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A REVIEW ON ETHNOMEDICINAL USES, PHYTOCHEMISTRY AND PHARMACOLOGICAL PROPERTIES OF COCCULUS HIRSUTUS (L.) DIELS AND COCCULUS PENDULUS (FORST) DIELS.

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ABSTRACT

Menispermaceae is an important angiosperm family containing several medicinally important plants including Cocculus. This review presents a comparative report of two species of this genus, namely, Cocculus hirsutus (L.) Diels and Cocculus pendulus(J. R. Forst. & G. Forst.) Diels. While both species are immensely used by the tribal folk in various forms, they are also abundantly utilised in western medicine. Phytochemical analysis of both species report the presence of several important phytochemicals like alkaloids, flavonoids, terpenoids, phenols, sterols, etc. The pharmacological studies of C. hirsutus(L.) and C. pendulus (Forst)report that the plants contain many properties such antibacterial, anticancer, antiviral, wound-healing, diuretic, analgesic, among others that are quite beneficial to human health. Though much analysis and research work has been reported for Cocculus hirsutus(L.), there are yet many studies to be done on the aspects of Cocculus pendulus (Forst).

Keywords: Cocculus hirsutus(L.), Cocculus pendulus(Forst),ethnomedicinal uses, phytochemical analysis, pharmacological activity, patents

1.INTRODUCTION

Menispermaceae is a cosmopolitan angiospermic family of mostly dioecious climbing plants, rarely trees, shrubs, or herbs, comprising about 70 genera and 500 species. Most members of this family are tropical, but a few are also found in temperate regions (i.e., all Menispermum L. and Cocculus DC. species) [1]. The genus Cocculus of the family Menispermaceae comprises about 35 species, out of which two species of Cocculus are prominently found in Gujarat; Cocculus pendulus (Forst)(synonym: Cocculus leaeba) and Cocculus hirsutus (L.) (synonym: Cocculus villosus[2]).

It is known by various names in local languages such as: Broom creeper (English); Huyer (Bengali); Jamti ki bel (Hindi); Vevdi (Gujarati), Parwatti (Gujarati), Kaage Mari (Kannada); Farid-buti (Urdu); Paathaalagarudakkoti (Malayalam), Kaanselaharo (Nepali); Garudi, Patalagarudi (Sanskrit), Chipuru-tiga (Telegu); Kattu-k-koti (Tamil), Ullarbillar (Sindhi), among others [2-5].

The plant Cocculus of Menispermaceaefamily has important medicinal properties and acts as antibacterial [6], anticancer [7], anti-inflammatory, and analgesic [8]. With respect to its ethnobotanical aspect, the leaves and roots of Cocculus are largely employed in the Indian traditional medicine for a variety of diseases including, hepatic obstruction, jaundice, bronchitis, diabetes mellitus, anorexia, gonorrhoea, and leprosy [9].

Furthermore, an open-label, multicenter, randomized controlled trial was conducted in India where a purified aqueous extract of Cocculus hirsutus (AQCH) has shown robust antiviral activity in in vitro studies [5, 10].

Thus, the aim of this report is to cumulate the available scientific information about the various reported elements of C. hirsutus(L.) and C. pendulus(Forst).

1.1 Classification

Table 1: Classification of Cocculus hirsutus (L.) and Cocculus pendulus (Forst)[2-4].

	C. hirsutus	**C. pendulus**
Kingdom	Plantae	Plantae
Division	Magnoliophyta	Magnoliophyta
Class	Magnoliopsida	Magnoliopsida
Order	Ranunculales	Ranunculales
Family	Menispermaceae	Menispermaceae
Genus	Cocculus	Cocculus
Species	hirsutus (L) Diels	pendulus (J. R. Forst. & G. Forst.) Diels

1.2 Distribution and Morphology

Plate A

Plate B

Plate C

Plate D

Plate A: Cocculus hirsutus (L.)female plant twig bearing fruits
Plate B: Cocculus hirsutus (L.)male plant twig bearing flowers
Plate C: Cocculus pendulus (Forst)female plant twig bearing fruits
Plate D: Cocculus pendulus (Forst)male plant twig bearing flowers

Cocculus is a perennial climber spread throughout the tropical and subtropical areas [11]. In Asia, it has been reported from India, Myanmar, Nepal and Pakistan and southern China. It is also distributed in Central Arabia and in Africa from Sudan and Eritrea south to South Africa [12]. In India, it is found in Andhra Pradesh, Gujarat, Haryana, Jammu & Kashmir, Karnataka, Madhya Pradesh, Maharashtra, Punjab, Tamil Nadu, Uttar Pradesh, and Rajasthan [4].

Both species of Cocculus are scandent twiners and similar in morphology except a few minor differences. Leaves are ovate to oblong, obtuse or subacute with a sharp short point, and subcordate at a base. C. hirsutus(L.)has soft hairs on both sides of its leaves [2] which are lacking in C. pendulus(Forst). Flowers are unisexual. Inflorescences cymose or thyrsoid, terminal, or axillary. Male flowers have 6-9 sepals, in 2-3 series, imbricate aestivation, the outer sepals are smaller and petals are 6 in number, normally bifid or emarginated apex, auricled below, stamens are usually 6-9, with free anthers, sub-globose and, cells bursting transversely. Female flowers are similar to male flowers in sepals and petals, carpels are 3-6 in number, and style is subulate, cylindrical and reflexed. Fruits are drupes, curved and obovoid in shape, slightly compressed from the lateral sides, and style scar is near the base, with a bony endocarp, and perforated on both sides. Seeds are curved, horse-shoe shaped, endocarp faintly tubercled, endospermic, and liguliform cotyledons [2, 3].

