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Review Article

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Sida cordifolia - an Update on Its Traditional Use, Phytochemistry, and Pharmacological Importance

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ABSTRACT

Drugs derived from natural sources have been a vital part of drug discovery for centuries. Many of the most successful drugs on the market today are derived from natural sources. Traditional knowledge or the traditional system of medicines is often used to select the most appropriate sources for drug discovery and it is a valuable tool in the search for new lead molecules. In Ayurveda, Sida cordifolia L (SC) is regarded as a highly effective medicinal plant and most of its parts have been traditionally used to treat a wide range of illnesses. SC is also known as "Bala" in Hindi and is considered a "Rasayana", which means that it has rejuvenating properties. All the relevant information on SC was retrieved through electronic databases, textbooks, and a library search. This review covers the available literature from 1980 to the end of December 2021. Phytochemical studies revealed that SC is rich in alkaloids, flavonoids, steroids, fatty acids, and other classes of secondary metabolites. Several studies have shown that SC extracts and their phytochemicals or isolated metabolites have anti-inflammatory, antioxidant, antibacterial, antiviral, anticancer, antihyperglycemic, and wound healing properties in in-vitro and in-vivo studies. The results of traditional uses, the presence of phytochemicals, and pharmacological investigations summarised in this review will help to further extend its therapeutic potential and give compelling evidence for its future therapeutic application in modern medicine.

Key words: *Sida cordifolia, Phytochemicals, Secondary metabolites, Pharmacological activity, In-vitro activity*

INTRODUCTION

Herbal compositions have been used as remedies for various disorders from the beginning of humanity to the modern era [1]. The use of medicinal plants is based on their traditional use in treating illnesses or diseases. Medicinal plants are used in various forms, including extracts, tinctures, teas, pills, and powders. Many people around the world still depend on herbal remedies to meet their basic healthcare needs. Approximately 80% of the world's population utilizes herbal therapies, according to a WHO report [2]. Additionally, the medications currently available to treat modern disorders are primarily found through the properties of plants that have traditionally been used for medicinal purposes [3]. A large proportion of drug research is devoted to the exploitation of natural resources and their constituents to combat the threat of continuously developing diseases in humans [4]. The pharmaceutical industry frequently relies on plants for crucial components and raw materials. It is primarily due to the increased demand for herbal raw materials, which has led to the commercialization of medicinal plants. *Sida* is a genus of flowering plants belonging to the family Malvaceae. Over 200 herbaceous species with ethnomedicinal importance are included in the genus. *Sida cordifolia* (SC) is one of the notorious species in the genus; it is used to treat a variety of diseases [5]. SC is a popularly recognized plant in India known as "*Bala"* and *"Country mallow"*one of the ingredients used to make various Ayurvedic formulations [6]. There are multiple benefits of SCs, including anti-inflammatory and analgesic activity, antibacterial, antioxidant, anti-diabetic properties, anticancer activity, and wound healing properties. Certain herbal formulations derived from the genus of Sida have already been patented for various health concerns [7, 8]. In the years between 1980 and 2021, the term "*Sida cordifolia*" was associated with a variety of terms to compile information published between these years. These terms included "biological activity," "pharmacological properties," "bioactive components," "active constituents," "ethnomedicinal use," "traditional use," etc. This information is accessible through various online databases like Google Scholar, PubMed, ResearchGate, Scopus, and the Web of Science. The various pharmacological activities of SC are depicted in **Figure 1**. The remedial properties of this plant are due to the presence of various biologically active phytocomponents. This review aims to provide comprehensive information related to SC's traditional uses, phytochemical constituents, and pharmacological relevance. This information will be useful for developing new drugs to treat serious illnesses.

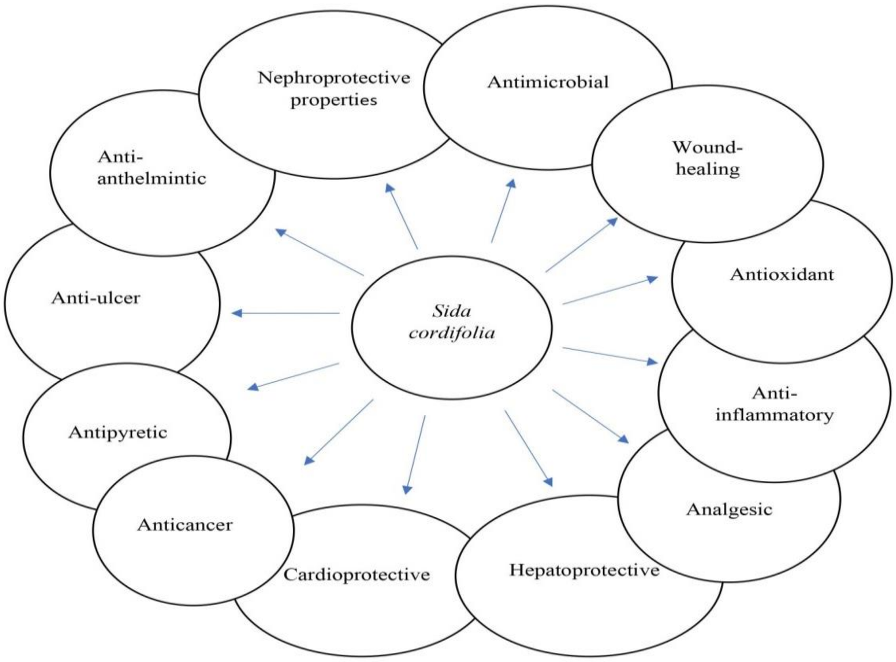


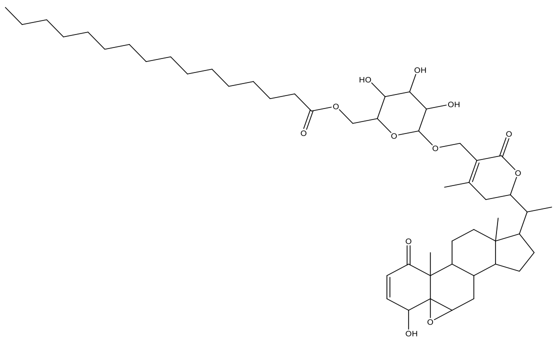
Figure 1. Pharmacological activities of *Sida cordifolia*

Traditional importance of Sida cordifolia L

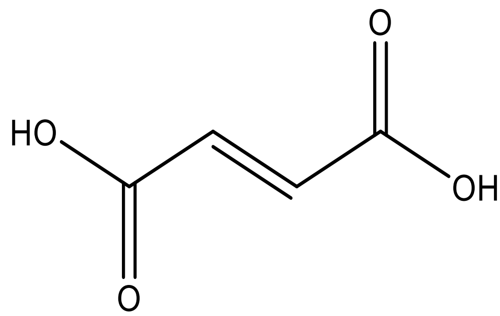
Sida cordifolia L is a plant from the Malvaceae family that is native to North-eastern Brazil. It has been found throughout India's tropical and subtropical plains, along with other species of this genus [9]. The plant is used in Ayurveda as a treatment for rheumatism and Parkinson's disease [10]. Many ailments can be treated using different plant parts of SC in Ayurveda. These include fever, convulsions, gonorrhea, urinary tract issues, neurological disorders, general debility, and heart problems. In traditional Indian medicine, the SC is used as a tonic and as an aphrodisiac. The seed extracts were found to cause an increase in blood pressure in rats [11, 12]. There are many uses for the roots, including the treatment of hemiplegia, facial paralysis, sciatica, weight loss, cervical spondylosis, neuralgia, and neurosis, and they are also used to treat asthma [8, 13]. The root bark of the SC is used as a stomachic, demulcent, tonic, astringent, bitter, diuretic, and antiviral agent [14]. Bark can be beneficial for problems with the blood, throat, and urinary system. It is also beneficial for piles, phthisis, and insanity [15]. The root of the SC is used to make a decoction that is given in intermittent fevers with cold shivering fits. The powder from the root and bark is also given with milk and sugar for frequent micturition. The oil prepared from the decoction of root bark mixed with milk and sesame oil finds application in diseases of the nervous system, such as facial paralysis and sciatica, and it is very efficacious in curing them [16]. Leaves made into a paste with juice of palmyra tree are applied locally to treat elephantiasis [17]. It is known as "Malva-Branca" in the northeast region of Brazil and is extensively used in traditional medicine for the treatment of rheumatoid arthritis**,** inflammatory conditions, breathing issues, and nasal congestion [18]. In Sokoto, the aqueous leaf extract of SC is widely used to treat stomach discomfort and bacterial infections by oral administration [19].

