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An updated review on *Bidens Pilosa* L.

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Abstracts

Herbal drugs from natural sources like plants are in used since the traditional system of medicine; they represent a precious reservoir of innovative bioactive molecules. Among them Bidens pilosa L is one of the important plant found in all tropical and subtropical region of the world. It is the herbaceous flowering plant, having white 'petals' around a intense bunch of orange florets, and it has been reported to possess effective pharmacological properties like Antibacterial activity, Anti-inflammatory and antiallergic activity, Antimalarial Activity, T helper cell modulator, Immunosuppressive antihyperglycemic, anti-hypertensive, antiulcerogenic, hepatoprotective, anti-leukemic, anticancer, antipyretic, anti-virus, anti-angiogenic, anti-rheumatic, antibiotic. The Bidens pilosa L. has various chemical constituents like polyacetylenes, Polyacetylenic glycosides, aurons, auron glycosides, p-coumeric acid derivatives, caffeoylquinic acid derivatives, pheophytins, diterpenes, tannins, phytosterols, ascorbic acid, carotene, essential oils, saponins, steroids and flavonoids and many others were recognized in this plant. In this review we provide an overview mainly on the pharmacognostic characteristics, conventional uses, phytochemistry and pharmacological actions of extracts or isolated compounds from Bidens pilosa L.

Key words: *Bidens pilosa* L, Natural products, Flavanoids, Polyacetylene, Aurone.

INTRODUCTION

Natural Products in drug discovery

Throughout the ages humans have relied on nature for their basic needs for the production of foodstuffs, shelters, clothing, means of transportation, fertilizers, flavors and fragrances, and, not least, medicines. Plants have formed the basis of sophisticated traditional medicine systems that have been in existence for thousands of years [1]. For thousands of years medicine and natural products have been closely linked through the use of traditional medicines and natural poisons.

Clinical, pharmacological, and chemical studies of these traditional medicines, which were derived predominantly from plants, were the basis of most early medicines such as aspirin, digitoxin, morphine, quinine, and pilocarpine [1-3].

Natural products have played a significant role in drug discovery. Over the past 75 years, natural product derived compounds have led to the discovery of many drugs in the therapeutic areas of cancer, antibacterials and antivirals, and immunosuppressives. These natural products are being developed to improve cancer therapy, to treat resistant bacterial and viral infections and to expand immunosuppressive therapy to diseases such as multiple sclerosis. Natural product compounds not only serve as drugs or templates for drugs directly, but in many instances lead to the discovery of novel biology that provides a better understanding of targets and pathways involved in the disease process [4]. Now improvements in instrumentation, robotics, and bioassay technology have increased the speed of bioassay guided isolation and structure elucidation of natural products considerably, and these improvements have allowed natural product research, fast and efficient [3].

Taxonomy of Bidens Pilosa L.

Kingdom	Plantae
Subkingdom	Tracheobionta
Division	Magnoliophyta
Class	Magnoliopside
Subclass	Asteridae
Order	Asterales
Family	Compositae
Genus	*Bidens*
Species	*B. pilosa*

Fig. *Bidens Pilosa* L.

Synonym: *Bidens biternata, Bidens chinensis,* Picao preto, clavelito de monte, Spanish needles

Geographical distribution

Bidens pilosa L. (Asteraceae, Heliantheae) is an herbaceous plants widely distributed in Africa, America, China, and Japan. *Bidens pilosa* L. is originally native to South America which today is spread all over the world, particularly in tropical and subtropical regions [5].

Morphology

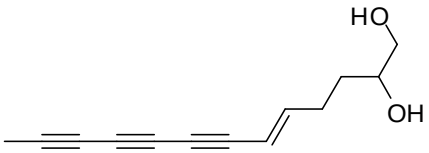
Erect annual herbs 60-90 cm. high. Stem quadrangular, grooved, branches apposite. Leaves pinnately compound, usually 2.5-13.5 cm long including petiole, leaflets 3-5. Heads 21-42 in compound cymes terminating main stem and lateral branches, and 0.7-1 cm in diameter including ray florets, peduncles 1-9 cm long; outer involucral bracts spatulate-tipped, 2.5-5 mm long; ray florets absent or 4-7 per head, rays white or yellowish, 2-8 mm long; disk florets 35-75

per head, perfect, corollas yellow; pappus of 2-3 barbed awns 1-2 mm long. Achenes dark brown or black, straight, wingless, 8-16 mm long, setose [6].

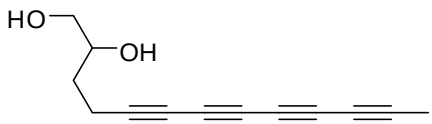
Phytochemistry

Bidens pilosa L. has the various class of chemical constituents as polyacetylenes [7-10,11,12], polyacetylenic glycosides [13,12-16], aurons, auron glycosides, *p*-coumeric acid derivatives, caffeoylquinic acid derivatives, flavonoids and flavonoid glycosides [17,18], sesquiterpenes, acetylacetone [12,19,20], phenylheptadiynol [11,21], phenylpropanoid glucosides [22], pheophytins [22] diterpenes [21,23].