2.ETHNOMEDICINAL USES

Every part of the Cocculus plant is being used one way or the other by the tribal folk in India.

2.1 Whole plant

- The juice of C. hirsutus(L.) mixed with sesame oil is applied to the head and body to reduce heat. To allay the stomach heat and for the treatment of blood dysentery, the plant paste is applied over the navel region [5].
- An infusion of C. pendulus(Forst)is used in removing thorns from the feet. In the drier parts, C. pendulus(Forst)is browsed by all livestock, especially camels and goats [4].

2.2 Root

- The roots of C. hirsutus (L.) are bitter, alterative, and laxative. They are used in treating fever, skin irritation, rheumatism, gout, and syphilitic cachexia, stomach ache in children [5, 13-14]. Roots of C. hirsutus(L.) are also used to treat urinary disorders [15]. The roots are also useful as an antidote to snake bites [16].
- The roots of C. pendulus(Forst)are used as tonic and febrifuge [17]. The root of C. pendulus (Forst)treats biliousness, menstrual pains, and also acts as a diuretic. Roots are part of medicines against constipation as laxatives, helminthics, malaria and are used as cholagogues. Roots decoction is used together with Tinosporabakis (A. Rich.) Miers, to prepare a stimulating tonic. Roots are also found to be used in jaundice, yellow fever, leprosy, inflammation, rheumatic pains and as an aphrodisiac [4].

2.3 Stem

- The stem of C. hirsutus (L.) is used in the treatment of conjunctivitis and other eye disorders as well as stomach disorders[5].
- Stem bark and root bark decoctions of C. pendulus(Forst)are used for intestinal parasites as well as gonorrhoea. Wood infusion is taken as an emetic [4].

2.4 Leaves

- The juice of leaves of C. hirsutus(L.) is taken internally as a cure for gonorrhoea [2, 5, 16]. Leaves also allay fever and rheumatism [2]. Leaves of C. hirsutus(L.)are also consumed as a vegetable and also as a cure for Leucorrhoea [5, 18]. The powder of C. hirsutus (L.) leaves is given orally for dysentery and diarrhoea [16, 19]. The leaves are moreover used to treat several other skin disorders such as prurigo, impetigo, eczema, sores, cuts, wounds, etc. [5].

The mucilaginous juice of leaves is diuretic and refrigerant, thus is helpful in curing burning micturition (difficulty during the flow of urine) and skin diseases [15-16].

- The leaves of C. pendulus(Forst)are mostly used in wound healing, nose bleeding, and fertility medicine for women, and to regulate the menstrual cycle. Decoction of leaves is used in constipation. Diluted leaf juice along with sugar is a good tonic as it contains mucilage and forms a jelly when mixed with water. This is applied externally to skin diseases [4].

2.5 Flowers and Fruits

- The juice of the ripe fruits of C. hirsutus(L.) have anthocyanin which turns the green, unripe fruits to bluish purple which is a natural food colourant in various food items [15].
- The flowers of C. pendulus(Forst)are consumed as food. The fruits are also edible and are used to make an intoxicating drink [4].

3.PHYTOCHEMISTRY

Along with being ethnomedicinally essential, Cocculus species are rich in various phytochemicals. The plant contains phytocompounds like ginnol, sitosterol, glycosides, sterols, among others. Out of these, the vital component is alkaloids [20].

Earlier investigations of various parts of C. hirsutus(L.) have led to the isolation of trilobine, coclaurine, magnoflorine, and sitosterol. Rasheed Tahir et al., (1991) isolated a new alkaloid, Hirsutine through their phytochemical investigations [21]. Ahmad, V. U. et al., (1987) isolated a novel isoquinoline alkaloid, Cohirsine, from Cocculus hirsutus (L.)[22]. Another triterpenoid alcohol, Hirsudiol, was also isolated through spectroscopic studies (Ahmad, V. U., et al., 1987)[23]. Other investigations of the plant parts have resulted in the isolation of trilobine, isotrilobine, coclaurine, magnoflorine, **α**- sitosterol, ginnol, and a monomethyl ether of inositol [25-26]. Furthering the spectral studies, isoquinoline alkaloids likeJamtine-N-oxide (Ahmad, V. U., et al., 1987)[24], Cohirsitinine(Ahmad, V. U., et al., 1992)[25], and Haiderine (Ahmad, V. U., et al.,1993)[26]were isolated as gums from the aerial parts of C. hirsutus. Haiderine was isolated from the C. hirsutus(L.) leaves by flash chromatography [26].

