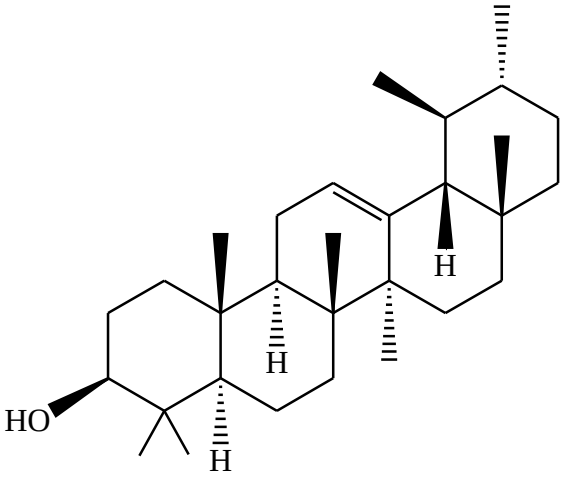
α−L-sarbopyranoside **(6)**



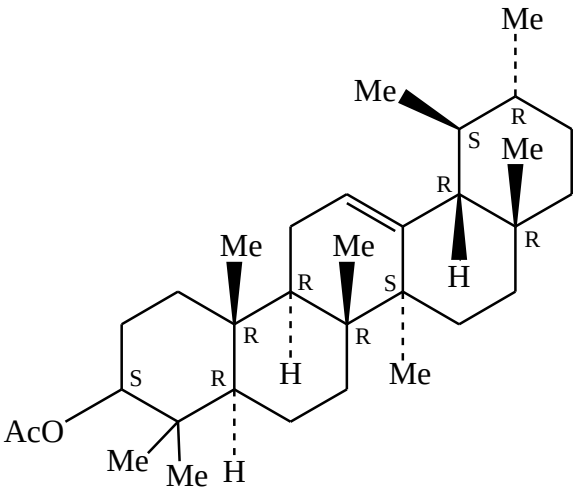
6,8,8-trimethylpentacosan-7-one **(7)**



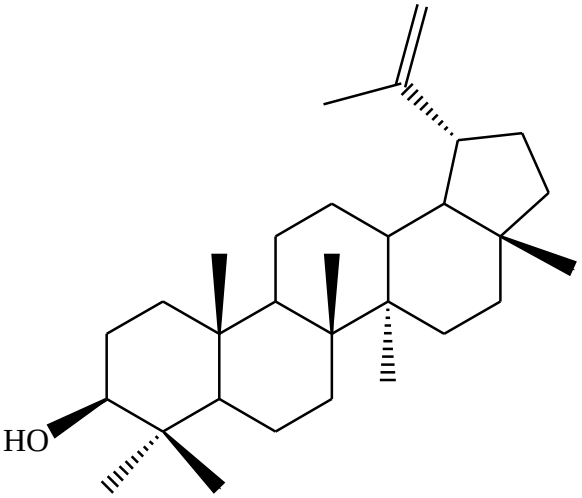
α−L-rhamnopyranosyl-(1➝ 4)-β -D-glucopyranosyl- (1➝ 3)- α -amyrin **(8)**



