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Sida cordifolia, a Traditional Herb in Modern Perspective – A Review

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Abstract: *Sida cordifolia* (Malvaceae) is a highly reputable medicinal herb in the Ayurveda and other traditional systems of medicine in India and various other countries. In the Ayurvedic system of medicine it is used as antirheumatic, analgesic, antipyretic, antiasthmatic, nasal anticongestant, antiviral, laxative, diuretic, aphrodisiac, hypoglycaemic, hepatoprotective and in the treatment of Parkinson's disease. In order to evaluate this traditional plant in a modern perspective, the current review presents essential aspects of *S. cordifolia* including taxonomy, uses in disciplined traditional medicines, geographical distribution, chemical constituents, pharmacological studies on plant extracts and on single entity constituents, toxicity, and standardization. The chemical composition of this herb comprises of alkaloids, flavonoids, phytoecdysteroids, sterols and fatty acids. The problem of plant misidentification, due to confusion with other related species, is discussed. This paper reviews the conflicting reports regarding the presence or absence of ephedrine and discusses the claimed utility of this herb as a weight loss aid on the basis of ephedrine purported to be present in this species.

Keywords: Ayurvedic medicine, *Bala*, chemistry, pharmacology, review, *Sida cordifolia.*

1. INTRODUCTION

Popularly known as '*bala'*, the root of *Sida cordifolia* L. (Malvaceae) is regarded as a valuable drug in the Ayurvedic System of Indian Medicine. It is also used in the traditional medicine systems in China, Brazil and other countries for a wide range of illnesses. The traditional indications of bala include antirheumatic, antipyretic, analgesic, antiasthmatic, laxative, diuretic, hypoglycemic, as a nasal anticongestant [1-3], and as a pain reliever in sciatica [4]. The root of *S. cordifolia* has been recently reported as a potential remedy to reduce severity of Parkinsonism [5]. Other plant parts, including the leaves, stems, and seeds are also employed in traditional medicine for several medicinal purposes [6]. A number of patented herbal formulations disclosed composition with *S. cordifolia* as one of their ingredients, for utility as aphrodisiac, weight reduction aid, health promoter, particularly immunoenhancing, hepatoprotective, cardiotonic, and in dental caries prevention (Table **1**).

2. NOMENCLATURE AND BOTANICAL IDENTIFI-CATION

The nomenclature and botanical identification of *Sida* species is often confusing. The source of the popular Ayurvedic formulation 'bala' (meaning *strength* in Sanskrit) is ambiguous as different literatures correlate 'bala' to different species of *Sida*. While the name 'bala' is said to be traditionally correlated to *Sida cordifolia* (*aka* North Indian *bala*), *S. alnifolia* (also known as South Indian *bala*) [7] and *S. rhombifolia* [8], the name is also shared by several other species of *Sida* as well as other unrelated taxa. *Sida cordifolia* was reported as the primary source for bala in Ayurvedic formulations while *S. acuta* and

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Table 1. Literature on medicinal uses of *Sida cordifolia* extracts or purified constituents.

Medicinal properties	Study model/ method	Nature of tested material	Plant origin	References
Anti-inflammatory	Rat / *in vivo*	Ethyl acetate and methanol extract of the root	India	[19]
Anti-inflammatory and analgesic	Mice / *in vivo*	Aqueous extract of leaves	Brazil	[22]
Analgesic activity	Mice / *in vivo*	Ethyl acetate extract of the aerial parts and root	India	[19]
Antipyretic and antiulcerogenic	Rat / *in vivo*	Methanol extract of the aerial parts	India	[49]
Anti-inflammatory, antioxidant, neuroprotective	Rat / *in vivo*	Ethanol extract of root	India	[47]
Antinociceptive activity	Mice / *in vivo*	Chloroform, ethanol, and methanol fractions of the leaves	Brazil	[21]
Vasorelaxation of the rat superior mesenteric artery, hypotensive action	Rat / *in vivo*	Aqueous fraction of the hydroalcoholic extract of leaves	Brazil	[50]
Protective effect against mycocardial infarction	Rat / *in vivo*	Hydroalcoholic extract of the leaves	India	[52]
Cardioprotection	Rat / *in vivo*	Hydroalcoholic extract of the leaves	India	[52]
Hypotensive action	Rat / *in vivo*	Aqueous fraction of hydroalcoholic extract of the leaves	Brazil	[83]
Hepatoprotective	Rat / *in vivo*	Aqueous extract of leaves	Brazil	[54]
Hepatoprotective	Rat / *in vivo*	50% ethanolic extract of the root	India	[55]
Sedative effect CNS depressant	Mice / *in vivo*	Hydroalcoholic extract of the leaves		[23]
Antioxidant	*In vitro* assays	Ethanol extract and water infusion of whole plant	India	[4]
Inhibition of lipid peroxidation	*In vitro* assays	Water infusion of whole plant	India	[4]
Antiproliferative	*In vitro* on HepG-2 cells	Methanol extract of whole plant	Cameroon	[59]
Antidiabetic	Rat / *in vivo*	Methanol extract and aqueous extract	India	[60]
Hypoglycemic	Rat / *in vivo*	Methanol extract of the root	India	[19]
Antihypercholestrolemic	Rat / *in vivo*	Aqueous extract of the aerial parts	India	[60]
Wound healing	Rat / *in vivo*	Ethanol extract of whole plant	India	[61]
Parkinson's disease	Rat / *in vivo*	Aqueous extract of the whole plant	India	[5]
Ant-osteoarthritis	Rat / *in vivo*	Aqueous suspension of root powder	India	[62]
Analgesic and anti-inflammatory	Mice / *in vivo*	5`-hydroxymethyl-1`-(1,2,3,9-tetrahydro-pyrrolo [2, 1-b] quinazoline-1-yl)-hepta-1-one) (**9**), isolated from the aerial parts	Bangladesh	[85]
Analgesic and anti-inflammatory	Mice / *in vivo*	3′-(3″,7″-dimethyl-2″,6″-octadiene)-8-C-β-D-glucosyl-kaempferol 3-O-β-D-glucoside (**11**)	Bangaldesh	[37]
Analgesic and anti-inflammatory	Mice / *in vivo*	5,7-dihydroxy-3-isoprenyl flavone (**9**) and 5-hydroxy-3-isoprenyl flavone (**10**)	Bangaldesh	[75]
Anti-HIV agent	*In vitro* assays and *ex vivo*	(10E, 12Z)-9-hydroxyoctadeca-10,12-dienoic acid (**20**), isolated from the whole plant	South America	[56]