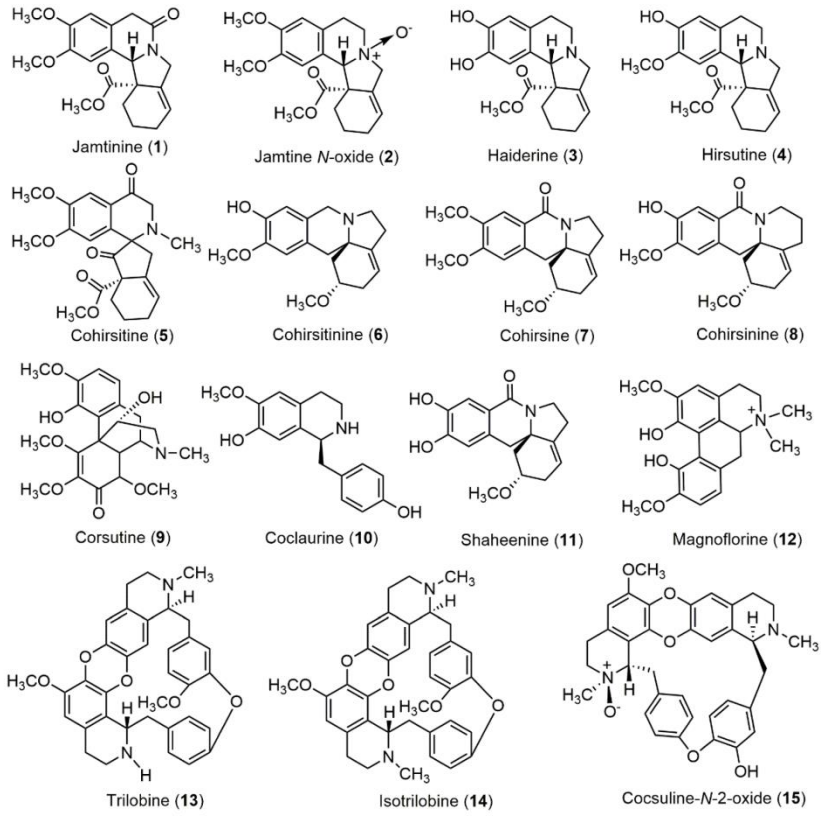

Figure 1: Structures of alkaloids reported from the extract of C. hirsutus (Logesh, R., et al.,) [5]

In Cocculus pendulus (Forst), a great variety of siddiquine, penduline, tetradine, isotrilobine, siddiquamine, kohatine, telobine, pateline, kurramine, isotrilobine and tricordatine, and many derivatives of these are found in the leaves and stems [4]. Rahman, A., et al., (2009) isolated the bisbenzylisoquinoline alkaloids from C. pendulus (Forst)[4, 27]. The alkaloidal extract of C. pendulus(Forst)also showed in vitro activity against acetyl- and butyrylcholinesterase [27]. Phytochemical investigation on Cocculus pendulus (Forst) resulted in the isolation of two new bisbenzylisoquinoline alkaloids; kurramine-2′-β-N-oxide and kurramine-2′-**α**-N-oxide (Rahman, A.,et al., 2004). The structures of these alkaloids were elucidated with the help of spectroscopic techniques. The cholinesterase inhibitory activities of these bisbenzylisoquinoline alkaloids were reported for the first time (Rahman, A.,et al., 2004)[28]. Al-Khalil, S., et al., (1993) reported the isolation of bisbenzylisoquinoline alkaloid; hernandezine, for the first time from the aerial parts of C. pendulus (Forst)by column chromatography [29]. Along with hernandezine, tetrandrine, penduline, cocsuline, and punjabine were also isolated [29]. Coccupendulusterol A (7,8-seco-stigmast-11,20(22)-diene-3b-ol.stigmast-5,20(22)-diene-9 a-ol) and Coccupendulusterol B (25-methyl tritriacont-21-ene-11-one-1-ol) were isolated from the stem of C. pendulus (Ali, M. et al., 1998)[30]. Guinaudeau, H., et al., (1987) yielded eight new bisbenzylisoquinoline alkaloids, namely (+)-kohatamine, (+)-1, 2- dehydrokohatine, (+)-1,2 - dehydrokohatamine, (+) -5'-hydroxyapateline, (+)-5′-hydroxytelobine, (+)-1, 2- dehydro-2′- nortelobine, (+)-siddiquine and (+)-siddiquamine from the leaves of Cocculus pendulus (Forst)[31].

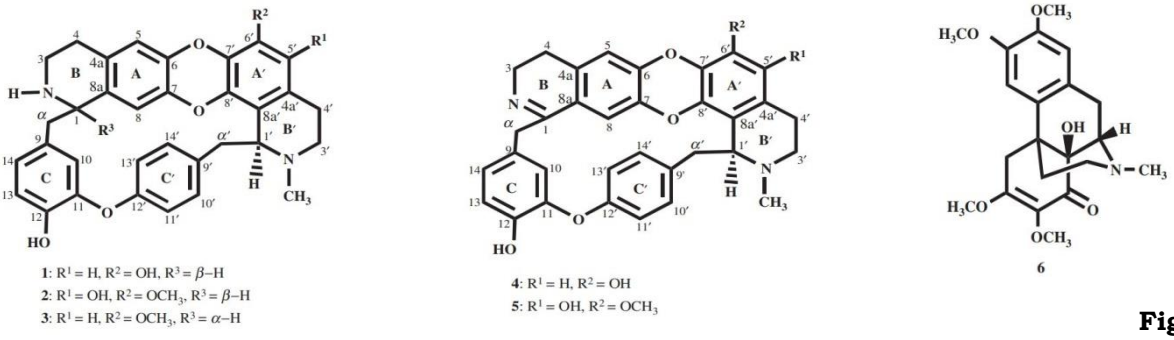

Figure 2: Bisbenzylisoquinoline alkaloids from C. pendulus (Forst): 1- 1,2-dihydrokurramine; 2- kohatine; 3- apateline; 4- kurramine; 5- 1,2-dehydrokohatine; 6- 14-hydroxyisostephodeline (Rahman, A., et al., 2009) [27]

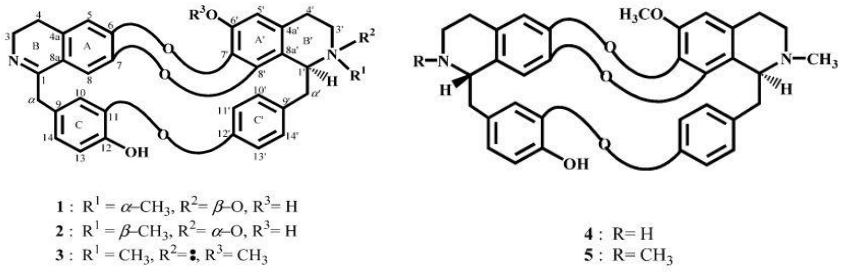

Figure 3: Bisbenzylisoquinoline alkaloids from C. pendulus(Forst): 1- Kurramine-2-β-N-oxide; 2- Kurramine-2-α-N-oxide; 3- 1,2-dehydroapateline; 4- cocsoline; 5- cocsuline (Rahman, A., et al., 2004) [28]

3.1 Bioactive Compounds

Bioactive compounds assay is very essential in order to confirm the application of the plant remedies for various ailments by traditional folk.Through several phytochemical investigations and analysis showed the presence of carbohydrates, steroids, alkaloids, glycosides, flavonoids, tannins, and saponins in various parts of the C. hirsutus plant [5, 34-38]. GC-MS chromatogram of the methanolic leaf extract of C. hirsutus(L.) showed 32 peaks indicating the presence of thirty-two compounds [34].

