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Review Article

A Review on Pharmacological Activity of *Sida species*

Akansha Tomar,*[1] Amit Kasabe[2] and Manmeet Singh Saluja[2]

[1]Research Scholars, Department of Pharmacy, SunRise University, Alwar, Rajasthan.

[2] Research Supervisor, SunRise University, Alwar, Rajasthan.

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Corresponding author: Akansha Tomar

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Abstract:

Sida species is one of the most varied genera in the Malvaceae family, and its species are used for the treatment of numerous ailments in many places across the globe, with such ethnomedicinal usage validated by pharmacological tests. The primary goal of this research is to update information on the biological and pharmacological activities, as well as the phytochemistry of Sida since the genus's previous review in 2020. Various scientific study platforms were used to gather ethnobotanical, pharmacological, and phytochemical data on the genus Sida. Our findings revealed that S. acuta, S. cordifolia, and S. rhombifolia have received the most attention, whereas S. galheirensis has received less attention. Sida species have historically been used to cure a variety of ailments, including ulcers, asthma, fever, pain, rheumatism, and diarrhea.

Keywords: *S. rhombifolia*.

INTRODUCTION

Sida L. is a genus of plants. is one of the most varied Malvaceae families, with around 200 species found worldwide, 189 of which exist in the Americas and 112 in Brazil (Brandao et al., 2017).

Yoshikawa et al. (2019) recently reported a new species of the genus, Sida uniaristata Gonc Alez & Yoshikawa, from Brazil, bringing the total to 113. Sida species are known as "guanxuma" in Brazil, derived from the Tupi "gwa'xima" (Constantin et al., 2007; Souza and Lorenzi, 2012). Morphologically, Sida differs from other Malvaceae genera by having two distinct features: I) a calyx with 10 veins, and II) schizocarp fruits with 5-10 one-seed mericarps (Fryxell, 1997; Brandao et al., 2017). Brandao et al. (2017) provide further taxonomic information.

Some Sida species, include Sida cordifolia L. and Sida rhombicfolia L., are invasive and/or weeds that may infest crops and cause agricultural harm (Ferreira et al., 1984). Other species are ethnomedicinal and are used to treat a variety of health issues, including asthma, ulcers, parasite infections, headaches, and inflammatory disorders (Dinda et al., 2015; Ahmed et al., 2018).

Several studies have been created to explore the compounds responsible for the diverse biological and pharmacological effects due to the various traditional usage (Jindal et al., 2012; Chaves et al., 2013; Biftu et al., 2014).

Until 2015, 142 chemical components of different classes have been recorded for Sida, according to the literature. Alkaloids, flavonoids, and phytosteroids were the most abundant, accounting for roughly 16%, 13%, and 11% of all classes discovered, respectively. Alkaloids and flavonoids were the components with the most biological and pharmacological properties found for the genus (Dinda et al., 2015).

Previous research has shown that several Sida species have medicinal potential. Antibacterial activity has been reported for Sida alba L. (Konate' et al., 2012a). Sida cordifolia var. acuta Burm. f. have analgesic properties (Konate' et al., 2012b). Burma's Sida cordata. f. Sida tiagii Bhan-Dari possesses anti-inflammatory and analgesic activities (Kumawat et al., 2012a, 2012b) and has hypoglycemic effect (Shah and Khan, 2014). Various formulations based on Sida species (e.g., Sida acuta, Sida cordifolia, and Sida rhombifolia L.) help to weight reduction, battle neurological and rheumatic diseases, and work as antimalarial medications, according to Dinda et al. (2015). Some of these formulas are already protected by patent.

Given the genus Sida's well-known ethnomedicinal use and pharmacological potential, the goal of this study was to update knowledge on the biological and pharmacological activities, as well as phytochemistry, of the genus Sida, with a focus on the last five years since the last review published by Dinda et al. (2015).