S. rhombifolia are considered as substitutes or adulterants, on account of similarity of their alkaloid profiles [9].

Sida cordifolia is widely used in Ayurveda, Folk, Siddha and Tibetan systems of Indian medicine. In India, the annual consumption of

'bala' during 2005-06 is estimated to be 5505 MT, and the raw material is solely sourced from wild habitats. The raw drug material traded under the name 'bala' includes materials (traded in the form of roots, seeds and whole plants) obtained from *Sida rhombifolia*, *S. acuta*, *S. cordifolia*, *S. cordata*, etc. [8].

Botanical names such as *Sida cordifolia*, *S. subcordata*, *S. caudata*, *S. cordifolioides* and *S. cordata* may be confusing to a layman due to similar specific epithets. Even in the field, an uninformed gatherer may find it difficult to distinguish species like *S. cordata*, *S. cordifolia* and *S. mysorensis* due to their similar leaf and flower morphology. However, observation of habit (branches trailing in *S. cordata*; erect in the other two species), arrangement of flowers (flowers in racemes in *S. mysorensis*; solitary in the others), features of fruits (mericarps about 10, and fruits exceeding calyx in *S. cordifolia*; mericarps about 5, and fruits not exceeding calyx in *S. cordata* and *S. mysorensis*) are helpful in proper identification of different species of *Sida* [10, 11]. A study found that the HPTLC markers of the aerial parts of *S. cordifolia*, *S. rhombifolia*, *S. acuta,* and *S. cordata* were different and thus can be used for discrimination of these species. The roots of *S. cordifolia*, *S. acuta* and *S. cordata* can also be differentiated based on their respective HPTLC fingerprints. However, the HPTLC profiles of the roots of *S. cordifolia* and *S. rhombifolia* were indistinguishable [34].

3. TAXONOMY AND DISTRIBUTION OF *SIDA CORDIFOLIA* L.

The genus *Sida* L. (Malvaceae) comprises about 250 species distributed primarily in the tropics [12]. The species *S. cordifolia* is probably indigenous to Africa, tropical and temperate Asia and S. America. It is naturalized elsewhere and is now almost pantropical. Report of this species as an endangered plant [13] is seemingly not based on any standard threat assessment or Red Listing procedures.

Botanical synonyms of *Sida cordifolia* L.: *Sida herbacea* Cav.; *S. holosericea* Willd. ex Spreng.; *S. hongkongensis* Gand.; *S. rotundifolia* Lam. ex Cav.

4. MORPHOLOGICAL DESCRIPTION OF *SIDA CORDIFOLIA*

Erect herbs or undershrubs, up to 1 m high leaves ovate, 2-5 × 1.5-4 cm, densely stellate-hairy, basally 5-7-nerved, base cordate to subcordate-obtuse, apex subacute to rounded, margin serrate-crenate; petioles about 3 cm long. Flowers yellow, about 1.5 cm across, solitary or fascicled, axillary or terminal. Mericarps, up to 8 mm across; usually 10, 2-awned at apex. Seeds subreniform, brown [11].

5. USES IN DIFFERENT TRADITIONAL MEDICINES

In India, *S. cordifolia* or 'bala' is considered to be one of the most valuable drugs in Ayurvedic medicine and has been widely used since ancient times [14]. The roots, leaves, and stems are utilized as traditional medicines in chronic dysentery, gonorrhea, and asthma [15]. It is also indicated for piles, to induce/promote aphrodisia, and as a remedy for neurodegenerative diseases, including Parkinson's disease [16] (Table **1**). The roots of *S. cordifolia* are administered as a curative agent for nervous disorders such as facial paralysis and hemiplegia, as well as in urinary disorders [17-19]. The root bark is exploited as stomachic, demulcent, tonic, astringent, bitter, diuretic, aromatic, and as antiviral agent [16]. The seeds of *S. cordifolia* are traditionally used as aphrodisiac and also indicated in the treatment of gonorrhea, cystisis, piles, colic and tenesumus. The pharmacological examination showed that seeds cause elevation of blood pressure in anesthetized animals [20]. In Brazil, *S. cordifolia* is generally recognized as 'malva branca' or 'malva branca sedosa' [21] and is used in Brazilian folk medicine for the treatment of inflammation of oral mucosa, asthmatic bronchitis, nasal congestion, blenorrhea [22], stomatitis, asthma [23, 24] and rheumatism, and as analgesic [2, 25]. It is also reportedly indicated in Brazilian traditional medicine as antirheumatic, antipyretic [26] laxative, diuretic, anti-inflammatory, analgesic and hypoglycaemic [19], antiviral [27], antimicrobial [28], and as aphrodisiac [29]. In China, *S. cordifolia* is considered as a herbal equivalent of *Ephedra* [16], while in Kenya it is utilized for dental hygiene [16].