Phytochemistry of Sida cordifolia

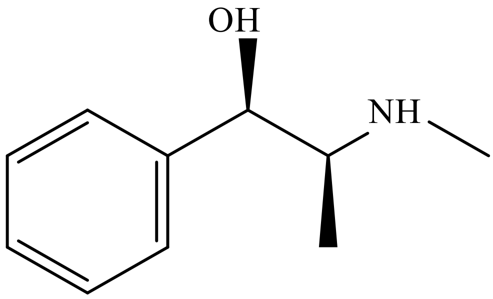
Sida cordifolia contains a variety of phytochemicals, with a focus on alkaloids and flavonoids. In **Figure 2** are listed the different classes of SC phytoconstituents. The biological activity of a medicinal plant is influenced by the presence and richness of phytochemicals, and the leaves of SC contain more phytochemicals than its stem bark. Moreover, an elemental analysis indicates that the concentrations of Mn, Cr, Mg, Na, and K in leaves of SC differ significantly from those in stem bark. However, the concentrations of Cu, Pb, Ca, Zn, and Ni in the leaves do not differ significantly from those in the stem bark [20]. An acylsterylglycoside derived from the roots of SC, known as Sitoindoside X, exhibits adaptogenic and immunostimulatory properties [21]. The fumaric acid isolated from the SC showed liver-protective properties [22]. SC was found to contain phenylethylamine alkaloids, ephedrine, and quinazoline alkaloids namely vasicine, vasicinol, and vasicinone, along with N-methyl tryptophan [23, 24]. The presence of four different alkaloids in the methanolic extract of the aerial part of the SC plant is confirmed and known as 1,2,3,9-tetrahydro-pyrrolo [2,1-b] quinazolin-3-ylamine, 5'-hydroxymethyl-1'- (1,2,3,9-tetrahydro- pyrrolo [2,1-b] quinazolin-1-yl)-heptan-1-one, 2-(1'-amino-butyl) indol-3-one, and 2'-(3H-indol-3-yl methyl) butan-1'-ol [25, 26]. Flavones have been found in the aerial part of a chloroform extract of SC and have been identified as 5,7-dihydroxy-3-isoprenyl flavone and 5-hydroxy-3-isoprenyl flavone. β-sitosterol and stigmasterol were also identified [27]. In seeds of SC, sidasterone A and sidasterone B have been identified [28]. The indoloquinoline alkaloidal compound cryptolepine was isolated from the SC plant [29]. The alkaloids ephedrine and hypaphorine were identified by GC-MS analysis of aerial parts of SC, along with other known compounds [30]. In SC seeds, two ecdysteroids are found, including 20-hydroxyecdysone and 20-Hydroxy-(25-acetyl)-ecdysone-3-O-β-glucopyranoside. The presence of these active components is detected by LC-UV [31]. Most of the seed oil of SC contains malvalic, sterculic, and coronaric acids [32]. A methanolic extract of SC containing the hydroxyl unsaturated fatty acid (10E, 12Z)-9-hydroxyoctadeca-10,12-dienoic acid [33].