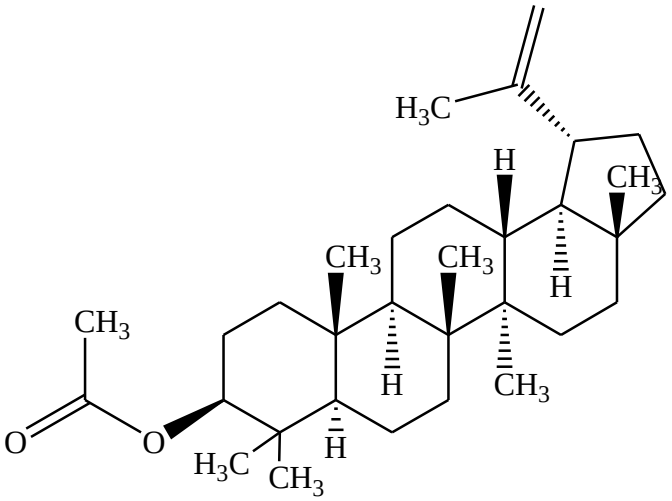
α– amyrin **(9)**



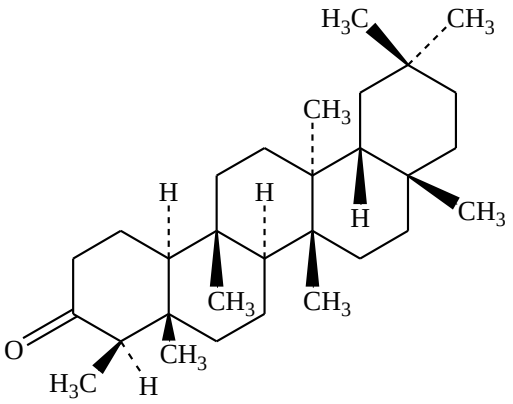
α–amyrin acetate **(10)**



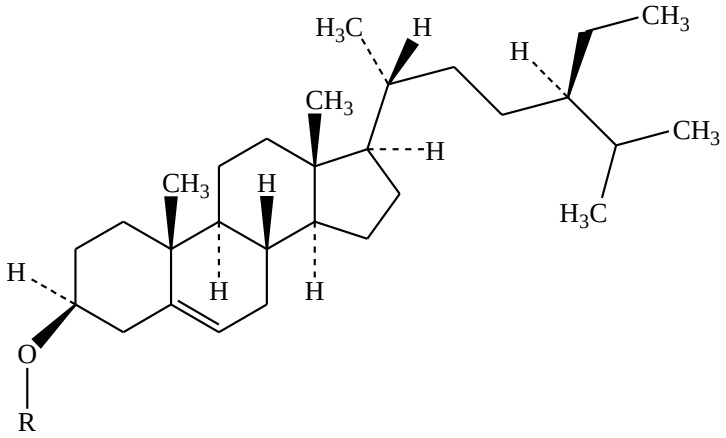
Lupeol **(11)**



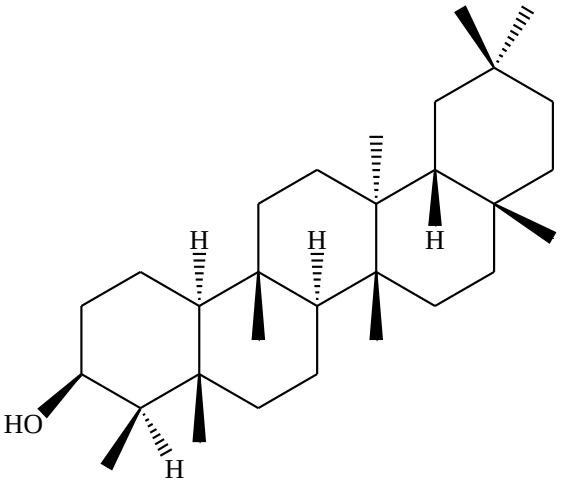
Lupeol acetate **(12)**



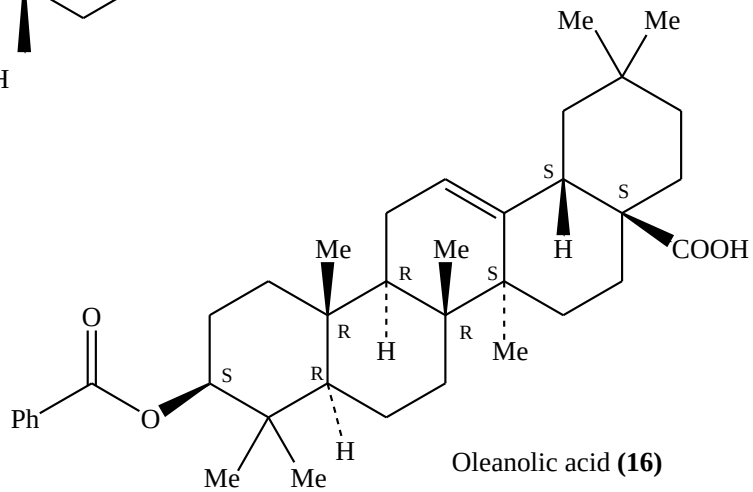
Friedelin **(13)**