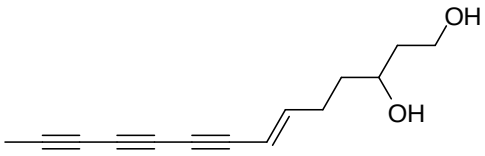
Polyacetylenes



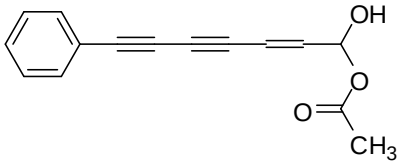
1,2-Dihydroxy-5(*E*)-tridecene-7,9,11-triyne



1,2-Dihydroxytrideca-5,7,9,11-tetrayne

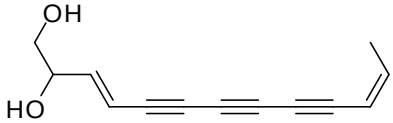


1,3-Dihydroxy-6(*E*)-tetradecene-8,10,12-triyne

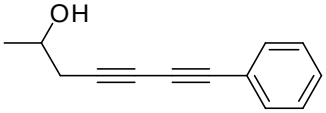


Acetylene 1-phenyl-1,3-diyn-5-en-7-ol-acetate

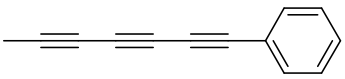
Trideca-2,12-diene-4,6,8,10-tetrayne-1-ol



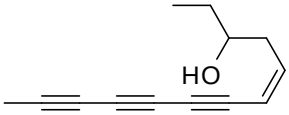
Trideca-3,11-diene-5,7,9-triyne-1,2-diol



7-Phenylhepta-4,6-diyn-2-ol



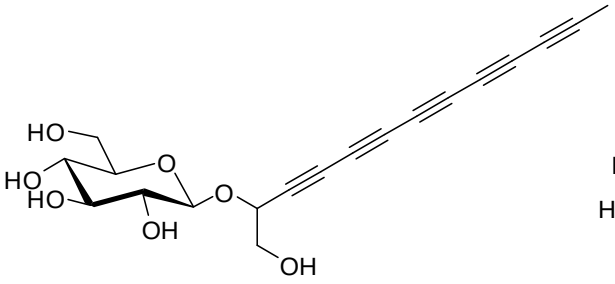
1-phenyl-1,3,5-heptatriyne



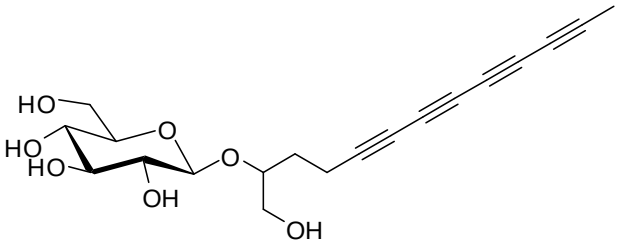
Trideca-5-ene-7,9,11-triyne-3-ol

Phenylheptatriyne

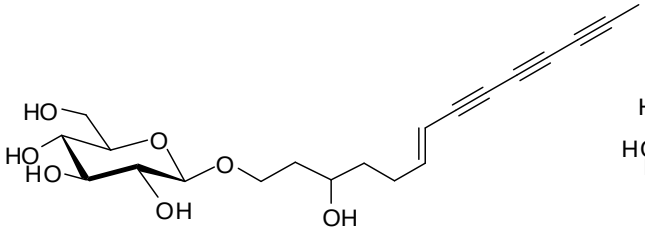
Polyacetylenic Glycosides



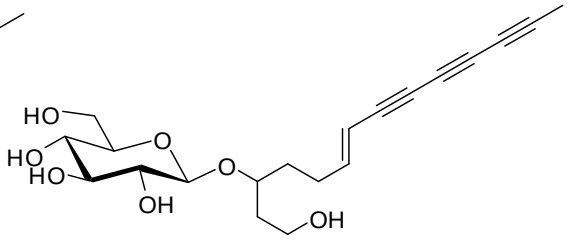
2-β-D-glucopyranosyloxy-1-hydroxy-trideca-3,5,7,9,11-pentayne



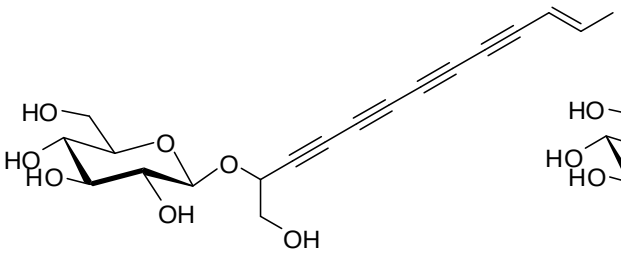
Cytopiloyne



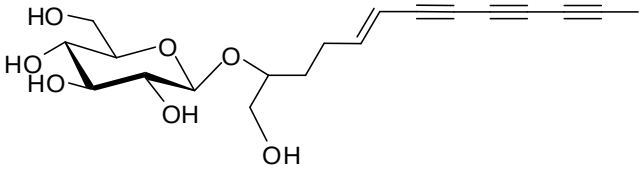
1-β-D-glucopyranosyloxy-3-hydroxy-6(*E*)-tetradecene-8,10,12-triyne