Despite the possible confusion in identification of *Sida cordifolia* and other closely related species, several publications dealing with investigation of *S. cordifolia* did not properly verify the botanical source of the plant material and did not furnish details of voucher specimens. While study of incorrectly identified plant could convey wrong information, the products derived from misidentified plant material may adversely affect the safety of the consumers.

6. CONSTITUENTS OF *SIDA CORDIFOLIA*

6.1. Alkaloids

The roots of *S. cordifolia* afforded two main types of alkaloids (Fig. **1**); *β*-phenethylamines including *β*-phenethylamine (**1**), two carboxylated tryptamines, (*S*)-(+)-N_b-methyltryptophan methyl ester (**2**) and hypaphorine (**3**), and three quinazoline alkaloids; vasicine (**4**), vasicinone (**5**), and vasicinol (**6**), in addition to the bases choline and betaine found in the water-soluble alkaloid fraction. Ephedrine was reported in *S. cordifolia* as well as allied species [30-34], while other studies reported the absence of ephedrine [35, 36]. Recently, an unpublished investigation, employing LC-MS analysis, was conducted on commercial samples of *S. cordifolia* and fresh samples of different parts of *S. rhombifolia*, concluded the absence of ephedrine in the examined samples (Khan, *unpublished work*). Six-month-old roots of *S. cordifolia* produced mainly quinazoline alkaloids. Two-year-old roots afforded carboxylated tryptamines as the major components. However, it was observed that the level of alkaloids in this plant declines by age [31]. An additional quinazoline alkaloid, named 5`-hydroxymethyl-1`-(1,2,3,9-tetrahydro-pyrrolo [2, 1-b] quinazoline-1-yl)-hepta-1-one) (**7**) was isolated from the aerial parts of *S. cordifolia*, and was reported to possess analgesic and anti-inflammatory activity in animal models [37]. The well-known indoloquinoline alkaloid, cryptolepine (**8**), is a possible constituent of *S. cordifolia,* where it was recently isolated from this plant [38]. In contrast, a previous study reported the absence of cryptolepine in *S. cordifolia* [39].

6.2. Flavonoids

Two flavones (Fig. **2**), namely 5,7-dihydroxy-3-isoprenyl flavones (**9**) and 5-hydroxy-3-isoprenyl flavones (**10**) [6] and a C-flavonol glycoside 3`-(3``,7``-dimethyl-2``,6``-octadiene)-8-C-β-D-glucosyl-kaempferol 3-O-β-D-glucoside (**11**) [40]

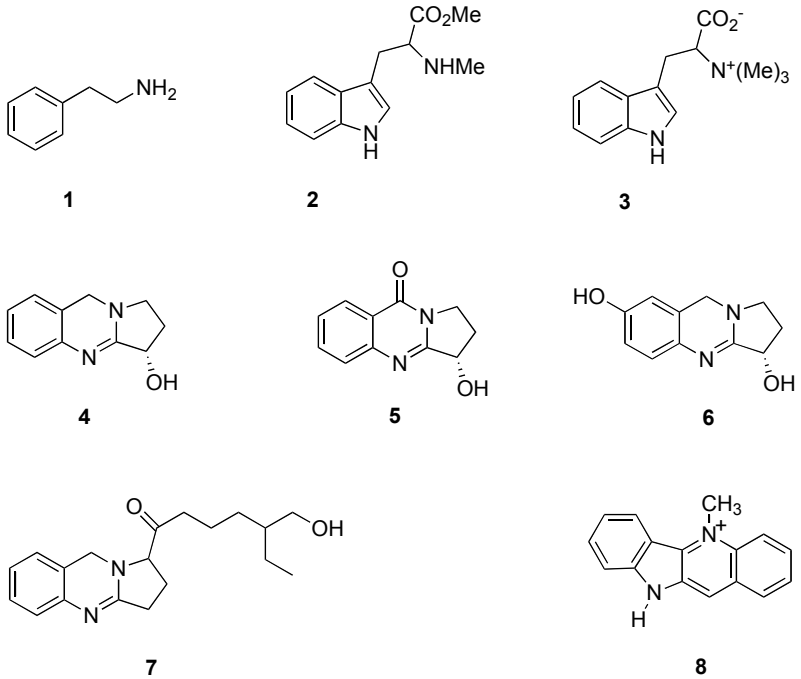

Fig. (1). Alkaloids in *S. cordifolia*. **1:** *β*-phenethylamine; **2**: S-(+)-N_b-methyltryptophan methyl ester; **3:** hypaphorine; **4**: vasicine; **5:** vasicinone; **6:** vasicinol; **7:** 5`-hydroxymethyl-1`-(1,2,3,9-tetrahydro-pyrrolo [2, 1-b] quinazoline-1-yl)-hepta-1-one); **8**: cryptolepine.