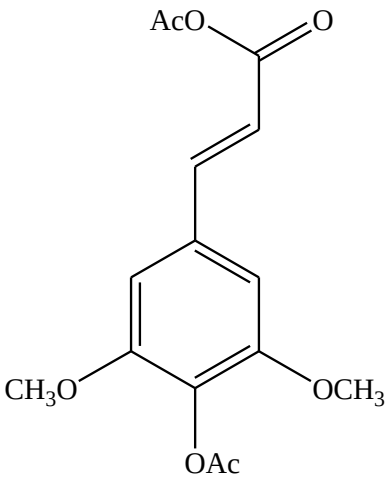
Epi-friedelinol **(14)**



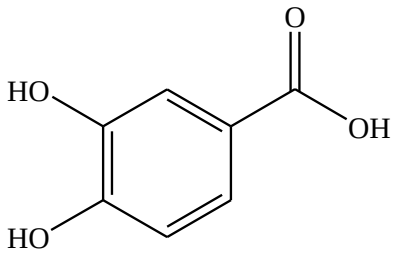
β–sitosterol**(15)**



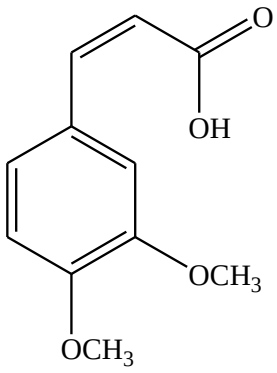
Oleanolic acid **(16)**



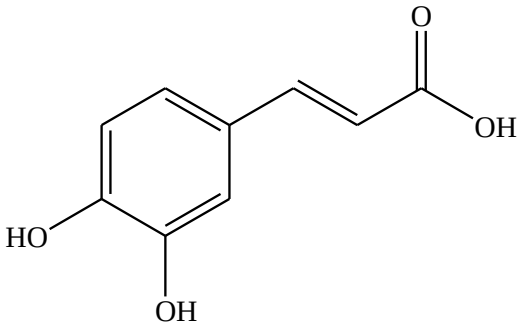
Sibapic acid **(17)**



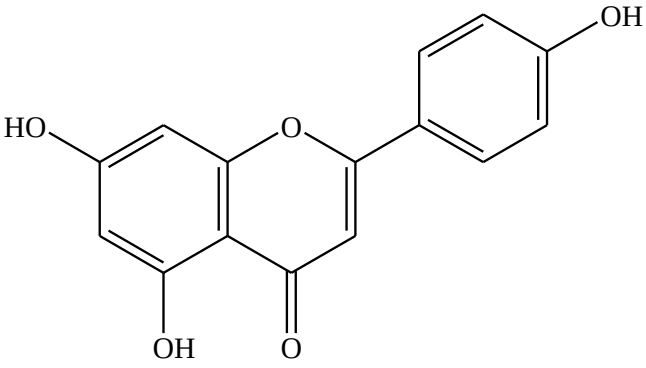
Protocatechuic acid **(18)**