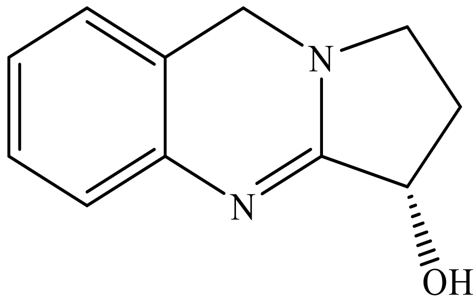
1. Sitoindoside X



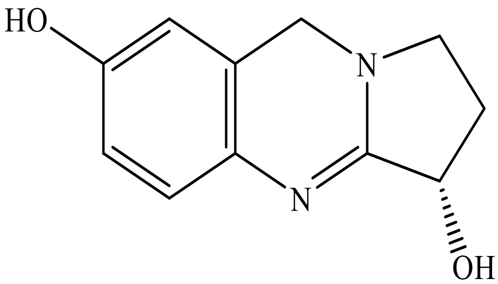
2. Fumaric acid



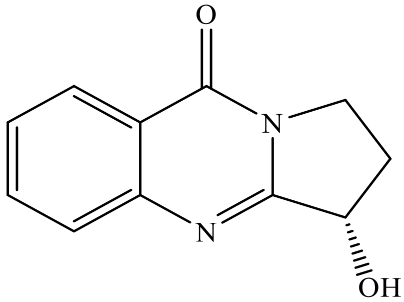
3. Ephedrine



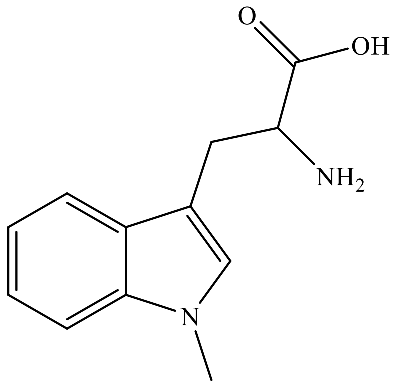
4. Vasicine



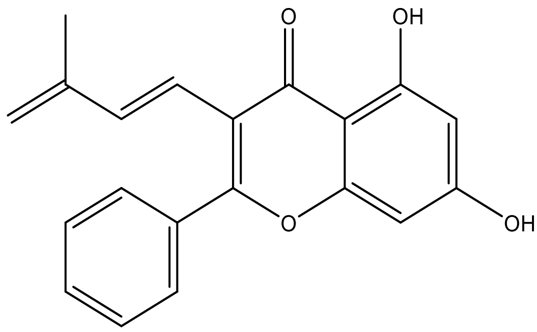
5. Vasicinol



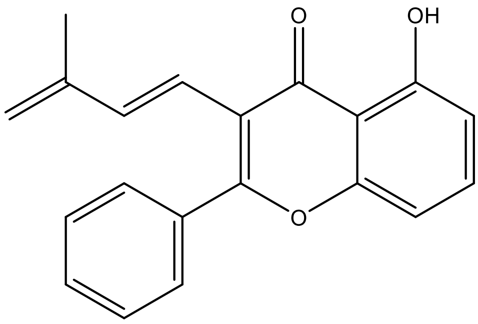
6. Vasicinone



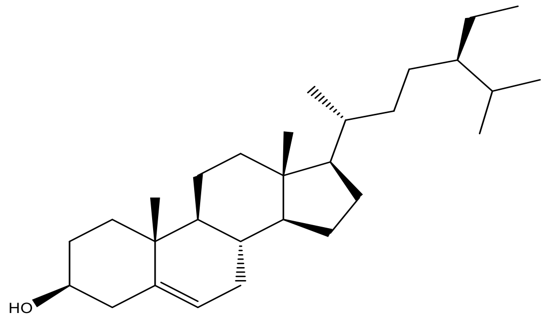
7. N-methyl tryptophan



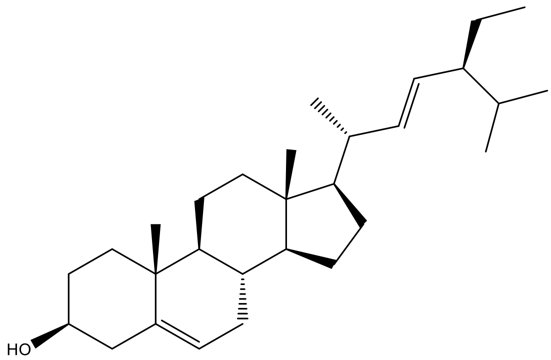
8. 5,7-dihydroxy-3-isoprenyl flavones



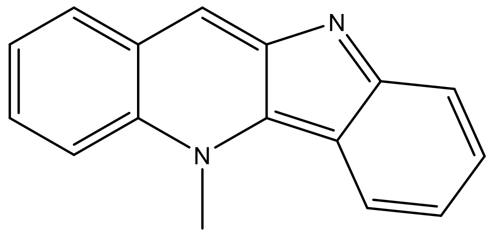
9. 5-hydroxy-3-isoprenyl flavones



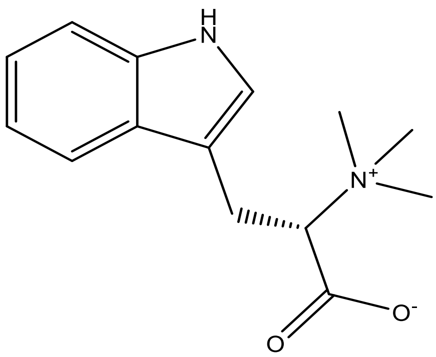
10. β-sitosterol



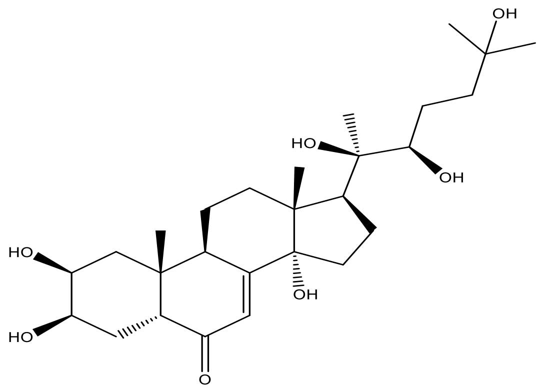
11. Stigmasterol



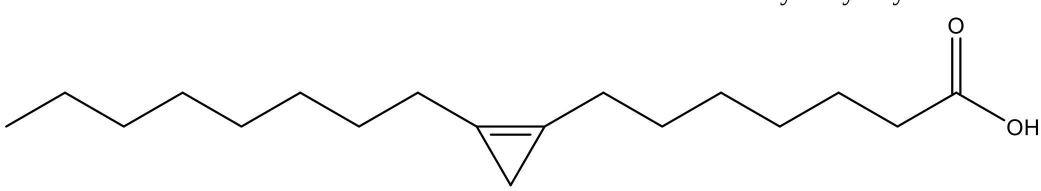
12. Cryptolepine



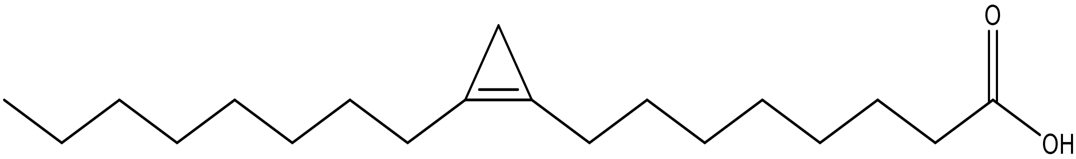
13. Hypaphorine



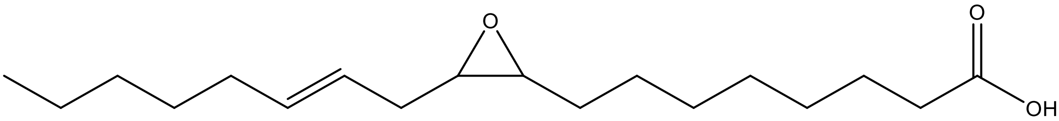
14. 20-hydroxyecdysone



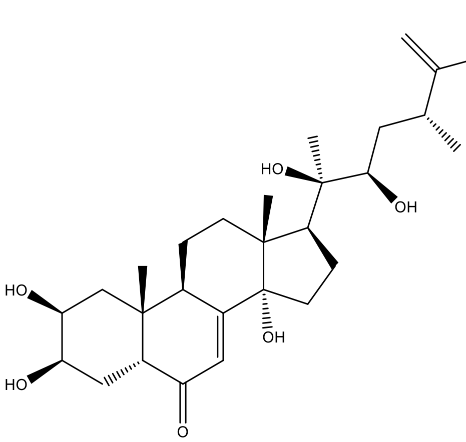
15. Malvalic acid



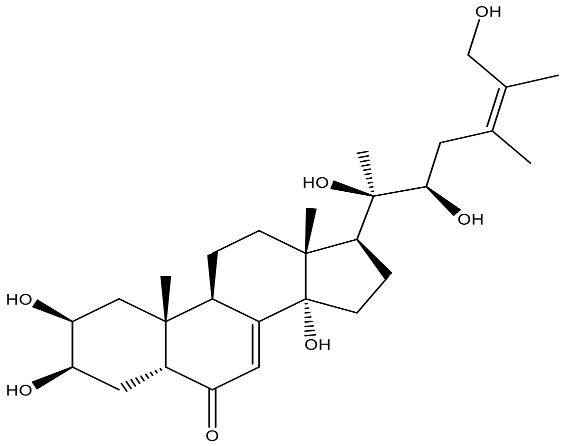
16. Sterculic acid



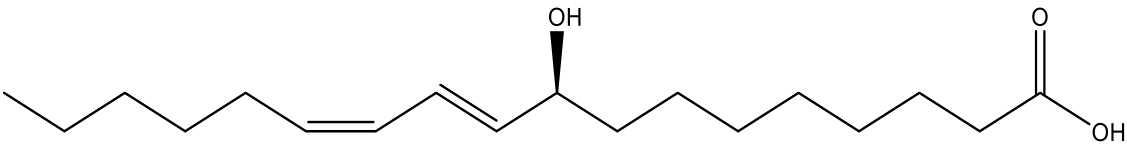
17. Coronoric acid



18. Sidasterone- A



19. Sidasterone- B



20. (9S, 10E, 12Z)-9-hydroxyoctadeca-10, 12-dienoic acid

Figure 2. Phytoconstituents in *Sida cordifolia*

Pharmacological importance of Sida cordifoilia

Antimicrobial activity

Human mortality has been dominated by infectious diseases in the recent past. There has been a concerted effort in the last two decades to discover chemically useful antibacterial or antifungal drugs from plants [34]. When compared with naturally-occurring antimicrobial agents, the use of synthetic antimicrobial agents has many disadvantages [35]. SC is an antimicrobial plant that has been used for centuries to treat various pathogenic infections. By hydro-distillation, the yellow-colored oil is obtained from the fresh leaves of SC. An antimicrobial evaluation of the essential oils was conducted against four bacterial and nine fungal stains. With an efficiency of about 80%, the essential oil was more effective against *S. aureus*, *S. epidermidis*, *C. guilliermondii*, and *T. Inkin* [36]. Two different extracts, petroleum and chloroform, are derived from SC seed oil. With a higher concentration of petroleum ether extract, it exhibits considerable effectiveness against *S. aureus* and *E. coli*. Both extracts exhibit significant antifungal activity against *A. niger* at higher concentrations, whereas they demonstrate promising antifungal activity against *C. Albicans* [37]. The alcoholic extract of the entire plant SC contains a flavone, 5,7-dihydroxy-3-isoprenyl flavone, and the glucoside 3,7-dimethyl-2,6-octadien-8-C--D-glucosyl-kaempferol 3-O--D glucoside. This promising inhibitory activity against *Vibrio cholerae* O1 can be attributed primarily to the presence of 5, 7-dihydroxy-3-isoprenyl flavones [38]. The phytosterol stigmasterol is isolated from ethanolic fractions of SC leaves. The structure was further confirmed through spectroscopic analysis. The isolated compound from the plant demonstrated significant antibacterial activity against gram-positive bacteria, such as *S. aureus* and *B. subtilis*, and gram-negative bacteria such as *E. coli* and *P. Aeruginosa* [19]. Aqueous extracts of the whole plant SC are used to synthesize silver nanoparticles. They are ultra-small, monodispersed spherical nanoparticles with a face-centered cubic structure and a mean particle size of 3–6 nm. The Ag nanoparticles exhibited significant antibacterial activity against five pathogenic fish species, including *A. hydrophila, P. fluorescence, F. branchiophilum, E. tarda*, and *Y. rukeri*, as well as four human pathogens, including *E. coli, K. pneumonia, B. subtilis*, and *S. aureus*. Ultra-small monodispersed Ag-NPs have a superior antibacterial activity to other Ag NPs. Alternatively, these ultra-small Ag NPs might have a larger surface area, be attached to a cellular membrane, or be able to penetrate bacterial cells more effectively if there were a large number of them [8]. The green fabricated iron oxide nanoparticles hematite (α-Fe_2O_3) are synthesized by utilizing plant extract from SC and have an average particle size of 38 nm. The agar well diffusion method indicates that α-Fe_2O_3 NPs are more effective at inhibiting *B. subtilis* growth, with a maximum zone of inhibition of 16.00±1.00mm. The green synthesized α-Fe_2O_3 NPs inhibited the growth of *S. aureus, E. coli,* and *K. pneumonia* atzones of inhibition of 13.67±0.58, 11.33±0.58, and 12.00±1.00 mm, respectively [39]. The methanolic fraction of SC roots contained two phytocompounds, rosmarinic acid, and rosmarinic acid 4-O-β-d-glucoside. There is a substantial antibacterial activity of the phytocompounds against gram-positive bacteria (MIC values range from 0.5 to 2.0 mg/ml), in particular against methicillin-resistant *Staphylococcus aureus* (MRSA). Rosamarinic acid 4-O-β-d-glucoside (100 μM; 99.9%) significantly lowers the MRSA in vivo microbial load in MRSA infected Galleria larvae [40].

Wound healing activity