were isolated from the aerial parts of *S. cordifolia.* In a further investigation, three flavonol C-glycosides were isolated from the same source, these are; 3′-(3″,7″-dimethyl-2″,6″-octadiene)-8-C-β-D-glucosyl-kaempferol 3-O-β-D-glucosyl[1→4]-α-D-glucoside (**12**), 6-(3″-methyl-2″-butene)-3′-methoxy-8-C-β-D-glucosyl-kaempferol 3-O-β-D-glucosyl [1→4]-β-D-glucoside (**13**) [41], in addition to the previously isolated compound **1**.

6.3. Phytoecdysteroids

In contrast to other *Sida* species, no phytoecdysteroids were detected or identified in seeds of *S. cordifolia* [42]. However, a different literature source reported the presence of ecdysteroids in *S. cordifolia* (Fig. **3**), from this species sidasterone A (**14**) and sidasterone B (**15**) were isolated [43]. A recent publication on quantification of ecdysteroids in *Sida* species, employing LC-UV technique, reported the detection of 20-hydroxyecdysone (**16**) and 20-hydroxy-(25-acetyl)-ecdysone-3-*O*-β-D-glucopyranoside (**17**) in *S. cordifolia* at levels of 0.001% and 0.003%, respectively [44]. Taken together, it appears that the majority of *Sida* species are either devoid or contain only low levels of ecdysteroids in their seeds.

6.4. Steroids and Fatty Acids

The seeds of *S. cordifolia* contain 30.7% oil, β-sitosterol and stigmasterol [6], epoxy and cyclopropenoid fatty acids [45] were isolated from the seeds. The oil of *S. cordifolia* afforded mainly malvalic (**18**, Fig. **4**) and sterculic acids (**19**, Fig. **4**), along with other fatty acids (C14:0, C15:0, C18:0, C18:1, C18:2, C18:3) and coronaric acid. *Trans* unsaturated lipids were absent. Fresh leaves of *S. cordifolia* contain 0.06% essential oil that has a yellow color and distinguished odor [46]. In a recent article, bioassay-directed fractionation of

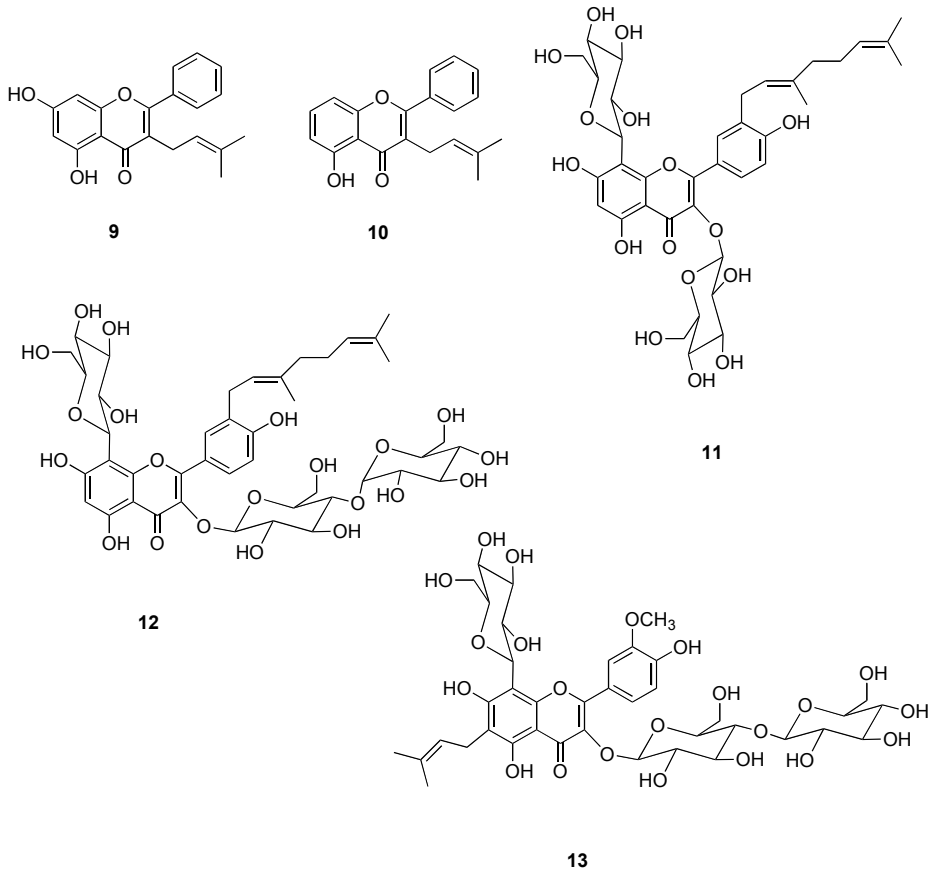

Fig. (2). Flavonoid constituents of *S. cordifolia*. **9:** 5,7-dihydroxy-3-isoprenyl flavones; **10:** 5-hydroxy-3-isoprenyl flavones; **11:** 3`-(3``,7``-dimethyl-2``,6``-octadiene)-8-C-β-D-glucosyl-kaempferol 3-O-β-D-glucoside; **12:** 3′-(3″,7″-dimethyl-2″,6″-octadiene)-8-C-β-D-glucosyl-kaempferol 3-O-β-D-glucosyl[1→4]-α-D-glucoside; **13:** 6-(3″-methyl-2″-butene)-3′-methoxy-8-C-β-D-glucosyl-kaempferol 3-O-β-D-glucosyl [1→4]-β-D-glucoside.