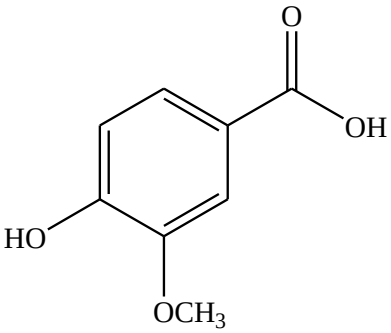
Ferulic acid **(19)**



Caffeic acid **(20)**

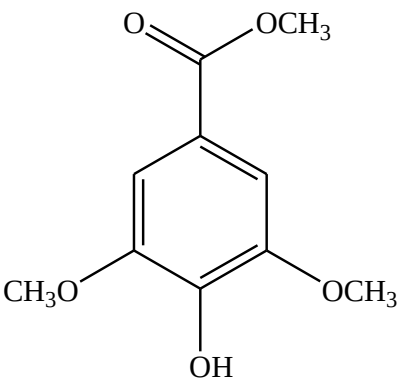


Apigenin **(21)**

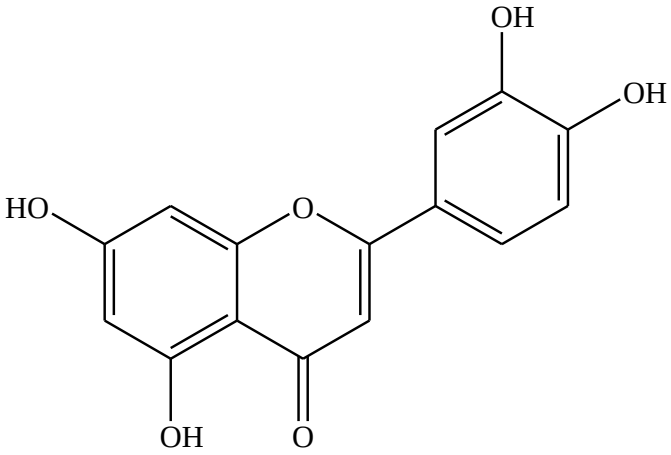


Vanillic acid **(22)**

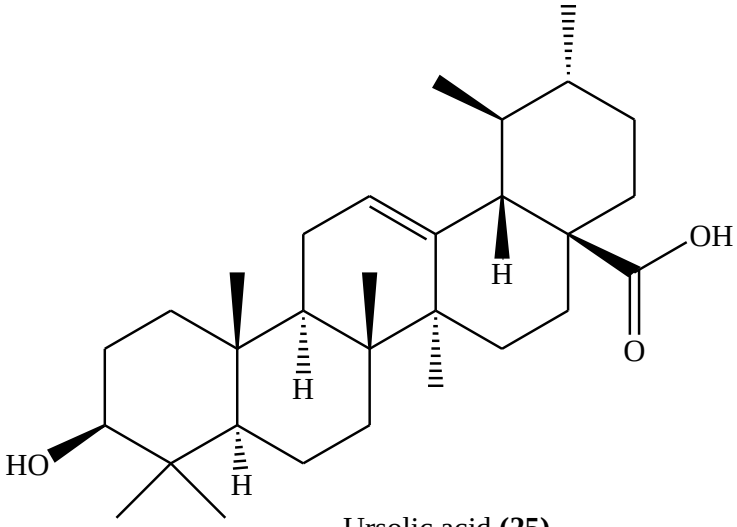
Phenolic Acids



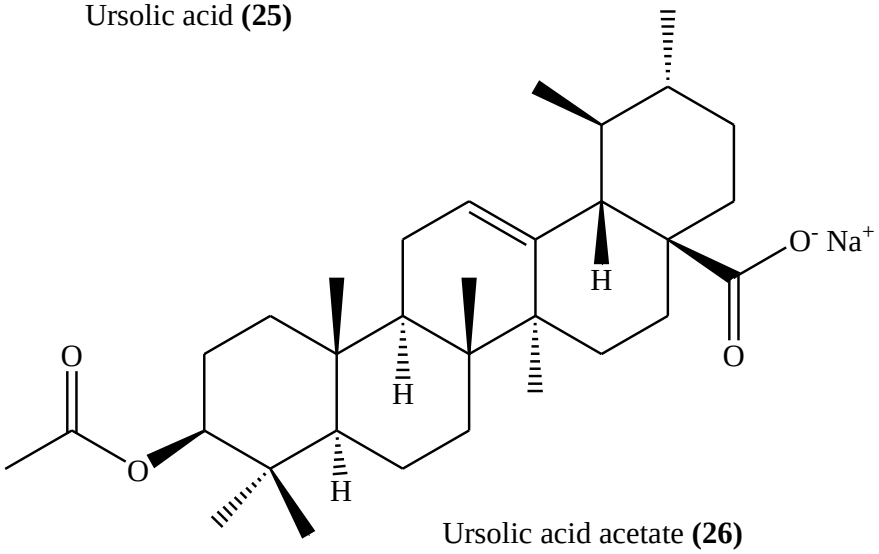