C. pendulus(Forst) reported the presence of carbohydrates, phytosterols, proteins, steroids, alkaloids, glycosides, flavonoids, tannins, saponins, triterpenes, and phenolic compounds from diverse plant parts through various phytochemical investigations and analysis [39-42].

3.2 A comparison between the phytochemicals present in C. hirsutus (L.) [32] and C. pendulus (Forst) [33].

Table 2: Phytochemicals present in the leaves of C. hirsutus(L.)and C. pendulus(Forst)

Sr No	Phytochemical	Cocculus hirsutus	Cocculus pendulus
1	(+)-Syringaresinol	+	-
2	1-Hentriacontanol	-	+
3	1,3-Dibenzylisoquinoline	+	+
4	beta-Sitosterol	-	+
5	Choline	-	+
6	Clionasterol	-	+
7	Coclaurine	-	+
8	Cocsoline	-	+
9	D-Galactose	-	+
10	Hernandezine	-	+
11	Isotrilobine	+	+
12	L-(+)-Arabinose	-	+
13	Menisarine	-	+
14	Nortrilobine	-	+
15	Oxyacanthan-12'-ol, 6',7-epoxy-6-methoxy-2,2'-dimethyl-, (1'alpha)-	+	+
16	Pendulin	+	+
17	Penduline	-	+
18	Pendulinine	-	+
19	Pentolinium tartrate	-	+
20	Punjabine	-	+
21	Quercitol	+	+
22	Sinactine	-	+
23	Tetrandrine	-	+
24	Trilobine	+	+

(+) = presence of phytochemical, (-) = absence of phytochemical

Table 3: Phytochemicals present in the stem of C. hirsutus(L.) and C. pendulus(Forst)

Sr No	Phytochemical	Cocculus hirsutus	Cocculus pendulus
1	Coclaurine	+	-
2	Trilobine	+	-
3	Isotrilobine	+	+
4	Magnoflorine	+	-
5	Nortrilobine	-	+
6	1,3-Dibenzylisoquinoline	-	+
7	Oxyacanthan-12'-ol, 6',7-epoxy-6-methoxy-2,2'-dimethyl-, (1'alpha)-	-	+
8	Hexacosane	-	+

9	Penduline	-	+
10	Pendulinine	-	+
11	Pentolinium tartrate	-	+
12	Tetrandrine	-	+

(+) = presence of phytochemical, (-) = absence of phytochemical

Table 4: Phytochemicals present in the roots of C. hirsutus(L.) and C. pendulus(Forst)

Sr No	Phytochemical	Cocculus hirsutus	Cocculus pendulus
1	Trilobine	+	-
2	Isotrilobine	+	-
3	Unii-kki91P85GE	-	+
4	Bebeerine	-	+

(+) = presence of phytochemical, (-) = absence of phytochemical

Table 5: Phytochemicals present in the whole plants of C. hirsutus(L.) and C. pendulus(Forst)

Sr No	Phytochemical	Cocculus hirsutus	Cocculus pendulus
1	Hirsutine	+	-
2	Coclaurine	+	-
3	Jamtine-N-Oxide	+	-
4	(S)-nonacosan-10-ol	+	-
5	Trilobine	+	-
6	Istrilobine	+	-
7	Magnoflorine	+	-
8	Hirsudiol	+	-
9	(+)-Syringaresinol	+	-
10	beta-Sitosterol	+	-
11	Pendulin	-	+
12	Palmatine	-	+
13	Oxyacanthan-12'-ol, 6',7-epoxy-6-methoxy-2,2'-dimethyl-, (1'alpha)-	-	+
14	Pendulinin	-	+

(+) = presence of phytochemical, (-) = absence of phytochemical

4.PHARMACOLOGICAL ACTIVITIES

Various pharmacological activities have been reported from the different plant parts of C. hirsutus(L.)and C. pendulus(Forst). Both of these species of Cocculus have demonstrated properties like anticancer [7], antioxidant [9], aphrodisiac [35], anti-inflammatory [8, 20, 40], wound healing [40], antimicrobial [6, 11, 43-44, 54-55], antimalarial [20, 38, 48-53], antiviral [44], analgesic [8, 20, 54, 60], and diuretic [20] among many others.

4.1 Antimalarial Activity

Brahmam, P. and Sunita, K. (2018) tested the efficacy of the antimalarial property of C. hirsutus(L.) and their results revealed that the stem bark ethyl acetate extract against K1 strain, root chloroform extract against 3D7 (chloroquine-sensitive strain) and K1 strains (non-chloroquine sensitive strain /chloroquine resistance strain), root ethyl acetate extract against K1 strain, root methanolic extract against 3D7 and K1 strains of P. falciparum of C. hirsutus(L.) have shown IC50 values of <5 µg/mL which indicate their excellent antimalarial activity [5, 38]. Elango, et al., (2011) evaluated the larvicidal activity of the leaves of C. hirsutus(L.)against malaria vector Anopheles subpictuslarvae and the different extracts

showed potent activity with percentage mortality at 24 hours and emergence inhibition values: hexane extract (60 ± 2.04 and 75 ± 2.44), chloroform extract (78 ± 2.56 and 85 ± 1.50), ethyl acetate extract (86 ± 1.29 and 69 ± 1.71), acetone extract (100 ± 0.00 and 68 ± 2.13) and methanol extract (81 ± 1.08 and 100 ± 0.00). Elango et al., (2009) also reported the larvicidal activity of the ethyl acetate and acetone extracts of the leaves of C. hirsutus(L.) against Culextritaeniorhynchusand Anopheles subpictus[5, 56-57].