3-β-D-glucopyranosyloxy-1-hydroxy-6(*E*)-tetradecene -8,10,12-triyne



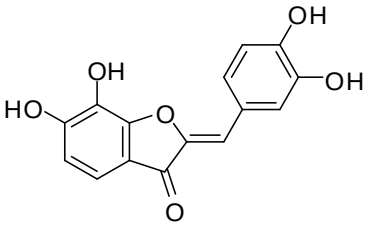
2-O-β -D-glucopyranosyloxy-1-hydroxy-11(E)-tridecene-3,5,7,9- tetrayne



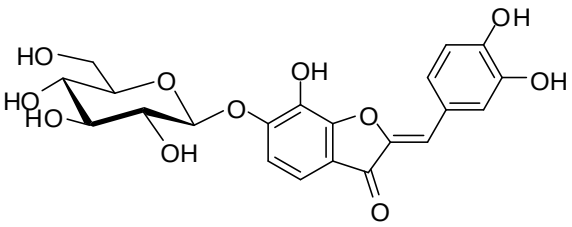
2-β-D-glucopyranosyloxy-1-hydroxy-5(*E*)-tridecene-7,9,11-triyne

Flavonoids

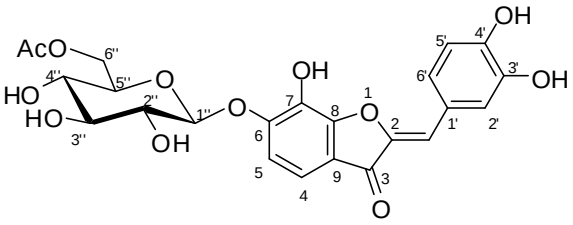
1. Aurons and their glycoside



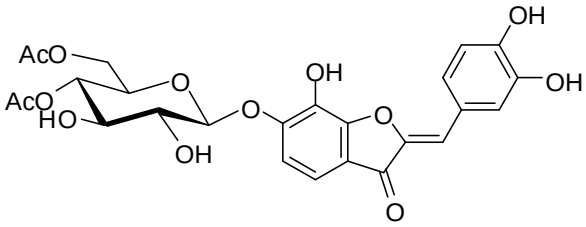
6,7,3',4'-tetrahydroxyaurone



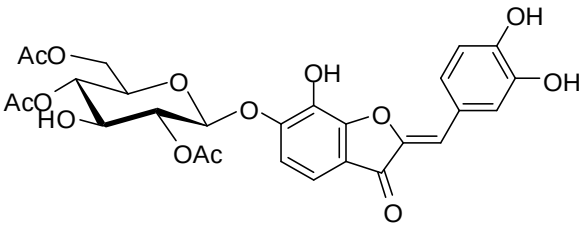
6-O-β-D-glucopyranosyl-6,7,3',4'-tetrahydroxyaurone



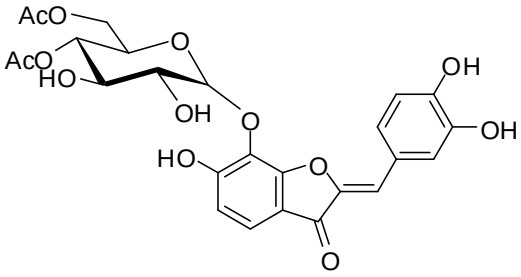
6-O-(6''-acetyl-β -D-glucopyranosyl)-6,7,3',4'-tetrahydroxyaurone