Syringic acid **(23)**



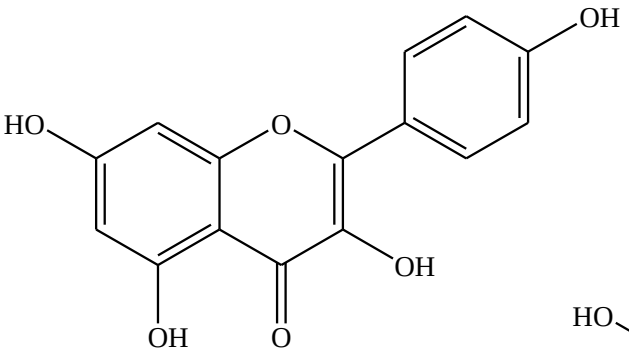
Luteolin **(24)**



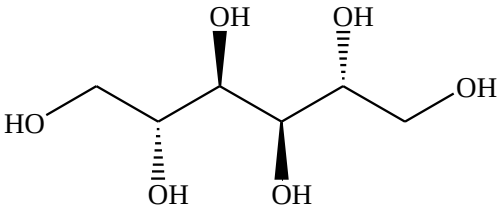
Ursolic acid **(25)**



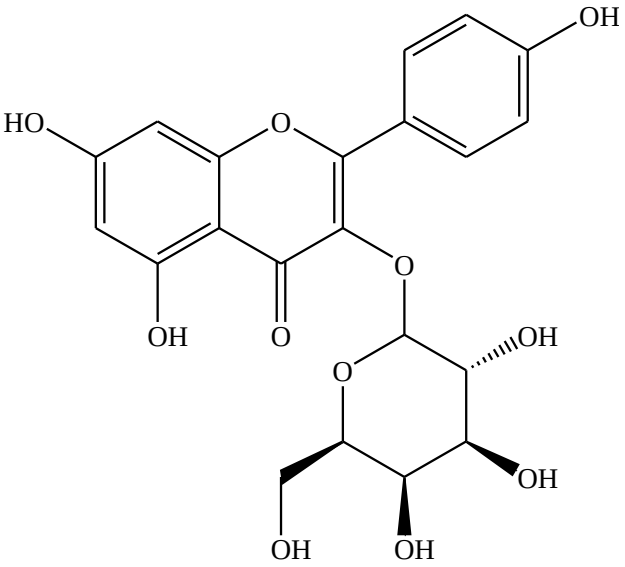
Ursolic acid acetate **(26)**



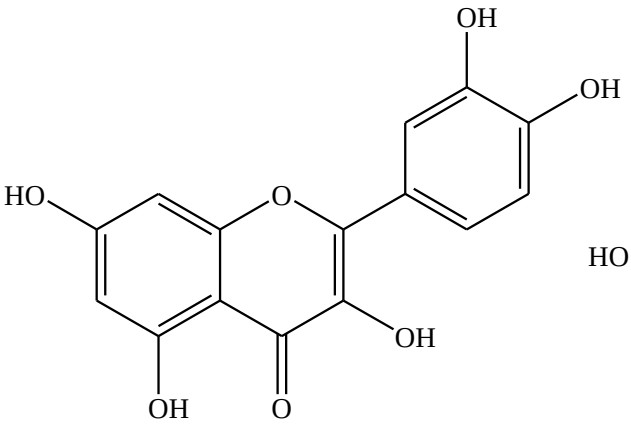
Kaemferol **(27)**



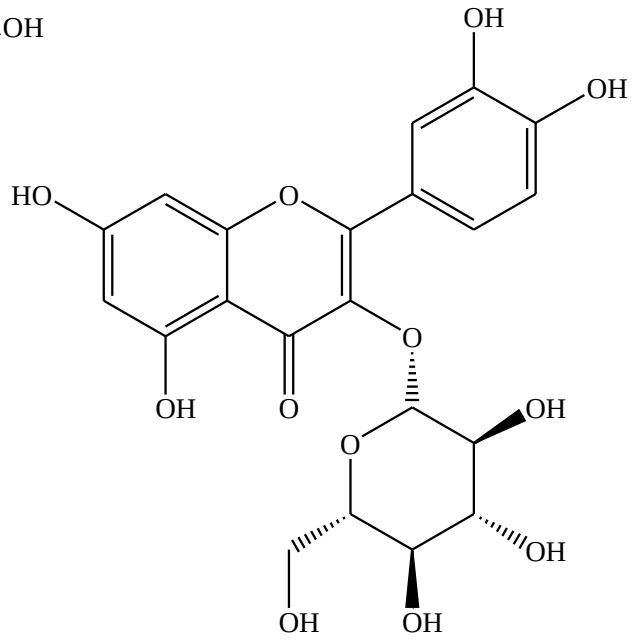