Valentine, A., et al., (1997) isolated the SR isomer of penduline from C. pendulus (Forst)and pycnamine[48-49]. Four alkaloids present in the leaves of C. pendulus(Forst), cocsoline and penduline (Bhakuni and Joshi, 1975), tetrandrine and isotrilobine (Jain et al., 1990), have in other studies shown low IC50 values; 0.2 mg/ml (François et al., 1992), 0.012–0.028 mg/ml, 0.070– 0.122 mg/ml (Valentin et al., 1997) and 2.06 mM (Marshall et al., 1994), respectively. The occurrence of all four alkaloids in the leaves from Cocculus pendulus (Forst) may explain the high antiplasmodial activity [50].

4.2 Antimicrobial Activity

Devi, K. B., et al., (2017) evaluated the anti-fungal activity of the aqueous extract of C. hirsutus(L.) against Rhizopus arrhizus, Sclerotium rolfsiiand Fusarium solanifungal strains and the extract showed antifungal activity against S. rolfsiiand F. solani[5, 20, 55]. Jeyachandran, R., et al., (2008) presented preliminary information on the antibacterial activity of C. hirsutus(L.). Petroleum ether, chloroform, ethyl acetate, acetone, methanol, and aqueous root extracts of C. hirsutus(L.)were tested against bacteria Escherichia coli, Enterobacter aerogens, Klebsiella pneumoniae, Salmonella typhi, Proteus vulgaris, Pseudomonas aeruginosa, Staphylococcus aureus, and Bacillus cereus.The in-vitro antimicrobial activity was performed by the agar disc diffusion method in which the disc diffusion assay showed that the chloroform root extract of C. hirsutus (L.) highly affected the activity of Pseudomonas aeruginosa and Bacillus cereus. Staphylococcus aureus and Enterobacter aerogenswere moderately affected and the rest of the strains had no activity [6]. Through Liquid Chromatography-Mass Spectroscopy (LC-MS), Kumudini, M. et al., (2018) have suggested that the methanolic extract of C. hirsutus(L.) leaf possesses medicinally significant antimicrobial compounds and thus justifies the use of this leaf as folklore medicine for preventing human microbial-related diseases [44].

Talreja, T., et al., (2012) isolated flavonoids from C. pendulus(Forst)and tested its antimicrobial activity against Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae and Candida albicans [43]. Nafees, M., et al., (2019) assessed the stem and root crude ethanolic extracts and their isolated fractions of C. pendulus(Forst)using the agar disc diffusion method for antimicrobial activity against 4 pathogenic bacteria Staphylococcus aureus, Xanthomonas sp, Clavibacterand Proteus sp. The stem and its isolated fractions at all doses showed remarkable results. The stem and its isolated fractions showed the highest zone amplitude reduction against Xanthomonas sp (17mm) by CSE (Crude Stem Extract). ACSE (Alkaloids from Crude Stem Extract) produced (18mm) against Xanthomonas sp and FCSE (Flavonoids from Crude Stem Extract) produced (18mm) against Proteus sp. Similarly, the root and its isolated fractions also showed remarkable zones of inhibition at higher doses. The highest zone amplitude reduction (18mm) was noted against Proteus sp, while ACRE (Alkaloids from Crude Root Extract) produced (18mm) zone of inhibition against Proteus sp and FCRE (Flavonoids from Crude Root Extract) produced (18mm) against Xanthomonas sp[54]. Rehman, F., et al., (2017) tested C. pendulus(Forst) among a few other Indian medicinal plants for their antimicrobial activity by using the agar well diffusion method against human pathogenic bacteria such as E. coli, Salmonella spp, Shigella spp, Clostridium sppand Klebsiella spp. C. pendulus(Forst)showed maximum zone of inhibition against Clostridium spp(26 mm), Klebsiella spp(20 mm), Shigella spp(17 mm) while E. coli and Salmonella spp were resistant to Cocculus pendulus (Forst) extract [54].

4.3 Antiviral Activity

The first ever pan-anti-dengue evidence was reported by Shukla, R., et al., (2021) from C. hirsutus-based phytopharmaceutical through extensive in vitro and in vivo experiments. It was reported that AQCH (Aqueous extract of Cocculus hirsutus) demonstrated robust antiviral activity in in vitro studies and in an animal model (AG129 mouse model) of dengue.

Five compounds were characterized in AQCH, out of which only sinococuline reported to have potent pan anti-dengue activity. It was concluded that Cocculus hirsutus (L.)possesses pan-anti-dengue activity and was found to be more potent than Cissampelos pareira[45].

EtOH (Ethanolic) extract of aerial parts of Cocculus pendulus (Forst) had shown antiviral, hypotensive and anticancer activities (Asolkar, Kakkar &Chakre, 2000) [27, 61].