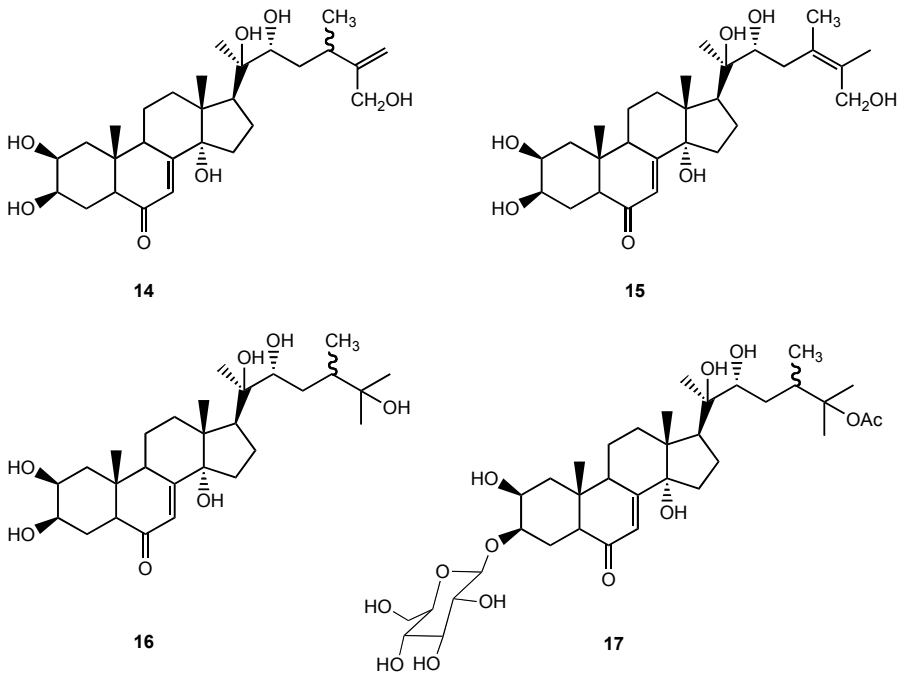

Fig. (3). Phytoecdysteroids of *S. cordifolia*. **14:** sidasterone A; **15:** sidasterone B; **16:** 20-hydroxyecdysone; **17:** 20-hydroxy-(25-acetyl)-ecdysone-3-*O*-β-D-glucopyranoside.

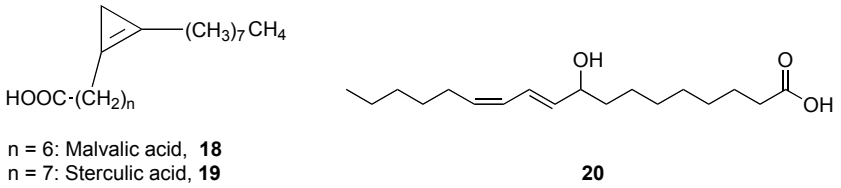

Fig. (4). Lypophilic constituents of *S. cordifolia*, two cyclopropene fatty acids; **18**: malvalic acid; **19**: sterculic acid; **20**: (10E, 12Z)-9-hydroxyoctadeca-10,12-dienoic acid.

the MeOH extract of *S. cordifolia* led to the isolation of a hydroxyl unsaturated fatty acid; (10E, 12Z)-9-hydroxyoctadeca-10,12-dienoic acid (**20**, Fig. **4**).

7. PHARMACOLOGY

The pharmacological and other biological effects of *Sida cordifolia* have been extensively elucidated to include actions on the cardiovascular system, CNS, anti-inflammatory, analgesic effect, hypoglycemic effect, anti-pyretic, anti-ulcerogenic activity, anti HIV-1 activity, and hepatoprotection. In a recent animal study on rats, to investigate the action of ethanolic extract of *S. cordifolia* root on quinolinic acid-induced neurotoxicity, *S. cordifolia* exhibited neuroprotective, anti-inflammatory and antioxidative effects comparable to the standard drug deprenyl. Quinolinic acid is an endogenous neurotoxin implicated in a number of neurological disorders, and is used as an investigational tool [47]. Some of the medicinal properties of *Sida* species might be ascribed to the presence of ecdysteroids [48].

7.1. Anti-inflammatory and Analgesic Effects

The ethyl acetate and methanol extracts of the root of *S. cordifolia*, when tested in rats, using the carrageenan-induced edema model, both produced anti-inflammatory effects. Nevertheless, the effect of the ethyl acetate, at a dose of 600 mg/kg, was equivalent to that of indomethacin. In addition, the ethyl acetate extracts of the aerial parts and root of this species exhibited substantial central and analgesic activity, employing the acetic acid induced writhing and hot plate methods [19]. In another work [47], the methanol extract of

S. cordifolia showed significant antipyretic and antiulcerogenic properties [49]. An aqueous extract of *S. cordifolia* leaves was examined in animal models for their pharmacological properties and found to possess anti-inflammatory and analgesic functions, with low acute toxicity in mice. Some experimental evidence suggested the latter effects are mediated *via* interference with cyclooxygenase pathways [22].