Mannitol **(29)**



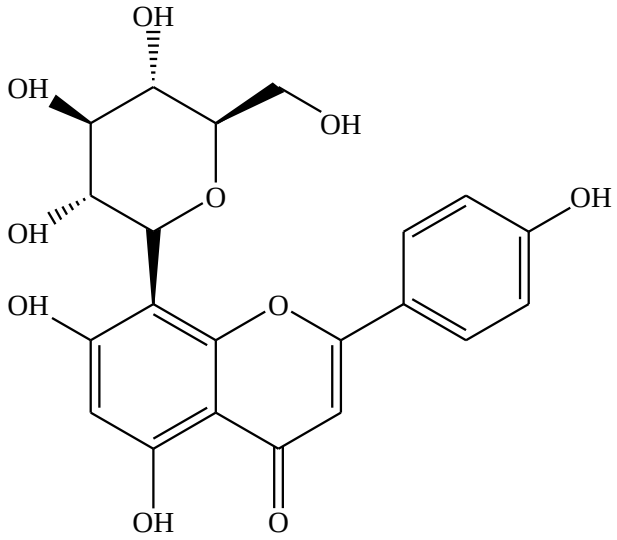
Kaemferol-3-galactoside (trifolin) **(28)**



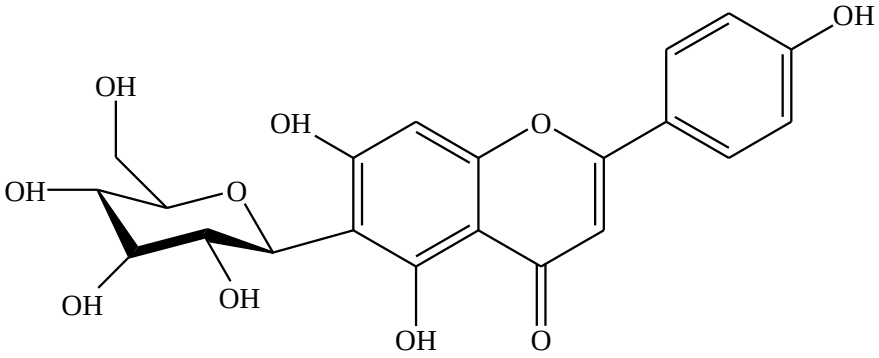
Quercetin **(30)**



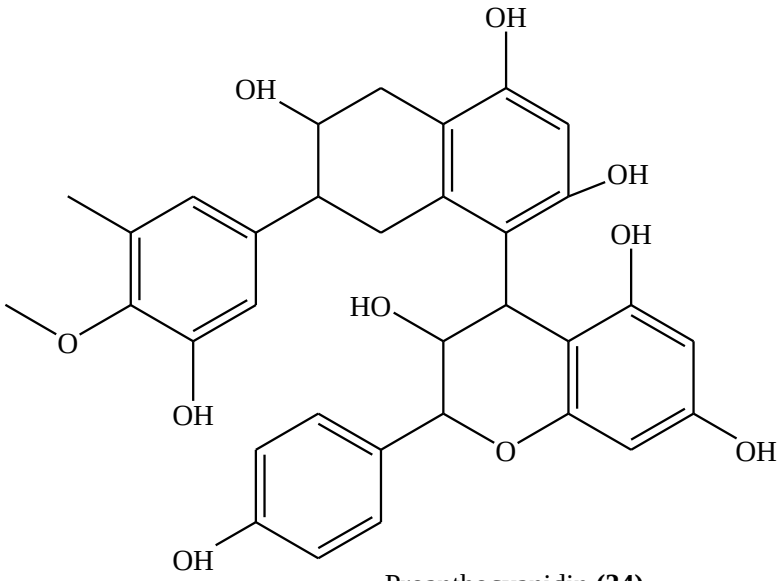
Quercetin-3-O-β– D-glucopyranoside **(31)**



Vitexin **(32)**



Isovitexin **(33)**



Proanthocyanidin **(34)**