4.4 Anticancer Activity

Thavamani, B. S., et al., (2014) assessed the in vitroantitumor activity of various C. hirsutus (L.) extracts against MCF-7 cancer cell line andin vivo antitumor activity of the active extract in DLA tumour-bearing mice. The results ofin vivo study revealed that MECH (Methanolic extract of C. hirsutus) with doses of 200 and 400 mg/kg body weight significantly ($p < 0.001$) reduced the packed cell volume, tumour cell count, and restored the haematological and serum biochemical parameters towards normal values [7]. De Wet et al.,(2009) tested the anticancer activity of crude alkaloidal extract of rhizomes of C. hirsutus(L.) in three cancer cell lines, i.e., breast (MCF7), melanoma (UACC62) and renal (TK10) cell lines and the extract showed moderate anticancer activity[5, 58].

Cocculus pendulus (Forst)has been reported for hypotensive and anticancer activities in the 50% ethanolic extract of the leaves and stems [27, 51]. Rastogi, R. P., & Dhawan, B. N. (1990) cited that C. pendulus(Forst) demonstrated anticancer activity [62].

4.5 Anti-inflammatory, Wound Healing, and Analgesic Activity

Anti-inflammatory: Sengottuvelu, S, et al., (2012) tested the anti-inflammatory activity of C. hirsutus(L.)in both in vivoand in vitroconditions. The methanolic extracts of the leaves of Cocculus hirsutus (L.)were assessed for in vitro anti-inflammatory activity by the HRBC (human red blood cell) membrane stabilization method. Significant anti-inflammatory activity was depicted in the methanolic extract of Cocculus hirsutus (L.)leaves in a concentration-dependent manner. Methanolic extract at 200 mcg/ml showed 53.7% protection of HRBC in a hypotonic solution. The standard Diclofenac showed 65.2% protection. The in vivo anti-inflammatory effect of the methanolic extract of C. hirsutus(L.)was assessed using the cotton pellet-induced granuloma method in Wistar rats where it showed significant anti-inflammatory activity at 100 and 200 mg/kg (p.o.) dose. The results indicate that C. hirsutus(L.) at the dose levels of 100 mg/kg and 200 mg/kg produced a significant decrease in the weight of the granuloma 55.2 ± 0.5 (57.4% inhibition) and 41.4 ± 0.5 (68.3% inhibition) respectively as compared to the standard drug Naproxen 31.8 ± 0.2 (76.0 % inhibition) [8].

Rabari, H, et al., (2010) experimented the anti-inflammatory activity of C. pendulus(Forst)by the Carrageenan-induced paw edema model where the chloroform extract showed 42.10% and 69.90% inhibition of paw edema at the doses of 200 and 400 mg/kg body weight respectively, while ethyl acetate extract showed 39.20% inhibition of paw edema at the dose of 200 mg/kg of body weight and 67.00% inhibition of paw edema at the dose of 200 and 400 mg/kg of body weight. Although, it was less than that of the standard drug, Aspirin (72.31%) [40].

Wound-healing: Ranjan, P. B. et al.,(2009)evaluated the wound-healing activity from C. hirsutus(L.)leaves and reported that the methanolic extract depicted the highest wound-healing activity among all the tested groups when compared to the standard [5, 59].

Rabari, H, et al., (2010) assessed the wound healing activity of C. pendulus(Forst) in rats through the Excision wound model in which the extract-treated animals showed a more rapid decrease in wound size, decreased time to epithelialization and reduction in scar area as compared to control rats that had received simple ointment base [40].

Analgesic: Sengottuvelu, S, et al., (2012) assessed the analgesic activity of methanolic extract of Cocculus hirsutus (L.)using the hot plate method in Swiss albino mice which showed analgesic activity at a reaction time of 90 min (8.6 ± 1.7) at 200 mg/kg dose.It was slightly lower than the standard drug Pentazocine (10.6±0.2) [8]. The analgesic effect of methanolic

extract of Cocculus hirsutus (L.)leaves on acetic acid-induced writhing was also assessed where the control mice produced 66.67 ± 0.5 writhes. The pretreatment of methanolic extract of C. hirsutus(L.)at doses of 100 and 200 mg/kg reported to have reduced the number of writhes 36.33 ± 0.5 (45.51% protection) and 23.67 ± 0.7 (64.50% protection) respectively. The dose at 200 mg/kg resulted a lower analgesic activity than the standard drug Indomethacin 19.67 ± 0.5 (70.50 % protection). It was observed that the onset of writhing was delayed and the duration of writhing was shortened [8]. Taur, D. J., et al., (2010) studied the aqueous extract of roots of Cocculus hirsutus (L.)at doses 75, 100 and 150 mg/kg i.p. for its analgesic activity using acetic acid-induced writhing and formalin-induced paw licking in male Swiss albino mice. The aqueous extract at different doses significantly (P> 0.001) inhibited acetic acid-induced writhing and formalin-induced pain [60].

Nafees, M., et al., (2019) assessed the stem and root crude ethanolic extracts and their isolated fractions of C. pendulus for the analgesic activity by the means of acetic acid-induced writhing model in albino mice. CSE (Crude Stem Extract) and CRE (Crude Root Extract) showed significant pain reduction at (50, 70 and 90mg/kg) which were (21.53, 39.44 and 53.64%) and (24.61, 43.07 and 53.84%) respectively. Similarly, ACSE (Alkaloids from Crude Stem Extract) and ACRE (Alkaloids from Crude Root Extract) at 30 and 45mg/kg doses showed results which were (38.01 and 55.23%) and (49.23 and 58.46%) respectively. FCSE (Flavonoids from Crude Stem Extract) and FCRE (Flavonoids from Crude Root Extract) at 30 and 45mg/kg doses showed significant results which were (32.73 and 53.50%) and (35.38 and 55.38%) respectively [54].