Every human being suffers from a wound, a common painful experience at some point in their life. If the wound does not heal properly or if it develops an infection, then it's important to get medical attention [41]. According to Ayurveda, many substances derived from plants, minerals, and animals are used for wound healing under the term Vranaropaka. The majority of medicines prescribed in Ayurveda are derived from plants for wound healing, and SC is one such plant [42]. SC is a primary component of *Bala taila parisheka*, an ayurvedic preparation used for wound healing. A single-blind clinical trial was conducted in which thirty individuals were randomly selected. *Bala taila parisheka* is extremely effective in the treatment of traumatic wounds. The presence of a multitude of phytochemicals may contribute to the healing process either individually or synergistically. By reducing pain, improving blood flow, and increasing drug permeability, the formulation aids in the rapid absorption of the drug [43]. Excision, incision, and burn wounds can be effectively healed with an ointment containing the ethanolic extract of the entire SC plant [44]. A topical application of SC aqueous extract in hydrogel form reverses or mitigates the wound retardation caused by dexamethasone. The aqueous extract hydrogel (HF_3) reversed the deleterious effects of dexamethasone by increasing wound contraction rate, decreasing epithelialization time, increasing vascular endothelial growth factor (VEGF) levels, and increasing collagen synthesis in delayed excision wounds [45].

Antioxidant activity

Oxidative stress occurs when an imbalance exists between the generation and neutralization of free radicals. ROS are unstable chemicals capable of damaging cells, leading to diseases such as cancer, CVD, Parkinson's disease, and accelerating the aging process, Smoking, air pollution, and poor diet can increase the risk of oxidative stress [46]. It is believed that a variety of medicinal plants have high antioxidant properties that can shield cells from oxidative damage, thus reducing the chances of developing cancer and heart disease [47]. The antioxidant activity of both alcoholic extracts and water infusions from the whole plant of SC was significant in rat brain homogenate. The ethanolic extract of SC showed strong antioxidant activity in ABTS experiments, and the IC50 value was 16.07 mg/ml. A considerable level of SC lipid peroxidation was observed, with an IC50 of 126.78 mg/ml [48]. The root of SC exhibits the highest level of antioxidant activity compared to other parts of the herb. HPTLC fingerprinting confirmed that the plant contains a high concentration of phenolic compounds, particularly flavonoids. SC root ethanolic extracts exhibit antioxidant activity due to their reductive properties. In liver and brain homogenates from rats, it prevented lipid peroxidation, which suggests that it inhibited the effects of free radicals on biological membranes. A high level of flavonoids in roots may explain their antioxidant activity [49]. SC extracts protect the liver from the oxidative damage caused by alcohol. An ethanolic extract of SC may exert its protective effects by inhibiting the metabolism of alcohol and, as a result, lowering the formation of acetaldehyde and reactive oxygen species [50]. The eight species of Sida, SC contained the highest amounts of total polyphenols (1.92±0.10 mg CAE/g; 2.13±0.11 mg TAE/g), total flavonoids (1.26±0.06 mg QE/g) and superior antioxidant properties. In-vitro anti-oxidant studies have indicated that SC has significantly greater antioxidant properties than other

Sida species. Possibly, this is due to the high content of phenolic compounds and flavonoids [51]. A study also found that both flower and leaf extracts of SC had significantly higher antioxidant activity [52].

Anti-diabetic activity

Diabetes is a life-threatening metabolic disorder that can lead to heart disease, stroke, renal failure, blindness, and amputations. Several commercially available drugs treat the complications of diabetes. The primary disadvantages of diabetes medicines are their high cost and that they are also associated with long-term adverse repercussions. Sulfonylureas, for example, can contribute to weight gain, while thiazolidinediones can increase the risk of heart failure. Herbal medicines are gaining popularity due to their low cost and enhanced therapeutic efficacy with fewer adverse effects [53]. Several herbal medications, either alone or in combination, are prescribed in the Indian traditional system of medicine for regulating blood sugar levels, and SC is one of them Based on a glucose tolerance test, a methanol extract of SC root (600 mg/kg) demonstrated significant hypoglycemic activity. Following administration of a methanol extract of SC, blood sugar levels were significantly reduced (31% reduction). After ingestion, the extract exerted a significant effect within two hours, with blood sugar levels returning to normal within six hours [6]. SC aqueous extract was compared with metformin, a commonly prescribed medication, on streptozotocin-induced diabetic rats. A dose-dependent decline in serum glucose levels was observed in rats treated with methanol or aqueous extract on days 7, 14, and 21 after administration. The greatest effect on serum glucose levels was found to be associated with the use of an aqueous extract at a dose of 1 g/kg. The results of the streptozotocin-induced diabetes model showed that the aqueous extract resulted in significant alterations in blood sugar levels on days 7, 14, and 21, as well as improved lipid profiles, and an increase in glycogen, and weight gain [9]. The aerial part of the alcoholic extract of SC (200 and 400 mg/kg) was found to produce an anti-diabetic effect in streptozotocin-induced (55 mg/kg) diabetes in Wistar rats. Glibenclamide (5 mg/kg) was used to counteract diabetes in diabetic rats. SC alcohol extract at a higher dose (400 mg/kg) was found to lower serum sugar levels and improve weight gain. The alcohol extracts of SC exhibited dose-dependent anti-diabetic activity. SC shows the hypoglycemic activity as well as positive effects on lipid profiles and significantly increased levels of antioxidant enzymes. There are several phytochemicals in SC that contribute to its promising biological activity [54].