6-O-(4'',6''-diacetyl-β-D-glucopyranosyl)-6, 7,3',4'-tetrahydroxyaurone

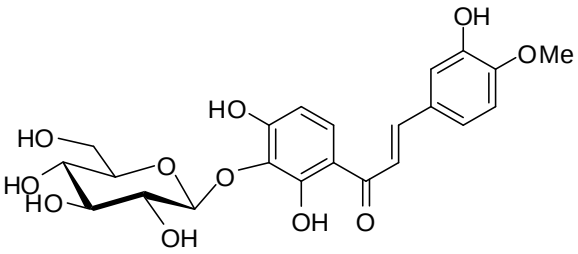


6-O-(2'',4'',6''-triacetyl-β-D-glucopyranosyl)-6, 7,3',4'-tetrahydroxyaurone

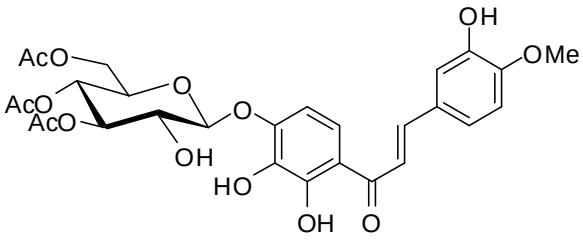


7-O-(4'',6''-diacetyl-β-D-glucopyranosyl)-6, 7,3',4'-tetrahydroxyaurone

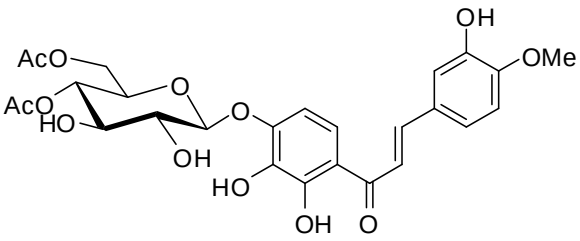
2. Okaninglycoside



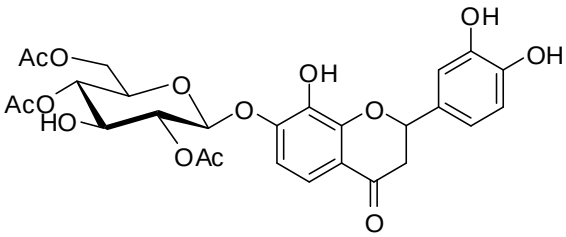
Okanin-4-methyl ether-3'-O-β-D-glucoside



Okanin-4'-O-β-D-(3'',4'',6''-triacetyl)-glucopyranoside

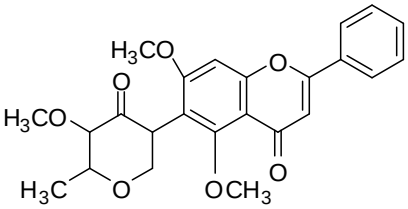


Okanin 4'-O-β-D-(4'',6''-diacetyl)-glucopyranoside

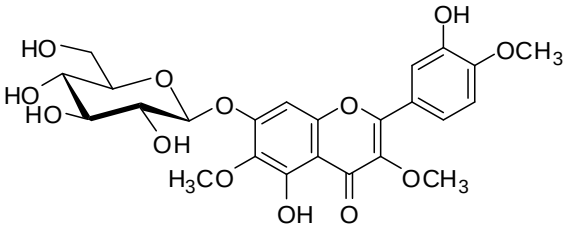


iso-okanin 7-β-D-(2'',4'',6''-triacetyl)-glucopyranoside

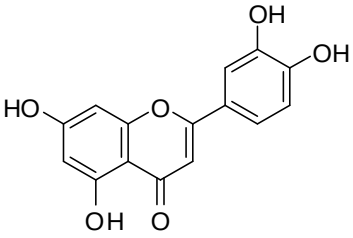
Other flavonoids



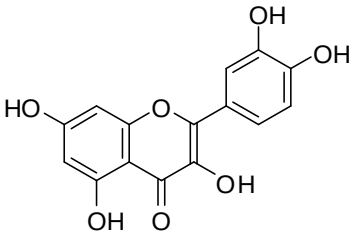
5-O-methylhoslundin



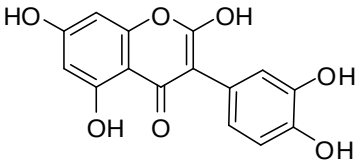
Centaurein



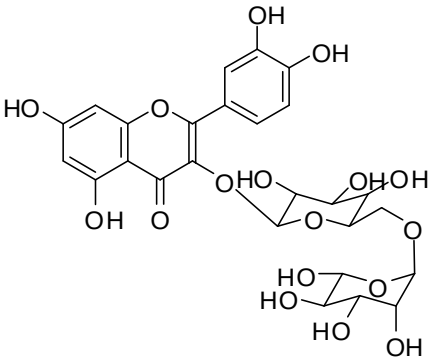
Luteolin



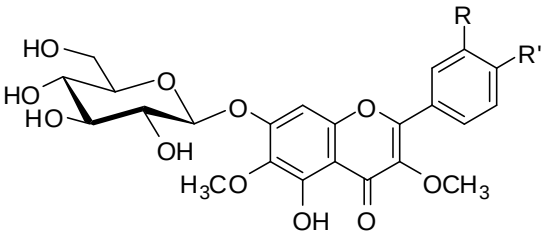
Quercetin



Isoquercitrin



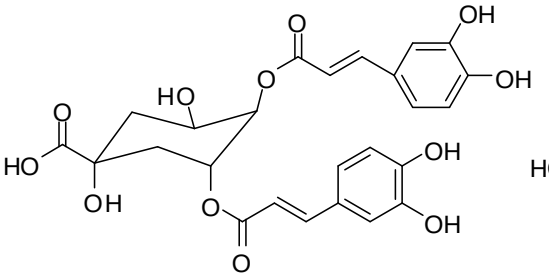
Quercetin 3-O-rabinobioside



R= OH, R'= OCH_3 Centaurein

R= OCH_3 R'= OH Jacein

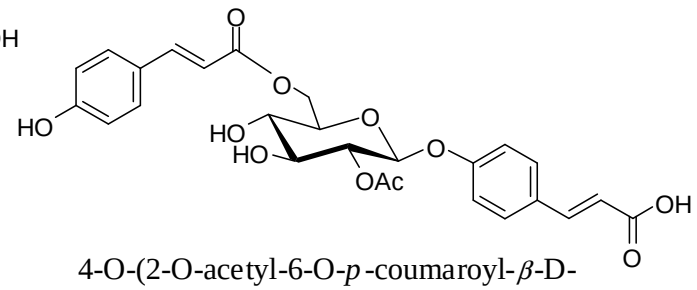
Caffeoylquinic acid and p-coumeric acid derivative