4.6 SARS-CoV-2 Inhibition Activity

Rajan, M., et al., (2022) studied the phytochemicals of Cocculus hirsutus (L.)for anti-COVID-19 activity via inhibiting main proteases of SARS-CoV-2. Phytochemicals from C. hirsutus(L.)were docked against SARS-CoV-2 main proteases (6LU7, 5R7Y, 5R7Z, 5R80, 5R81, 5R82) using the PyRx virtual screen tool and discovery studio visualizer. It was found that betulin, coclaurine, and quinic acid of C. hirsutus (L.) had significant binding affinity to SARS-CoV-2 Mpro as compared to control. It was thus reported that these compounds could be potential leads for developing target-specific anti-COVID-19 therapeutics while ethnomedicinal uses of this herb could further be needed for its detailed antiviral therapeutic exploration [63].

4.7 Anti-Hyperglycemic Activity (Antidiabetic Activity)

Badole, S., et al., (2006) tested the antihyperglycemic activity of aqueous extract of leaves of C. hirsutus(L.)in alloxan-induced diabetic Swiss albino mice and concluded that the aqueous extract of leaves of C. hirsutus (L.) has antihyperglycemic activity as it lowered the serum glucose level ($P<0.01$) in diabetic mice and significantly increased glucose tolerance after treating with the aqueous extract of leaves of C. hirsutus (L.) (250, 500, and 1000 mg/kg) for a period of 28 days. Maximum reduction of serum glucose level occurred at the dose of 1000 mg/kg, p.o.[5, 64].

4.8 Antihepatotoxic Activity

Goodla, L., et al., (2017) estimated the protective/curative potency of Cocculus hirsutus (L.)leaves extract against CCl_4 (carbon tetrachloride) intoxication via its antioxidant property in Male Wistar rats. The study indicated that the EECH (Ethanolic extract of Cocculus hirsutus) has a potent hepatoprotective activity on carbon tetrachloride-induced hepatocellular destruction in rats. It was also elucidated that its hepatoprotective nature may be due to its antioxidative and free radical scavenging properties [9].Thakare et al.,(2010) studied the liver toxicity activity of C. hirsutus (L.) methanolic extract in albino Wistar rats and discovered that oral administration of the extract at dose levels of 100, 200, and 400 mg/kg significantly reduced the total bilirubin, LDH, AST, ALP, ALT, direct and cholesterol [5, 20, 65].

4.9 Spermatogenic Activity (Aphrodisiac Activity)

Sangameswaran and Jayakar (2007) evaluated the spermatogenic activity of C. hirsutus (L.) in streptozotocin-induced diabetic rats and the increase in the sperm count was observed at 400 mg/kg p.o (102.83 ± 1.85) and 800 mg/kg p.o. (117.83 ± 3.49) when compared to the

normal group (74.83 ± 1.97) (5, 66). Patil, S. A., et al., (2014) tested the aphrodisiac activity in the aerial parts of C. hirsutus(L.) where adult virgin male albino rats of the Wistar strain were used and it was concluded that C. hirsutus(L.)exhibited a remarkable increase in the spermatogenic activity [35].

4.10 Spermicidal Activity

Verma V., and Lall S. B., (2000) evaluated the effect of leaf and stem extracts of Cocculus pendulus (Forst) on cauda epididymal sperm of Swiss albino mice treated at a dose rate of 0.4 mg/kg body weight of ethanol soluble extract of stem and leaf of Cocculus pendulus (Forst)caused a reduction in sperm motility, increase in the number of dead sperm at day 7 post-treatment. However, the cytoarchitecture of the sperm remained unaffected. As such it may be considered a potent ingredient of post-coital spermicidal jellies and creams used in family planning schemes [67].

4.11 Cardiotonic Activity

Satyanarayana, K., et al., (1994) tested the methanol extract of roots ofCocculus hirsutus (L.)for its hypoglycemic and cardiotonic effects on diabetic rats and an isolated perfused frog heart respectively. The methanol extract exhibited significant hypoglycemic activity on diabetic rats and cardiotonic activity on normal and hypodynamic frog heart preparation [68].

4.12 Diuretic and Laxative Activity

The aqueous extract of the aerial parts of C. hirsutus (L.) was studied for its diuretic activity in normal mice at doses of 100 and 200 mg/kg, p.o. respectively (Ganapatyet al., 2001). The experiment resulted in a significant increase in the urinary concentrations of Na^+ and K^+ which suggested potent diuretic activity. At the same doses, the extract, orally given to rats, induced a significant laxative effect [69]. Badole, S. et al., (2009) also reported significant diuretic activity of ethanolic extract of leaves of C. hirsutus(L.)in Wistar rats which was administered at 100, 200 and 400 mg/kg, p.o.doses respectively [70].

Though Cocculus pendulus (Forst)have also been suggested as a diuretic and laxative agent in folk medicine, not enough scientific studies or analysis have been reported for the same.

4.13 Antioxidant Activity

Ameena, S., et al., (2022) tested the antioxidant activity of green synthesised copper nanoparticles of Cocculus hirsutus (CH-CuNPs)through various methods. The total antioxidant activity by the phosphomolybdenum method showed a higher percentage of total antioxidant activity in CH-CuNPs as compared to C. hirsutus leaf extract. Ameena, S., et al., (2022) also subjected C. hirsutus leaf extract and CH-CuNPs to Hydrogen Peroxide (H_2O_2) free radical scavenging to determine the antioxidant activity where CH-CuNPs showed the elevated percentage (71% at250 µg/ml of concentration) of H_2O_2 free radical scavenging activity compared to C. hirsutus leaf extract [46].

Bhardwaj L., et al., (1993) examined the effect of antioxidants and adsorbents on explants and callus of C. pendulus(Forst) producing intense brown substances in the medium causing necrosis. Antioxidants such as ascorbic acid, cysteine and dithiothreitol along with a few adsorbents were used in different concentrations to prevent the browning of the tissues. It was determined that the browning was caused by both peroxidase and phenolase. More phenols were likely subjected to peroxidative oxidation, increasing the peroxidase activity, but phenolase activity dipped due to a lack of substrate. Faster tissue growth as a result of this further decreased phenolase activity [4, 71].