Anti-inflammatory and analgesic activity

Inflammation is a process that is critical for the body to fight infection and clear away damaged tissue, but when it becomes chronic, inflammation can lead to a wide range of diseases [55]. Pain is a perceptible sensation felt throughout the body. It is frequently described as a sharp or burning sensation. Pain can also be a symptom of a variety of different disorders [56]. There is a great need for new therapies that can effectively resolve inflammation and relieve pain in a way that is safe and well-tolerated by the body. Traditional medicines are typically plant-based, and many are effective in treating a wide range of medical conditions [57]. Phytochemicals found in medicinal plant extracts can possess various therapeutic effects, including analgesic and anti-inflammatory properties. The aerial and root parts of SC extracts showed promising anti-inflammatory properties in a carrageenan-induced oedema model in rats. Compared to indomethacin (6 mg/kg) at the same dose level (600 mg/kg), ethyl acetate extract outperformed, whereas methanol extract performed similarly. Extracts of the aerial part have more significant anti-inflammatory activity than the root, and also the effect is dose-dependent manner. Both the extracts exhibited substantial peripheral and central analgesic effects, as evidenced by the acetic acid writhing and hot plate tests [6]. Another study found that the aqueous extract of SC at a dose level of 400 mg/kg orally significantly inhibited rat paw oedema induced by carrageenin. Nevertheless, it failed to prevent oedema caused by arachidonic acid. The aqueous extract of SC decreased the number of writhes caused by acetic acid and increased the latency period for mice in the hotplate test at the same dose as well [58]. Quinolinic acid treatment caused neurotoxicity in rats. In rats treated with the toxin, inflammatory response indicators such as cyclooxygenase and lipoxygenase were elevated. Treatment with SC ethanolic root extracts reduces these inflammatory markers [59]. Aqueous acetone extracts of SC produced significant analgesic effects in both the acetic acid writhing test and the hot plate method in a dose-dependent fashion [60]. The aqueous leaf extract of SC contains polar compounds. The presence of polar compounds produced significant anti-inflammatory effects even at a concentration of 10 µg/ml. SC aqueous leaf extracts inhibited the synthesis of prostaglandins, resulting in significant anti-inflammatory effects [61].

Hepatoprotective effect

In the human body, the liver is one of the largest and most important organs and it is responsible for the majority of metabolic and excretory processes. An important function of the liver is the production of bile, protein synthesis, and drug detoxification. In addition, the liver is responsible for the metabolism of drugs and alcohol. Damage to the liver can result in a range of serious health complications [62]. The hepatoprotective properties of SC have been documented in several studies. An antibody specific for proliferating cell nuclear antigen (PCNA) was used to assess the effect of this action using immunohistochemical staining to evaluate hepatocyte proliferation and liver regeneration. Aqueous extracts of SC (100 and 200 mg/kg) were administered orally to rats with partial hepatectomy, leading to enhanced hepatocyte proliferation and regenerated liver tissue [63]. In rats, an 50% ethanolic extract of SC roots effectively prevents alcohol-induced liver toxicity. SC exerts hepatoprotective effects by reducing both oxidative stress and transcription factor expression [64].

Effect on the cardiovascular system

Heart disease dominates the global health agenda, causing the most deaths. Various factors can lead to cardiovascular disease, including genetics, lifestyle choices, and environmental factors [65]. Cardiovascular disease is still not fully understood; however, it is known that it involves inflammation and damage to the blood vessels. Consequently, there has been an increase in interest in finding natural and herbal cardioprotective agents with minimal or no side effects. The quinazoline group of alkaloids, Vasicine, is isolated from the leaves of SC. An aqueous extract of a hydroalcoholic extract of SC leaves was administered to non-anesthetized, normotensive rats and caused hypotension accompanied by bradycardia. An investigation of the mechanism of action suggested that hypotension and bradycardia may be attributed to indirect cardiac muscarinic activation mediated by vagal stimulation and direct vascular endothelial muscarinic receptor activation and followed by nitrous oxide release [18]. In another study, the aqueous fraction of the hydroalcoholic extract of SC leaves was found to cause hypotension and bradycardia, primarily as a result of direct stimulation of endothelium vascular muscarinic receptors and indirect cardiac muscarinic activation [66]. Hypertension and atherosclerosis have a complicated aetiology that is still not understood. It is now known that oxidative and inflammatory stress plays a critical role in many diseases, like atherosclerosis, stroke, myocardial infarction, arthritis, and cancer. Pre-treatment with two different doses of 100 mg/kg and 500 mg/kg hydroalcoholic extract of the leaves of SC provides dose-dependent protection against myocardial injury produced by isoproterenol and ischemia-reperfusion injury. The antioxidant effects of flavonoids in the hydroalcoholic extract of SC leaves and the finding that both doses cause a concomitant increase in SOD and catalases have been associated with cardioprotection [67].

Anti-cancer activity

The second leading cause of death worldwide is cancer. Cells can multiply uncontrollably as a result of these mutations, pushing out neighboring cells and causing the growth of cancerous tumors [68]. Over time, these tumors may metastasize and spread to other parts of the body. Even though there is no cure for cancer at present, medicines can help prolong life and improve quality of life [69]. Both *in-vivo* and *in-vitro* studies have found that many phytochemicals have anticancer properties. They may have these effects due to their ability to inhibit cancer cell proliferation or scavenge cancer-causing substances from the body [4, 70]. In a human osteosarcoma cell line, Cryptolepine, an alkaloid isolated from an SC methanolic extract, induces cell cycle arrest and $p21^{WAF1/CIP1}$ expression. By activating $p21^{WAF1/CIP1}$, cryptolepine inhibits the growth of MG63 cells without the assistance of p53. The activator is a specific Sp1 site within the promoter region [29]. The SC methanolic extract shows a strong antiproliferative activity when tested *in-vitro* in HepG-2 cells, forty-eight hours after contact with the cells. As well, after forty-eight hours, the SC methanolic extract was found to increase antioxidant enzyme activities, including SOD, CAT, and GSTs [71]. Silver nanoparticles derived from SC leaf extract possess enhanced antioxidant and anticancer properties. They synthesized silver nanoparticles from leaf extracts of the SC plant. In addition, they found that they were more effective in reducing free radicals than standard drugs and less toxic than commercially available drugs. Nanoparticles prepared from the leaves of the SC plant have shown promising inhibitory effects against cancer cells such as EAC and HT-29, with IC_{50} values of 204 and 129 µg/mL, respectively [12]. In another study, an aerial part of the ethanolic extract of SC displayed significant DPPH, H_2O_2, and NO radical scavenging activity.

Furthermore, the extract demonstrated dose-dependent cytotoxicity when tested on cancer cell lines. The most sensitive cells were A375 and HT29, with IC_{50} values of 16.51 and 49.86μg/mL, respectively [72].