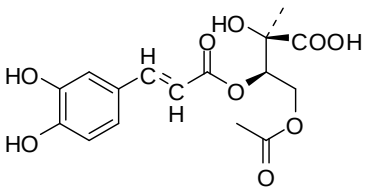
3,4-*Di*-O-caffeoylquinic acid

4,5-*Di*-O-caffeoylquinic acid

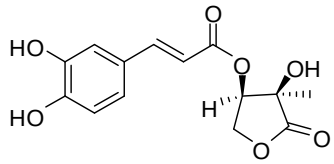
3,5-*Di*-O-caffeoylquinic acid



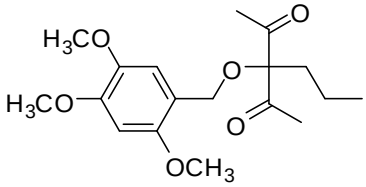
4-O-(2-O-acetyl-6-O-*p*-coumaroyl-*β*-D-glucopyranosyl)-*p*-coumaric acid



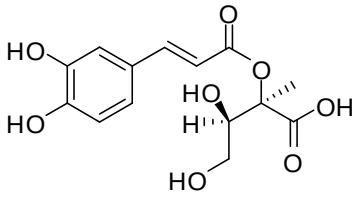
Caffeic acid ester



3-O-Caffeoyl-2-C-methyl-D-erythrono-1,4-lactone

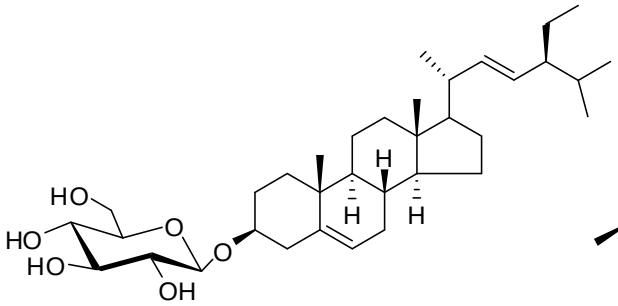


3-Propyl-3-(2,4,5-trimethoxy) benzyloxy -pentan-2,4-dione

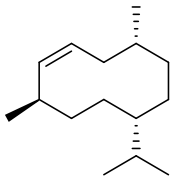


2-O-Caffeoyl-2-C-methyl-D-erythronic acid

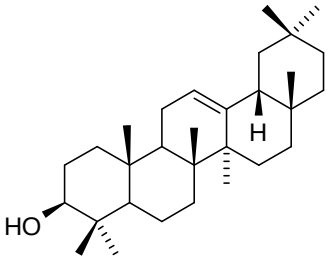
Sesquiterpenes



Stigmastero-3-O-β-D-glucoside

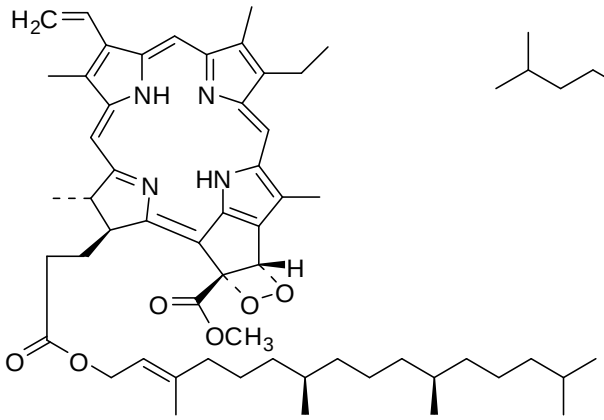


Germacrene D



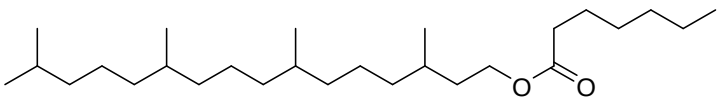
β-Amyrin

Pheophytins

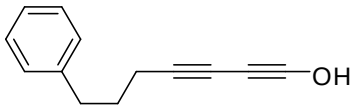


Bidenphytins A

Diterpenes



phytyl heptanoate



Phenylheptadiynol

Figure 2- Phytochemicals from *Bidens pilosa* L.

Traditional uses

The whole herb has been used as a folk medicine against various diseases, such as inflammation and rheumatism, astringent, antihaemorrhagic, styptic, urogenital system tonic, mucous membrane tonic throughout the body, anti-microbial activity, and neoplastic [6].