7.2. Anti-pyretic and Anti-ulcerogenic Activity

A methanol extract of the aerial parts of *Sida cordifolia* exhibited a significant anti-pyretic effect in rats, when tested orally at a dose of 500 mg/kg. The same extract also showed substantial antiulcerogenic effects against aspirin and ethanol-induced ulcers [49]. Chloroform, ethanol, and methanol fractions derived from an extract of *S. cordifolia* leaves were examined for their antinociceptive effect on orofacial nociception. The experiments were conducted in mice by using the glutamate- and formalin-induced orofacial nociception models. All of the three extracts exhibited significant antinociceptive activity in the first and second phases, in the formalin test, while in the glutamate-induced nociception, only the chloroform and the methanol fractions showed significant reduction of nociception [21].

An aqueous fraction obtained from the hydroalcoholic extract of *S. cordifolia,* was reported to induce vasorelaxation of the rat superior mesenteric artery, in a concentration-dependent relationship, stimulated for contraction by phenylephrine. It has been shown that endothelium-derived factors such as NO, PGI_2, and K^+ channels are implicated in the vasorelaxation activity exerted by *S. cordifolia* that led to hypotensive action [50].

7.3. Action on Cardiovascular System

In a published study, the influence of a hydroalcoholic extract of *Sida cordifolia* leaves on the biochemical and antioxidant profile of serum/ perfusate and heart tissue homogenate representing isoproterenol and ischemia reperfusion-induced myocardial infarction in rats, was evaluated. The extract of *S. cordifolia* displayed protective effects against myocardial infarction. The simultaneous elevation of the antioxidant enzymes superoxide dismutase (SOD) and catalase has been recognized as indication of cardioprotection [51]. Pretreatment of animals with the hydroalcoholic extract of *S. cordifolia* resulted in marked elevation of the levels of SOD and catalase activity when compared to the control. The latter action indicated the ability of *S. cordifolia* to induce cardioprotection [52].

Additionally, it was noted in a published study that the aqueous fraction of an hydroalcoholic extract of *S. cordifolia* leaves induced noticeable hypotension accompanied with intense bradycardia, when administered to normotensive non-anethetized rats [53]. The study investigated the mechanism of action and found that it is possible that the induction of hypotension and bradycardia might be attributed to indirect cardiac muscarinic activation mediated by vagal stimulation, and direct activation of endothelial vascular muscarinic receptors and subsequent release of nitrous oxide.

7.4. Hepatoprotective Effect

Sida cordifolia has been reported to possess experimentally demonstrated hepatoprotective effect. An aqueous extract of *S. cordifolia* leaves, orally administered to rats with partial hepatectomy, at a dose of 100 mg/kg, was observed to stimulate hepatic regeneration, through hepatocyte proliferation. This action was evaluated by immunohistochemical staining for proliferating cell nuclear antigen (PCNA), using the PC-10 monoclonal antibody [54]. Orally administered 50% ethanolic extract of the root of *S. cordifolia,* displayed substantial hepatoprotective activity against alcohol-induced hepatotoxicity in rats. The hepatoprotection was found to be mediated *via* reduction of the oxidative stress and down-regulating the expression of transcription factors. In connection, the rise in the levels of alcohol intoxication markers, including alanine aminotransferase, aspartate aminotransferase, and γ -glutamyltransferase was quenched after administration of *S. cordifolia* extract. Adding to this, the diminished activities of the antioxidant enzymes and glutathione, due to alcohol toxicity, were restored after administration of the extract [55].

7.5. Action on the CNS

The hydroalcoholic extract of the leaves of *S. cordifolia* -induced CNS depression in mice, which was demonstrated as alterations in the behavior of mice. This effect was also evidenced

from reduction of the motor activity of the animals, nevertheless, without interfering with motor coordination [23].

7.6. Anti HIV-1 Activity

From the whole plant of *Sida cordifolia,* the compound (10E, 12Z)-9-hydroxyoctadeca-10,12-dienoic acid (**20**, Fig. **4**) was isolated. This hydroxyl unsaturated fatty acid was found to be an exceptional NES (nuclear export signal) non-antagonistic inhibitor for nuclear export of Rev. Replication of HIV-1 is essentially dependent on the regulatory protein Rev or the Rev protein. The latter is involved in the nucleus-cytoplasm export of mRNA, which is in turn responsible for synthesis of the viral proteins necessary for viral replication. Several analogs of **20** were synthesized and tested for nuclear export of Rev inhibitory activity, but the parent compound proved to be the most potent. Previously, compound **20** was recognized as a natural anti-HIV agent [56].

7.7. *Sida cordifolia* in Neurodegenerative Diseases

In the Ayurvedic system of medicine, the part which deals with prevention and treatment of neurodegenerative diseases, such as Parkinson's, Alzheimer's, and loss of memory, is termed rasayana and the plants having such properties are known as rejuvenators. Amongst the plants in rasayana is *S. cordifolia* which is used clinically in the treatment of neurodegenerative diseases. It has been found that these plants (rasayanas) are generally characterized by possessing strong antioxidant activity [57]. Free radicals have been extensively reported to be implicated in neurodegenerative diseases [58]. Verification of the antioxidant capacity of *S. cordifolia* may justify its indication for treatment of neurodegenerative diseases in the traditional medicine.