Antipyretic and anti-ulcerogenic activity

Traditionally, indigenous healers used medicinal plant extracts to treat and prevent stomach ulcers. The phytochemicals act by interacting with the bacteria in the gut, which helps regulate gastrointestinal function. In addition, phytochemical treatments may stimulate the production of gastric acid, which may prevent the formation of stomach ulcers. In a study, oral administration of a methanolic extract of SC aerial parts had a strong antipyretic effect in rats when dosed at 500 mg/kg. SC's methanolic extract exhibited substantial anti-ulcerogenic activity against ulcers produced by aspirin and ethanol [73].

Toxicity study

Testing for toxicity is an essential part of the evaluation of new medications before their use in humans or patients. The purpose of toxicology testing is to determine if a medicine is both safe and effective for human use. Drugs that are unsafe or ineffective may not survive the initial screening process and may never reach patients [74]. The aqueous extract of SC showed low toxicity in a mice animal model, up to an oral dose of 3 g/kg [58]. In addition, another study on acute toxicity in mice demonstrated that SC has an LD_{50} of 3.4 g/kg [60]. PC12 is an immortalized rat pheochromocytoma cell line that resembles the original foetal neuron culture and is commonly used in neurological research. PC12 cells were exposed to the aqueous extract of the SC plant, and it was found not to be toxic for them [48].

Miscellaneous

Certain medicinal plants and natural compounds are useful for preventing or alleviating neurological disorders and symptoms. There is strong evidence that medicinal plants protect brain nerve cells from damage, and clinical trials are investigating the possibility of using plant-derived chemicals to manage multiple neurological disorders. The hydro-alcoholic extract of SC leaves exhibits depressive activity in the central nervous system. As evidenced by behavioral changes, the hydro-alcoholic extract of SC leaves induced CNS depression in rats. It was also evident that the animals' motor activity was reduced, although this did not impair their coordination [75]. Anthelmintic activity is observed in ethanolic and aqueous extracts of SC against *Pheretima Posthuma.* Different doses of ethanolic and aqueous extracts (10, 20, 30, and 40 mg/ml) paralyze the *P. Posthuma* at different times in a bioassay. Comparisons are made with the activity of the reference standard, albendazole. Compared with ethanolic extract, SC whole-plant aqueous extract is more effective [76]. According to another study, both methanolic and aqueous extracts of SC's whole plant possess anthelmintic activity against *P. Posthuma*. In both extracts, secondary metabolites are believed to be responsible for this activity [77]. A hydroalcoholic extract of SC roots proved effective in treating both castor oil and magnesium sulfate-induced diarrhea in Wister albino rats. In rats, hydro-alcoholic extracts of SC roots (100, 200, and 400 mg/kg) reduced defecation frequency and diarrhea severity in a dose-dependent manner. In a model induced by Castrol oil, intestinal fluid secretion was reduced, gastric emptying was delayed, and the passage of charcoal meal through the gastrointestinal tract was decreased [78]. The aqueous root extracts of SC are protective against gentamicin and cisplatin-induced nephrotoxicity. The aqueous extract of SC (200 and 400 mg/kg) effectively prevents kidney damage by normalizing elevated levels of renal indicators. The anti-oxidant properties of SC are largely responsible for its nephroprotective effects [79].

CONCLUSION

Several physiologically active drugs originate from traditional medical systems. A wide variety of pharmaceutically active substances are obtained from natural sources, and they can be used to treat a broad range of illnesses. The purpose of this study was to collate information on the traditional uses, phytochemistry, and pharmacological properties of the SC from 1980 to the end of December 2021. A diverse range of pharmacological studies, both *in-vitro* and *in-vivo*, strongly support the ethnomedicinal relevance of SC. Moreover, the presence of phytochemicals proved SC to be a potential source of bioactive compounds. The most recent scientific findings confirm the pharmacological relevance of SC and establish it as a reliable source of natural products. Pharmacological studies indicate that this plant exhibits antimicrobial, wound-healing, antioxidant, anti-inflammatory, analgesic, hepatoprotective, cardioprotective, anticancer, antipyretic, anti-ulcer, anti-anthelmintic, and nephroprotective properties. Plant-derived chemicals are gaining popularity in the pharmaceutical industry due to their perceived safety and the fact that patients treated with them experience few or no adverse effects. However, until recently, very little research has been conducted on this plant. In most studies of SC, plant extracts have been used, and only a few bioactive metabolites have been identified. Identifying the most promising SC compounds is therefore imperative. In the past few years, the results of the study on traditional uses of SC have been partially validated. Identifying lead compounds and increasing the plant's usage will require an exploratory study of phytochemicals. Different cultivars of SC exhibit a range of chemical compositions. These varying compositions have a direct correlation to their therapeutic potential. Further evidence, such as toxicological and clinical data, will be needed to develop a herbal formulation. It is necessary to conduct a toxicological study to determine the concentrations of microorganisms, heavy metal content, and pesticide residues. In addition, the study should establish the general toxicity of SC extracts and their purified components. The information in this review article is up-to-date, so it might be helpful for researchers looking to find out more about SC health benefits.

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REFERENCES

1. Srinivasan N. Pharmacognostical and phytochemical evaluation of *Cassia alata* Linn. J Med Plants Stud. 2018;6(5):69-77.
2. Mohanty SK, Swamy MK, Sinniah UR, Anuradha M. *Leptadenia reticulata* (Retz.) Wight & Arn.(Jivanti): botanical, agronomical, phytochemical, pharmacological, and biotechnological aspects. Molecules. 2017;22(6):1019.
3. Srinivasan N, Dhanalakshmi S, Pandian P. Encouraging leads from marine sources for cancer therapy a review approach. Pharmacogn J. 2020;12(6):1475-81.
4. Srinivasan N. Medicinal plants for cancer treatment: A review approach. Int J Biology Res. 2018;3(4):57-61.
5. Dinda B, Das N, Dinda S, Dinda M, SilSarma I. The genus Sida L.–A traditional medicine: It is ethnopharmacological, phytochemical, and pharmacological data for commercial exploitation in the herbal drugs industry. J Ethnopharmacol. 2015;176:135-76.
6. Ravi Kanth V, Diwan P. Analgesic, antiinflammatory and hypoglycaemic activities of *Sida cordifolia*. Phytother Res. 1999;13(1):75-7.
7. Rodrigues FC, de Oliveira AFM. The genus Sida L.(Malvaceae): An update of its ethnomedicinal use, pharmacology, and phytochemistry. S Afr J Bot. 2020;132:432-62.
8. Pallela PNVK, Ummey S, Ruddaraju LK, Pammi S, Yoon SG. Ultra Small, monodispersed green synthesized silver nanoparticles using aqueous extract of *Sida cordifolia* plant and investigation of antibacterial activity. Microb Pathog. 2018;124:63-9.
9. Kaur G, Kamboj P, Kalia A. Antidiabetic and anti-hypercholesterolemic effects of aerial parts of *Sida cordifolia* Linn. on Streptozotocin-induced diabetic rats. Indian J Nat Prod Resour. 2011;2(4):428-34.
10. Nagashayana N, Sankarankutty P, Nampoothiri M, Mohan P, Mohanakumar K. Association of L-DOPA with recovery following Ayurveda medication in Parkinson's disease. J Neurol Sci. 2000;176(2):124-7.
11. Sharma AK. Medicinal properties of Bala (*Sida cordifolia* Linn. and its species). Int J Ayurveda Pharma Res. 2013;1(2):1-9.
12. Srinithya B, Kumar VV, Vadivel V, Pemaiah B, Anthony SP, Muthuraman MS. Synthesis of biofunctionalized AgNPs using medicinally important *Sida cordifolia* leaf extract for enhanced antioxidant and anticancer activities. Mater Lett. 2016;170:101-4.
13. Vassou SL, Kusuma G, Parani M. DNA barcoding for species identification from dried and powdered plant parts: a case study with authentication of the raw drug market samples of *Sida cordifolia*. Gene. 2015;559(1):86-93.