Pharmacological Action

The whole plant (roots and arial part) of *Bidens pilosa* L. has been reported for various biological activities as following

Anti-mycobacterium [24], Antimicrobial [25], IFN-α promoter [27], Anti-Angiogenic [7], Anticancer [8,9], Antidiabetic [26], Antimalarial and antibacterial [7] Antiinflammatory and antiallergic [28], Immunomodulatory [29], Antioxidative [30], Gastric antisecretory and Antiulcer [31] etc.

Antibacterial activity

Antibacterial activity of Methanolic Leaf extract of *Bidens pilosa* (with two-fold serial dilutions of plant extracts from 8.0- 0.25 mg/ml) was evaluated by agar dilution method against *S. aureus*, *S.* epidermis and *B. subtilis.* Minimum inhibiting concentrations (MIC) were determined for extracts with antibacterial activity > 0.60, Extract showed the MIC value as in *S. aureus* (2.0), *S. epidermis* (8.0), *and B. subtilis* (4.0). MIC values were taken as the lowest concentration of extract that completely inhibited bacterial growth after 18 h of incubation at 37°C. Neomycin was used as the reference and appropriate controls with no extract 'and solvent were used [32].

Anti-inflammatory and antiallergic activity

Dried powder of *Bidens pilosa* used for *In vitro* experiments, the crude drug was extracted with water for 24 hr at 100℃. In the In vitro experiments the suspension of *Bidens pilosa* in 0.25% carboxy-methyl-cellulose sodium (CMC-Na) was used. The animals (male wistar rates (200 g), Male ddY mice (18-20 g), and male BALB/c mice (18-20 g), were administered pharmacologic dose of *Bidens pilosa* 100, 250, 500 mg/kg

In this study the effect of oral administration of *Bidens pilosa* suspension in CMC-Na solution on the production of IgE. The level of IgE in serum after 10 days of antigen immunization was higher than that at 5 or 15 days. *Bidens pilosa* dose dependently, in conjugation with cyclophosphamide as a positive control, inhibited the serum IgE level after 10 days of immunization. These results suggest that *Bidens pilosa* have the potential to regulate the host immune response to type I allergy. Therefore *Bidens pilosa* or flavonoids of *Bidens pilosa* may suppress the production of IgE by improving the helper T cell balance [28].

Antimalarial Activity

Dried plant roots were powdered (100 g each), extracted by percolation with 80% ethanol at room temperature, and the solvent evaporated to dryness at 45°C maximum. Dried extracts were submitted to *in vivo* and *in vitro* antimalarial assays or chemical analysis. Swiss albino adult mice, weighing 20–22 g, were used for the antimalarial and toxicity tests.

The *in vitro* antimalarial activity of *B. pilosa* tested against three *P. falciparum* isolates with various susceptibilities to chloroquine was similar, based on each inhibitory concentration dose (ICs). The IC50 of plants cultivated in standard soil ranged from 25 to 36 µg/mL [33].

T helper cell modulator

Cytopiloyne (a polyacetylene) functions as a T cell modulator that may directly contribute to the ethnopharmacological effect of *Bidens pilosa* extract on preventing diabetes. Cytopiloyne was able to inhibit the differentiation of human Th0 cells into Th1 cells in a more effective way. CD4+ T cells were isolated from lymph nodes of BALB/c mice for Th cell differentiation study. It is found that cytopiloyne concentration- dependently (1-5 µg/ml) decreased the percentage of INF-γ-producing cells (i.e. Th1 cells) from 72.0% to 59.8%. Since Th1 and Th2 cell differentiation is cross-regulated and mutually antagonized next examined whether cytopiloyne could modulate Th2 cell differentiation. It is found that an addition of cytopiloyne to the differentiating Th cells increased the percentage of mouse IL-4-producing cells from 23.7% to 30.9% in a concentration-dependent manner. Cytopiloyne at these doses did not show any cytotoxicity toward the differentiating cells even after 24 h incubation. So it is concluded that cytopiloyne inhibited Th1 cell differentiation but increased Th2 cell differentiation in mouse T cells [15].

Activity on KCl- and norepinephrine-induced contractions of rat aorta

Effect of leaf aqueous extract of *Bidens pilosa* L. on KCl- and norepinephrine-induced contractions of rat aortic strips was studied. In aortic strips with endothelium intact, contractions induced using 60 mM KCl and 10^{-5} M norepinephrine were dose-dependently relaxed by the extract, a more significant effect being seen with norepinephrine- induced contractions. Following mechanical damage to the aortic endothelium, inhibition of contractions was more prominent (105%) with the norepinephrine-induced contractions compared with KCl-induced contractions (15%) when the maximal dose (8 mg/ml) of the extract was used. The results suggest that the relaxation effect of the extract may be due to the blockade of the influx of extracellular Ca^{2+} into the cell [44].