In an *in vitro* and *ex vivo* study, the ethanol extract and the water infusion of *S. cordifolia* were examined for their antioxidant properties, utilizing 2,2`-azinobis-3-ethyl-benzothiazoline-6-sulfonic acid (ABTS) radical cation decolorization assay. The ethanol extract exhibited significant potency (IC50 16.1 μg/mL), while the aqueous infusion showed moderate antioxidant effect (IC50 342.8 μg/mL) [4]. The aqueous extract was also examined for inhibition of lipid peroxidation and showed moderate effect with IC50 126.8 μg/mL. The aqueous extract was tested for toxic action on viability of PC12 cell line, and it did not display toxicity [4].

7.8. Antiproliferative and Antioxidant Activities

Methanol extract of *S. cordifolia* when tested *in vitro* on HepG-2 cells, it exhibited significant antiproliferative activity after 48 h of contact with the cells. In addition, the same extract was demonstrated to elevate the activity of the antioxidant enzymes, superoxide dismutase, catalase, and glutathione S-transferase after 48 h [59].

7.9. Antidiabetic and Antihypercholesterolemic Effects

A recently published article described a study on the effect of methanol and aqueous extracts of *Sida cordifolia* on oral glucose tolerance test (OGTT) in addition to investigating the action of the aqueous extract on streptozotocin-induced diabetic rats in comparison with the clinically used drug metformin. The study revealed that administration of methanol extract or aqueous extract to normal rats resulted in reduction of the serum glucose level on days 7, 14, and 21, in a dose dependent manner. The maximum decrease in serum glucose level was observed with the aqueous extract at a dose of 1 g/kg. When the aqueous extract (1 g/kg, b.w.) was orally administered in the streptozotocin-induced diabetic model, a noticeable reduction in the serum glucose level was observed on days 7, 14, and 21, with concomitant improvement in the lipid profile, glycogen content, and gain in body weight [60]. In another account, it was found that the methanol extract of *S. cordifolia* root elicited a substantial hypoglycemic effect, when orally administered at a dose of 600 mg/kg to rats [19].

7.10. Wound Healing Properties

An ointment made of ethanol extract of *Sida cordifolia* was shown to accelerate wound contraction, and increase tensile strength of excision, incision and burn wounds in rats. In this study [61], the parameters indicating wound healing, including wound contraction, epithelialization period, hydroxyproline content, tensile strength, and histopathological features were compared with the effect of the standard drug, in this case silver sulfadiazine.

7.11. Alleviation of Parkinson's Disease Symptoms

In a recent investigation, the aqueous fraction as well as its sub-fractions, including the hexanes, chloroform and the aqueous ones, were assessed for their effects on the rotenone-induced biochemical, neurochemical, histopathological, and behavioral changes in rat model of Parkinson's disease. Rotenone-induced oxidative damage resulted in elevation in catalepsy and posture instability accompanied with reduction in rearing behavior. These signs of the disease were substantially diminished as a result of co-treatment with different doses of the aqueous extract (the first aqueous extract) and the aqueous extract that was partitioned between hexanes and then chloroform (the second aqueous extract). Additionally, the reduction in the level of dopamine in the midbrain region of the rat was reversed on co-treatment with the aqueous extracts. The maximum effect was achieved by the second aqueous extract. As such, the aqueous fractions of *S. cordifolia* might be medicinally useful in treatment of Parkinson's disease. This effect is possibly mediated by the antioxidative properties of the aqueous extracts.

7.12. Influence of *Sida cordifolia* on Collagenase-induced Osteoarthritis in Rats

A study [62] was initiated to explore the anti-osteoartheritic effect of *S. cordifolia,* on the basis of its utility in traditional medicine as anti-inflammatory. *S. cordifolia,* as a suspension in water, was orally administered to rats with collagenase type II-induced osteoarthritis. The results demonstrated that *S. cordifolia* possesses potent anti-osteoartheritic effects. The protective effects of this medicinal plant on joints was observed to be stronger than that of *Zingiber officinale* (Zingiberaceae). Histological examination also substantiated the protective properties of *S. cordifolia* on synovium and cartilage matrix of the knee joint in rats.

7.13. Pharmacology of Vasicine and Vasicinone

The pharmacological functions and the toxicity of vasicine, a respiratory stimulant, have been elucidated and reviewed to a large extent [63]. Vasicine was originally isolated from *Adhatoda vasica* (Acanthaceae) as the major alkaloid at a level of 0.05-1.11%. In *S. cordifolia* vasicine content is close to 0.01%, approximately five times less than that in *A. vasica*. At a low concentration, it evokes bronchodilation of the tracheal muscle, however, at higher doses it confers protection against histamine-induced bronchospasm in guinea pigs [64]. In addition, vasicine is a uterine stimulant, with properties similar to oxytocin [63, 65, 66]. Vasicinone is an autooxidation metabolite of vasicine. It was reported to possess *in vitro* and *in vivo* bronchodilatory effects [64, 67], cardiac stimulatory, and anti-anaphylactic effects [64, 68]. Further, both vasicine and vasicinone demonstrated anti-inflammatory properties in animal studies [69].