14. Halde U, Wake R, Patil N. Genus Sida–The plants with ethnomedicinal and therapeutic potential. Gold Res Thoughts. 2011;1:1-4.
15. Agharkar S. Medicinal plants of Bombay Presidency Scientific Pub. India. 1991;199:48-9.
16. Koman. Indian Materia Medica Gazette. 1921.
17. Jain A, Choubey S, Singour P, Rajak H, Pawar R. *Sida cordifolia* (Linn)–an overview. J Appl Pharm Sci. 2011;1(2):23-31.
18. Silveira A, Gomes M, Silva Filho R, Santos M, Medeiros I, Barbosa Filho J. Evaluation of the cardiovascular effects of vasicine, an alkaloid isolated from the leaves of *Sida cordifolia* L.(Malvaceae). Rev Bras Farmacogn. 2003;13:37-9.
19. Halilu M, Muhammad I, Dangoggo S, Farouq A, Ahmed A, Shamsuddeen A, et al. Phytochemical and antibacterial screening of petroleum ether and ethanol extracts of *Sida cordifolia* leaves. J Chem Soc Nigeria. 2016;41(2):137-42.
20. Dibyajyoti S, Swati P. Chemical composition of the leaves and stem bark: Methanol extract of *sida cordifolia* L. J Sci Arts. 2013;13(3):281-6.
21. Ghosal S, Kaur R, Bhattacharya S. Chemistry and bioactivity of sitoindosides IX and X. Planta Med. 1988;54(06):561.
22. Kurma S, Mishra S. Isolation and assessment of hepatoprotective activity of fumaric acid obtained for the first time from *Sida cordifolia* Linn. Indian Drugs. 1997;34(12):702-6.
23. Asha B, Bannerjee NR. Polarographic studies on active constituents of *Sida cordifolia*. Curr Sci. 1985;54(14):690-2.
24. Gunatilaka AL, Sotheeswaran S, Balasubramaniam S, Chandrasekara AI, Sriyani HB. Studies on medicinal plants of Sri Lanka. Planta Med. 1980;39(05):66-72.
25. Sutradhar RK, Matior Rahman A, Ahmad MU, Saha K. Alkaloids of *Sida cordifolia* L. Indian J Chem. 2007;48B:1896-900.
26. Sutradhar RK, Rahman AM, Ahmad M, Chandra BS, Saha A, Guha SK. Bioactive alkaloid from *Sida cordifolia* Linn. with analgesic and anti-inflammatory activities. Iran J Pharmacol Ther. 2006;5(2):175-8.
27. Sutradhar RK, Rahman AM, Ahmad MU, Bachar SC. Bioactive flavones of *Sida cordifolia*. Phytochem Lett. 2008;1(4):179-82.
28. Prakash A, Ghosal S. Phytoecdysones. J Sci Ind Res. 1979;38(11):632-47.
29. Matsui TA, Sowa Y, Murata H, Takagi K, Nakanishi R, Aoki S, et al. The plant alkaloid cryptolepine induces p21WAF1/CIP1 and cell cycle arrest in a human osteosarcoma cell line. Int J Oncol. 2007;31(4):915-22.
30. Joseph B, Ajisha A, Kumari S, Sujatha S. Effect of bioactive compounds and its pharmaceutical activities of *Sida cordifolia* (Linn.). Int J Biol Med Res. 2011;2(4):1038-42.
31. Avula B, Joshi V, Wang YH, Jadhav AN, Khan IA. Quantitative determination of ecdysteroids in *Sida rhombifolia* L. and various other Sida species using LC-UV, and their anatomical characterization. Nat Prod Commun. 2008;3(5):705-10.
32. Farooqi J. *Sida cordifolia* seed oil: a rich source of HBr-reactive fatty acids. Chem Ind. 1985:483-4.
33. Galal A, Raman V, A Khan I. *Sida cordifolia*, a traditional herb in modern perspective–a review. Curr Tradit Med. 2015;1(1):5-17.
34. Samy RP, Ignacimuthu S, Raja DP. Preliminary screening of ethnomedicinal plants from India. J Ethnopharmacol. 1999;66(2):235-40.
35. Hostettmann K. Strategy for the biological and chemical evaluation of plant extracts. Pure Appl Chem. 1999;70(11):1-9.
36. Nunes XP, Maia GLdA, Almeida JRGdS, Pereira FdO, Lima EdO. Antimicrobial activity of the essential oil of *Sida cordifolia* L. Rev Bras Farmacogn. 2006;16:642-4.
37. Ternikar S, Alagawadi K, Pasha I, Dwivedi S, Rafi MA, Sharma T. Evaluation of antimicrobial and acute anti-inflammatory activity of *Sida cordifolia* Linn seed oil. J Cell Tissue Res. 2010;10(3):2385-8.
38. Sahu BP, Gouda P, Patnaik C. Studies on the Phytochemistry, Spectroscopic Characterization and Antibacterial Efficacy of *Sida cordifolia* (Linn). Int J Sci Res. 2016;5(8):1458-64.
39. Pallela PNVK, Ummey S, Ruddaraju LK, Gadi S, Cherukuri CS, Barla S, et al. Antibacterial efficacy of green synthesized α-Fe_2O_3 nanoparticles using *Sida cordifolia* plant extract. Heliyon. 2019;5(11):e02765.
40. Iqbal H, Wright CL, Jones S, da Silva GR, McKillen J, Gilmore BF, et al. Extracts of *Sida cordifolia* contain polysaccharides possessing immunomodulatory activity and rosmarinic acid compounds with antibacterial activity. BMC Complement Med Ther. 2022;22(1):1-17.