Activity on various gastric ulcer models in rats

The methanol, cyclohexane and methylene chloride extracts of *Bidens pilosa* was studied for anti-ulcerogenic activity using the HCl: Ethanol gastric necrotizing solution. The methylene chloride extract, which showed the highest activity (100% inhibition) at a dose of 750 mg/kg compared with the methanol and cyclohexane extracts (41 and 46% inhibition, respectively), was further tested using the indomethacin-HCl:ethanol, absolute ethanol and pylorus ligation-induced ulcer methods. Pre-treatment with indomethacin significantly reduced the protective effect of the extract against HCl: ethanol solution to 31%. The extract had very little gastric mucosal protection against absolute ethanol (9.8% inhibition at 750 mg/kg) compared with the controls and neither reduced gastric acid secretion *in vivo* nor the acidity of gastric juice following i*n vitro* incubation [5].

Hypotensive effects in rats

The effects of the aqueous (150–350 mg/kg) and methylene chloride (150–300 mg/kg) extracts of *Bidens pilosa* was performed on fructose-induced hypertension in rats. The aqueous and methylene chloride extracts of *Bidens pilosa* reversed the high blood pressure and

hypertriglyceridemia developed due to fructose feeding but did not have any effects on plasma levels of insulin and glucose. High doses of the extracts reduced plasma creatinine levels and tended to increase plasma cholesterol. These results suggest that the extracts of *Bidens pilosa* possess hypotensive effects whose mechanism of action is not related to insulin sensitivity [35].

Stimulate IFN-expression

Hot water crude extracts from *Bidens pilosa* and its butanol subfraction increased IFN-γ promoter activity up to two- and six-fold, respectively. Finally, centaurein (EC50 =75µg/ml) and its aglycone, centaureidin (EC50 = 0.9µg/ml), isolated from this butanol subfraction, augmented IFN-γ promoter activity by about four-fold. Consistent with the role of centaurein or its aglycone in IFN-γ regulation, it showed that centaurein induced the activity of NFAT and NF□B enhancers, located within the IFN-γ promoter, in Jurkat cells. Overall, the results showed that centaurein regulated IFN-γ transcription, probably via NFAT and NF□B in T cells [27].

Gastric antisecretory and antiulcer activities

The ethanolic extract (0.5-2 g/kg) decreased the gastric juice volume, acid secretion, as well as pepsin secretion in pylorus ligated rats. *Bidens pilosa* extract showed antiulcer activity against indomethacin-induced gastric lesions. The extract effectively inhibited gastric haemorragic lesions induced by ethanol, and with an effective dose of 2 g/kg being more potent than sucralfate (400 mg/kg). *Bidens pilosa* ethanolic extract exerts a cytoprotective effect in addition to its gastric antisecretory activity that could be due, partly at least, to the presence of flavonoids of which quercetin was identified by HPLC [13].

Immunosuppressive activity

The immunomodulatory effect of the methanolic extract obtained from dried leaves of *Bidens pilosa* L. and the polyacetylene 2-*O*-*β*-D-glucosyltrideca-11*E*-en-3,5,7,9-tetrayn 1,2-diol, isolated from it was investigated. The extract inhibited the proliferative response in two *in vitro* models: **human lymphocytes** stimulated by 5 µg/ml phytohemagglutinin or to 100 nM 12-*O*-tetradecanoyl phorbol-13-acetate plus 0.15 µM ionomycin and **murine lymphocytes** stimulated by 5 µg/ml concanavalin A (Con A) or in the mixed leukocyte reaction (IC_{50} =12.5 to 25 µg/ml) 2-*O*-*β*-D-glucosyltrideca-11*E*-en-3,5,7,9-tetrayn 1,2-diol was 10-fold more potent than the original extract in blocking both human and murine lymphocyte proliferation (IC_{50}= 1.25 to 2.5 µg/ml.

In mice, the intraperitoneal administration of methanolic extract of *Bidens pilosa* significantly reduced the size of the popliteal lymph node after the inflammation induced by zymosan. One week after the injection of zymosan (150 µg) in the foot pad, PLN weighed 4.6 ±6 mg in comparison with 0.5 ±0.07 mg of the contralateral non-inflamed foot pad. The intraperitoneal treatment with 10 mg extract from day 2 to day 6 after zymosan injection reduced the PLN weight to 1.8 ±0.3 mg [29].

Antioxidant activity

Aqueous infusion of *Bidens pilosa* is studying for antioxidant activity by its protective effect on the hemolysis induced by an initiator of radicals such as 2,2´-azobis (2-amidinopropane) dihydrochloride (AAPH). The amount of *Bidens pilosa* infusion that halved the hemolysis

induced by AAPH was 6 µl, which corresponds to an IC_{50} of 1.19 mg of dry weight per milliliter of infusion. Thus, the oxidative hemolysis of erythrocytes induced by AAPH was suppressed by an aqueous infusion of *Bidens pilosa*, which is a very active antioxidant and exerts its protective effect at low amounts [36].