7.14. Pharmacology of Cryptolepine

Cryptolepine (**8**), is an indoloquinoline alkaloid, previously isolated from the West African plant *Cryptolepis sanguinolenta* (Apocynaceae), and was synthesized for the first time in 1906 by Fichter and Boehringer [70]. Several approaches for its synthesis have been reported [71-73]. Cryptolepine is an antimalarial agent, inhibitor of topoisomerase II [74, 75], DNA intercalator, and possesses substantial cytotoxicity. Despite the untoward effects of cryptolepine, it holds promise as an anticancer agent [38, 76], beside antileishmanial [77], antibacterial activity, and induction of apoptosis in HL-60 leukemia cells [78]. Cryptolepine was reportedly isolated from *Sida cordifolia* [38]. However, a review of the literature reveals conflicting reports about the presence of cryptolepine *in S. cordifolia* and *S. acuta* [39, 79, 80] owing to the uncertainty about the identity of the plant material used in some of these studies. This uncertainty of the plant identity arises from the lack of indications of proper authentication, or possibly because the plant material was obtained from unreliable sources. Recently, cryptolepine, as a DNA intercalator, was observed to inflict DNA damage in the mammalian cells, and that may result in genotoxicity [81]. Thus the uncertainty about the presence of cryptolepine in *S. cordifolia* makes its safety questionable and hence consumption of food supplements that contain cryptolepine as a component poses a potential health risk.

8. TOXICITY

The aqueous extract of *Sida cordifolia* was tested for toxic effect on viability of PC12 cell line with no signs of toxicity [4]. A further toxicity

study on *S. cordifolia* was conducted in mice and was found to be very low, approximately 3g/Kg. p.o. [82, 83]. The LD_{50} of the hydroalcoholic extract of the leaves was determined in mice to be 2.639 g/kg with 90% confidence limits of 2.068-3.367g/kg, when administered intraperitoneally. Administration of doses up to 5.0g/kg, was found not lethal to the animals.

9. STANDARDIZATION

Sida cordifolia has been standardized on the basis of its bioactive alkaloids visicine and vesicinone. Reverse phase HPLC and normal phase HPTLC densitometric methods have been developed and validated for this purpose. The HPLC procedure involved using acetonitrile-phosphate buffer-glacial acetic acid as mobile phase with UV detection at 300 nm in isocratic mode. The HPTLC method utilized normal-phase silica and detection under the UV light at 298 nm to achieve quantification of these alkaloids as markers for standardization. In this analysis *S. cordifolia* was found to contain vasicine and vasicinone at levels of 0.011% and 0.0065%, respectively [84]. In a previous study, an HPTLC method was described for discrimination between *S. cordifolia* and allied species viz. *S. cordata*, *S. rhombifolia*, and *S. acuta*. The study showed that the HPTLC fingerprints of the aerial parts of *S. cordifolia*, *S. rhombifolia*, *S. acuta,* and *S. cordifolia* were different, which can be utilized for discrimination between the four species. The analysis exhibited that root of *S. cordifolia* could be differentiated from the root of *S. cordata* and *S. acuta* by comparing the HPTLC fingerprints of their extracts. However, the chromatographic profiles of the roots of *S. cordifolia* and *S. rhombifolia* were indistinguishable [34].

CONCLUSION

Sida cordifolia is prescribed in traditional medicine in India, China, Brazil and other countries for a wide range of indications including bronchitis, asthma, nasal congestion, inflammation of oral mucosa, rheumatism, neurodegenerative diseases, chronic dysentery, and gonorrhea. Additionally, it possesses antiviral, analgesic, antipyretic, laxative, diuretic, and aphrodisiac properties, and is also used as a hypoglycaemic agent. Nevertheless, the presence of ephedrine in *S. cordifolia* and in allied species, as the putative causative agent for many of the medicinal uses of this herb, has been controversial. Although there are a number of accounts that provide evidence for the presence of ephedrine in *S. cordifolia* as well as other species, other studies, including in-house unpublished investigations, have not detected ephedrine in the examined samples. Therefore, iniation of thorough studies involving different species of *Sida* with a large number of samples acquired from different geographical regions and at different plant growth stages, is warranted in order to confirm the presence or absence of ephedrine and cryptolepine in the species of *Sida*.

The existence of a potent bronchodilator-vasicinone in *Sida cordifolia* may justify its therapeutic utility in the Ayurvedic system of medicine for conditions similar to those treated with ephedrine. Despite there have been no reports of toxicity associated with *S. cordifolia,* the presence of alkaloids such as vasicine-type alkaloids and cryptolepine which have not been adequately evaluated yet, raises concerns about its safety and possible toxicity. Some of the exomorphic features of *Sida cordifolia* are similar to those of other closely allied species in the genus and may often be misidentified. It has been reported that in several cases the market samples of bala are in fact derived from materials obtained from various closely allied species, perhaps due to confusion in the identification. Hence, proper authentication is mandatory for use of commercial bala samples in scientific studies and for medicinal purposes. Adding to this, many of the research publications do not provide essential details about plant materials such as the source/origin, details of collection, method of identification and information on voucher specimens.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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