41. Kumarasamyraja D, Jeganathan N, Manavalan R. A review on medicinal plants with potential wound healing activity. Int J Pharm Pharm Sci. 2012;2:105-11.
42. Biswas TK, Mukherjee B. Plant medicines of Indian origin for wound healing activity: a review. Int J Low Extrem Wounds. 2003;2(1):25-39.
43. Tripathy R, Otta S, Siddram A. Bala taila parisheka–A traditional approach in wound healing. Indian J Tradit Knowl. 2011;10(4):643-50.
44. Pawar RS, Chaurasiya PK, Rajak H, Singour PK, Toppo FA, Jain A. Wound healing activity of *Sida cordifolia* Linn. in rats. Indian J Pharmacol. 2013;45(5):474-8.
45. Kumar S, Lakshmi P, Sahi C, Pawar RS. Sida cordifolia accelerates wound healing process delayed by dexamethasone in rats: Effect on ROS and probable mechanism of action. J Ethnopharmacol. 2019;235:279-92.
46. Benguiar R, Benaraba R, Abdellah F, Hammou AS, Bouriah M, Moulayat KE. Effect of Green Tea "*Camellia sinensis*" Extract on Antioxidant Activity of Fresh-cut Apple during Cold Storage. J Biochem Technol. 2021;12(3):91-5.
47. Krishnaiah D, Sarbatly R, Nithyanandam R. A review of the antioxidant potential of medicinal plant species. Food Bioprod Process. 2011;89(3):217-33.
48. Auddy B, Ferreira M, Blasina F, Lafon L, Arredondo F, Dajas F, et al. Screening of antioxidant activity of three Indian medicinal plants, traditionally used for the management of neurodegenerative diseases. J Ethnopharmacol. 2003;84(2-3):131-8.
49. Dhalwal K, Deshpande Y, Purohit A, Kadam S. Evaluation of the Antioxidant Activity of *Sida cordifolia*. Pharm Biol. 2005;43(9):754-61.
50. Rejitha S, Prathibha P, Indira M. Nrf2-mediated antioxidant response by ethanolic extract of *Sida cordifolia* provides protection against alcohol-induced oxidative stress in the liver by upregulation of glutathione metabolism. Redox Rep. 2015;20(2):75-80.
51. Subramanya M, Pai SR, Upadhya V, Ankad GM, Bhagwat SS, Hegde HV. Total polyphenolic contents and in vitro antioxidant properties of eight Sida species from Western Ghats, India. J Ayurveda Integr Med. 2015;6(1):24.
52. Arshad S, Hussain I, Ibrahim M, Imran M, Assiri MA, Thind S, et al. Biochemical studies on protein, phenolic contents and antioxidant activities of *Sida cordifolia* extracts. Bull Chem Soc Ethiop. 2020;34(2):427-34.
53. Tran N, Pham B, Le L. Bioactive compounds in anti-diabetic plants: From herbal medicine to modern drug discovery. Biology. 2020;9(9):252.
54. Ahmad M, Prawez S, Sultana M, Raina R, Pankaj NK, Verma PK, et al. Anti-hyperglycemic, anti-hyperlipidemic and antioxidant potential of alcoholic-extract of *Sida cordifolia* (Aerial part) in streptozotocin-induced-diabetes in Wistar-rats. Proc Natl Acad Sci India Sect B Biol Sci. 2014;84(2):397-405.
55. Recio MC, Andujar I, Rios JL. Anti-inflammatory agents from plants: progress and potential. Curr Med Chem. 2012;19(14):2088-103.
56. Almeida R, Navarro D, Barbosa-Filho J. Plants with central analgesic activity. Phytomedicine. 2001;8(4):310-22.
57. Amer OS, Dkhil MA, Hikal WM, Al-Quraishy S. Antioxidant and Anti-Inflammatory Activities of Pomegranate (*Punica granatum*) on Eimeria papillata-Induced Infection in Mice. BioMed Res Int. 2015. doi:10.1155/2015/219670
58. Franzotti E, Santos C, Rodrigues H, Mourao R, Andrade M, Antoniolli A. Anti-inflammatory, analgesic activity and acute toxicity of *Sida cordifolia* L.(Malva-Branca). J Ethnopharmacol. 2000;72(1-2):273-7.
59. Swathy S, Panicker S, Nithya R, Anuja M, Rejitha S, Indira M. Antiperoxidative and antiinflammatory effect of *Sida cordifolia* Linn. on quinolinic acid-induced neurotoxicity. Neurochem Res. 2010;35(9):1361-7.
60. Konaté K, Bassolé IHN, Hilou A, Aworet-Samseny RR, Souza A, Barro N, et al. Toxicity assessment and analgesic activity investigation of aqueous acetone extracts of *Sida acuta* Burn f. and *Sida cordifolia* L.(Malvaceae), medicinal plants of Burkina Faso. BMC Complement Altern Med. 2012;12(1):1-11.
61. Martins CAF, Campos ML, Irioda AC, Stremel DP, Trindade ACLB, Pontarolo R. Anti-inflammatory effect of *Malva sylvestris*, *Sida cordifolia*, and *Pelargonium graveolens* are related to inhibition of prostanoid production. Molecules. 2017;22(11):1883.
62. Srinivasan N, Sathyanarayana D. Hepato Protective Activity of Various Extracts of *Indigofera barberi* Gamble against D-galactosamine Induced Toxicity In Rats. Ann Plant Sci. 2013;02(10):401-4.

63. Silva RL, Melo GBd, Melo VAd, Antoniolli ÂR, Michelle PRT, Zucoloto S, et al. Effect of the aqueous extract of *Sida cordifolia* on liver regeneration after partial hepatectomy. Acta Cir Bras. 2006;21(supplement 1):37-9.
64. Rejitha S, Prathibha P, Indira M. Amelioration of alcohol-induced hepatotoxicity by the administration of ethanolic extract of *Sida cordifolia* Linn. Br J Nutr. 2012;108(7):1256-63.
65. Otunola GA, Oloyede OB, Oladiji AT, Afolayan AJ. Selected spices and their combination modulate hypercholesterolemia-induced oxidative stress in experimental rats. Biol Res. 2014;47(1):1-6.
66. Medeiros I, Santos M, Nascimento N, Duarte J. Cardiovascular effects of *Sida cordifolia* leaves extract in rats. Fitoterapia. 2006;77(1):19-27.
67. Kubavat J, Asdaq S. Role of *Sida cordifolia* L. leaves on biochemical and antioxidant profile during myocardial injury. J Ethnopharmacol. 2009;124(1):162-5.
68. Halimah E, Hendriani R, Indradi B, Sofian FF. Cytotoxicity of ethanol extract and its fractions from Acalypha wilkesiana against breast cancer cell MCF-7. J Adv Pharm Educ Res. 2022;12(1):17-20.
69. Yehya AH, Asif M, Majid AM, Oon CE. Complementary effects of *Orthosiphon stamineus* standardized ethanolic extract and rosmarinic acid in combination with gemcitabine on pancreatic cancer. Biomed J. 2020;6(4):694-708.
70. Kooti W, Servatyari K, Behzadifar M, Asadi-Samani M, Sadeghi F, Nouri B, et al. Effective medicinal plant in cancer treatment, part 2: a review study. Evid Based Complement Altern Med. 2017;22(4):982-95.
71. Pieme C, Penlap V, Ngogang J, Costache M. In vitro cytotoxicity and antioxidant activities of five medicinal plants of Malvaceae family from Cameroon. Environ Toxicol Pharmacol. 2010;29(3):223-8.
72. Bhutkar PM, Suganthi V, Bhutkar MV, Kothai R. In vitro antiproliferative activity of ethanolic extract of *Sida cordifolia* Linn against various cancer cell lines. Al Ameen J Med Sci. 2020;13(4):234-41.
73. Philip BK, Muralidharan A, Natarajan B, Varadamurthy S, Venkataraman S. Preliminary evaluation of anti-pyretic and anti-ulcerogenic activities of *Sida cordifolia* methanolic extract. Fitoterapia. 2008;79(3):229-31.
74. Arome D, Chinedu E. The importance of toxicity testing. Int J Pharma Bio Sci. 2013;4:146-8.
75. Franco C, Morais L, Quintans-Júnior L, Almeida R, Antoniolli A. CNS pharmacological effects of the hydroalcoholic extract of *Sida cordifolia* L. leaves. J Ethnopharmacol. 2005;98(3):275-9.
76. Pawa RS, Jain A, Sharma P, Chaurasiya PK, Singour PK. In vitro studies on *Sida cordifolia* Linn for anthelmintic and antioxidant properties. Chin Med. 2011;2(2):47.
77. Kumar SPN, Kanthal L, Durga S, Satyavati K. Phytochemical Evaluation and Screening of Cardiotonic, Antibacterial and Anthelmintic Activities of *Sida cordifolia* L. Int J Pharm Sci Nanotechnol. 2014;7(3):2567-73.
78. Shahed-Al-Mahmud M, Jahan T, Islam T. Antidiarrheal activities of hydroalcoholic extract of *Sida cordifolia* roots in Wister albino rats. Orient Pharm Exp Med. 2018;18(1):51-8.
79. Makwana MV, Pandya NM, Darji DN, Desai SA, Bhaskar V. Assessment of the nephroprotective potential of *Sida cordifolia* Linn. in experimental animals. Der Pharm Lett. 2012;4(1):175-80.