4.14 Nanoparticles Synthesis

Cocculus hirsutus (L.)has also been used for the green synthesis of various nanoparticles. Ameena, S.,et al., (2022) reported that C. hirsutus (L.) can be exploited as a source for green synthesis of copper nanoparticles (CuNPs), having potent in vitro antioxidant, antibacterial, and anti-diabetic properties synthesized by reducing 3 mM copper acetate solution with aqueous leaf extract of Cocculus hirsutus. A colour change from deep brown to dark greenish brown indicated the formation of copper nanoparticles. The so-formed CuNPs were illustrated by using UV spectroscopy, FTIR, SEM, and EDX analyses which described sheet-like

structure morphology having a typical size of 63.46 nm. Later, the synthesized CuNPs efficiency was evaluated against bacterial pathogens and was found highly toxic to B. subtilis and S. aureus strains [46]. Bar, H., et al., (2012) reported a green method for the synthesis of gold nanostructures of variable morphologies using the aqueous extract of Cocculus hirsutus (L.)leaves where 5 mL leaf extract was added to 5 mL of 0.25 mM aqueous chloroauric acid, and the mixture was heated to 80°C on oil bath. The solution turned violet in colour after 40 min of heating. UV–Vis spectra showed strong surface plasmon resonance (SPR) band at 528 nm and which indicated the formation of gold nanoparticles [47].

5.TOXICOLOGY

Ganapaty, S., et al., (2002) tested the acute toxicity of the aqueous extract of C. hirsutus(L.)in normal mice. When orally administered to mice in graded doses from 100 to 3000 mg/kg of test extract, the aqueous extract of C. hirsutus (L.) produced sedation, increased urination and defecation at all the tested doses. However, there was no mortality reported at the end of the 14 days of observation [20, 69].

Nafees, M., et al., reported acute toxicity of C. pendulus(Forst) stem and root in albino mice of either sex at doses 100, 150 and 200mg/kg respectively. All the doses showed 100% mortality. Further diluting the doses to 80, 100 and 120mg/kg resulted in 60% mortality. Hence, the doses were further diluted even more to 50, 70 and 90mg/kg which was proven safe and did not show any mortality [54]. Rabari, H., et al., (2010) conducted an acute toxicity study for C. pendulus(Forst) by the stair-case method on Wistar rats of either sex. The rats were fed with plant extracts in increasing doses of 250, 500, 1000, 2000 and 4000 mg/kg body weight respectively. The doses up to 4000 mg/kg body weight did not produce any signs of toxicity and mortality [40].

6.PATENTS

There are several patents in India that have been registered for the utilisation of various formulae and compounds from C. hirsutus(L.)[72-77].

Table 6: A few of the registered patents for products derived from Cocculus hirsutus (L.)under Intellectual Property India.

Sr No	Invention Title	Publication Date	Application Number	Name of Inventor/s	Organisation
1	Extract of Cocculus hirsutusfor Treatment of COVID-19 [72]	14 May 2021	202027044178	Dhawan, S., Joglekar, S., Khuroo, A. H., Gurulue, S. J., Panigrahy, B. K., Maiti, S., Lal, A.,	Sun Pharmaceutical Industries Limited, Mumbai, Maharashtra
2	Herbal Formula Containing Cocculus hirsutusExtract for the Treatment and Management of Tuberculosis [73]	10 May 2019	201821050047	Jethva, K. D., Zaveri, M. N., Deshpande, S. S.	SV Innovation Foundation, Mehsana, Gujarat
3	Use of Cocculus hirsutusExtract for Treating Dengue [74]	12 June 2020	201821046412	Nayyar, K., Arora, U., Palla, S., Saravanan, A., Prasad, M., Madan, S., Khanna, N., Poddar, A., Shukla, R., Kothekar, M., Sood, R.	Dept of Biotechnology, New Delhi, International Centre for Genetic Engineering and

					Biotechnology, New Delhi, Sun Pharmaceutical Industries Limited, Mumbai
4	A Process for the Extraction and Stabilisation of Mucilage from Cocculus hirsutusUsing Nanoparticle [75]	17 May 2019	201841040921	Dr. Mala, R., Celsia, A. S. R., Prasath, N. H., Keerthana, R. C.	Department of Biotechnology, MEPCO Schlenk Engineering College, Sivakasi, Tamil Nadu
5	Herbal Composition for Therapeutic Management of Respiratory Tract Diseases [76]	12 January 2018	201611023226	Mina, M.	Udaipur, Rajasthan
6	A Plus - 5 Herbal Tonic [77]	19 June 2020	201841046941	Dr. Rajendran, A.	Mannargudi, Tamil Nadu

7.CONCLUSION

Cocculus hirsutus (L.)and Cocculus pendulus (Forst) are widely growing climbers. With a few minor changes morphologically and anatomically, it can subsequently be concluded that both the species; Cocculus hirsutus (L.)and Cocculus pendulus (Forst)are ethnomedicinally important. Both species of Cocculus contain numerous phytochemicals and possess many medicinally important properties which can be efficiently utilised for the betterment of human health. While there are numerous studies reported on the different properties and pharmacology of C. hirsutus(L.), detailed bioassays and evaluation of C. pendulus(Forst) are lacking. The assessment of C. pendulus(Forst) in further depth could be an interesting field of study with great revelations of the potency of C. pendulus(Forst).

8.CONFLICTS OF INTEREST

The authors as a result of this declare no conflicts of interest.

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