Protection from oxidative damage in normal human erythrocytes

The ethanol (EtOH) and ethyl acetate/ethanol (EA/EtOH) extracts from the whole *Bidens pilosa* plant have the property to protect normal human erythrocytes against oxidative damage *in vitro*. It was determined that the oxidative hemolysis and lipid/protein peroxidation of erythrocytes induced by the aqueous peroxyl radical [2,2´-azobis(2-amidinopropane) dihydrochloride (AAPH)] were suppressed by both EtOH (50–150 µg/ml) and EA/EtOH (25–75 µg/ml) extracts of *Bidens pilosa* in concentration- and time-dependent manners. *Bidens pilosa* extracts also prevented the decline of superoxide dismutase (SOD) activity and the depletion of cytosolic glutathione (GSH) and ATP in erythrocytes. These results imply that *Bidens pilosa* may have protective antioxidant properties [30]

Protective effects on animal liver injury and liver fibrosis

Total flavonoids of *Bidens pilosa* L. (TFB) (25, 50 and 100 mg/kg) were administered via gavages daily for 10 days to CCl_4 treated mice as well as TFB (30, 60 and 90 mg/kg) administered for 6 weeks to CCl_4 treated rats. The results showed that TFB (50 and 100 mg/kg) effectively reduced the CCl_4 induced elevated liver index, serum ALT, AST levels, hepatic MDA content, and restored hepatic SOD, GSH-Px activities in acute liver injury mice. TFB (60 and 90 mg/kg) treatment significantly inhibited NF-□B activation in liver fibrosis of rats. The histopathological analysis suggested that TFB reduced the degree of liver injury in mice and severity of liver fibrosis in rats. These results suggested that TFB had a protective and therapeutic effect on animal liver injury, which might be associated with its antioxidant properties and inhibition of NF-□B activation [37]

Anticancer and antipyretic activity

The extract from whole plant *Bidens pilosa* L was extracted with *n*-hexane, chloroform and methanol extract (E1- E3). Screening of different extracts and fractions has been conducted using the *in- vitro* comet assay for anticancer and the antipyretic action, which was done with *in-vivo* models. *n*-hexane extract shows remarkable anticancer activity and methanolic extract bears maximum antipyretic activity. In the antipyretic activity, paracetamol was used as the standard test drug. The most promising material (LC50 < 1500 µg / ml) was F1 ethyl acetate fractions of methanolic extract and methanolic crude extract of whole plants. The extract obtained from the whole plant of *Bidens pilosa* L. showed a significant cytotoxic effect to methanolic extract against Hela cells by *in vitro* method and showed a comparable antipyretic activity effect to paracetamol in rabbit pyrogen test [8].

Herbal preparation

An odd or unusual characteristic of this unique herbal drug is its wealth in multi-species formulas that have been used across the centuries. These formulations thus represent a social heritage, and their ethnobotanical information can add much to the understanding of local folk medical systems. While *Bidens pilosa* L. and *Cissus sicyoides* are principal in mixtures for respiratory problems, which form the major ethno-medical category in terms of number of

preparations. Juice extract of *Bidens pilosa* L. (Arial part) and Solanum *torvum* (leaves) was used to treat Catarrh. Decoction of (aerial part), *Cassia fistula* (fruits), *Cissus sicyoides* (fruits), *Crescentia cujete* (fruits), *Phyla scaberrima* (aerial part), *Ruellia tuberosa* (root) and bee's honey was used to provide coolness at the uterus and treat menstrual irregularity [38].

Contraindications

1. *Bidens pilosa* has evidenced weak uterine stimulant activity in guinea pigs. As such, it should not be used during pregnancy.
2. This plant contains several coumarin derivatives. Coumarins are a group of chemicals that thin the blood. Those on blood thinning medications such as Warfarin should use *Bidens pilosa* with caution and monitor these possible effects.
3. The plant has been documented to lower blood sugar levels in several animal studies. Those with hypoglycemia or diabetes should only use *Bidens pilosa* under the supervision of a qualified health care professional and monitor their blood sugar levels accordingly.
4. *Bidens pilosa* has been documented with hypotensive activity in several animal studies. People with heart conditions and those taking antihypertensive drugs should consult their doctors prior to using this plant to monitor these possible effects.

Drug Interactions

None clinically documented in humans; however, the use of this plant may potentiate antidiabetic, anticoagulant, and antihypertensive drugs (based on animal studies).

CONCLUSION

In recent years, plants have become gradually more important as a source of biologically active natural products. It is expected that 25% of all medicines have plant derivative. An example is taxol, obtained from *Taxus baccata*. Among the medicinal plants are species of Asteraceae (Compositae), the largest flowering plant family in the world. This family is characterized by the presence of polyacetylenes in all parts of the plant. Several compounds with biological actions have been isolated from different species of Asteraceae. Among these is *Bidens pilosa* L. widely distributed in tropical regions. Literature survey showed that *Bidens pilosa* has large range of pharmacological activity, this wide spectrum of activities are due to presence of diverse class of chemical constitutes like polyacetylenes, aurons, chalcones and their glycosides. So if further research work need on *Bidens pilosa* for the practical clinical applications, which can be used in future for next generation human being

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