Source of Information Collection

To collect information published from 2015 to 2021, the keyword "Sida" was associated with "biological activity", "pharmacology", "bioactive", "ethnomedicinal use", "traditional use", "ethnobotany", "ethnopharmacology", "toxicity", "natural products," and "phytochemistry". There was no use of patent databases. The Plant List was used to validate and confirm the names of the species. Species names, synonyms, and authors were corrected when needed. Ethnomedicinal usage, antioxidant activity, antibacterial potential, anti-inflammatory activity, toxicity, antiparasitic potential, anticancer activity, hypoglycemic activity, healing potential, analgesic action, and other activities were among the results.

Sida's Ethnomedicinal Uses

Sida cordifolia is a well-studied species of the genus. In Brazil, it is often known as "malvabranca" (white mallow), and different portions of the plant are used to treat inflammatory disorders such as gonorrhea, asthma, nasal congestion, and stomatitis (Ahmed et al., 2018). In India, Sida cordifolia is used as a diuretic and to treat rheumatism, Parkinson's disease, and wounds (Srinithya et al., 2016), and its roots are used to strengthen the central nervous system and treat neurological disorders such as hemiplegia, facial paralysis, sciatica, weight loss, cervical spondylosis, neuralgia, neurosis (Vassou et al. 2019)

Sida acuta is a versatile species that is used to cure malaria, diarrhea, asthma, headaches, colds, fevers, skin disorders, urinary infections, ulcers, snake bites, and facial paralysis in Colombia and Central American nations. It is also utilized as a sedative and anti-fertility drug (George et al., 2017; Senthilkumar et al., 2018). The juice of Sida acuta leaves is cooked in oil and administered to scrotal swellings and elephantiasis in Ayurvedic therapy. Sida acuta leaves are used as a poultice for wound therapy in the Philippines, and they

also have anticancer action (Senthilkumar et al., 2018).

Sida corymbosa is a plant that is widely utilized in traditional Nigerian medicine (Chukwuemeka et al., 2018). It is used to heal ulcers and wounds, as well as to treat and cure liver disease (Jacob et al., 2018). Sida rhombifolia is widely used in India to treat hypertension, diabetes, and gout (Chaves et al., 2017). Sida rhombifolia, also known as "matapasto", "relo'gio", or "guanxuma" in Brazil, is used to cure renal and skin problems, bleeding, toothaches, diarrhea, gastritis, and fever (Heinichen et al., 2017). Sida glutinosa Roxb is a species found in India. Das et al. (2016) report that (a synonym for Sida glutinosa Cav.) is utilized to treat pulmonary tuberculosis and rheumatism.

Sida tuberculata is widely used to treat hyperglycemia, hypercholesterolemia, inflammation, and infections in southern Brazil (Rosa et al., 2018a). Sida pilosa Mill in Cameroon. [Analogous to Melochia pilosa (Mill.) Fawc. & Rendle] is used to treat intestinal helminthiasis. The suggested method of preparation is to macerate the whole plant in water and drink it until cure is complete (Jatsa et al., 2018).

Sida spinosa L. grows in Kantakinibala, India. (Sharma et al., 2018) is used to treat ulcers, urinary and skin disorders, asthma, snake bites, arthritis, bronchitis, burning sensations, hemorrhoids, intermittent fever, and general weakness. Sida planicaulis var. planicaulis Cav. (synonym of Sida acuta), which is native but not indigenous to Brazil, is used to relieve bodily discomfort in numerous Brazilian states (Sobreira et al., 2018). Sida cordata (Burm.f.) Borss. is found in Nepal. Waalk. is used to eliminate pus from wounds in the form of juice (Paudel et al., 2018).

Sida's biological and pharmacological activities

The medicinal potential of the genus Sida has received considerable attention. The most commonly reported pharmacological activity to date are shown in Fig. 1. Studies have shown a significant antioxidant potential, which has received the greatest attention in recent years, accounting for 27% of the citations. It is worth noting that the antioxidant potential of plant species has received considerable attention in recent years due to their ability to reduce the occurrence of free radicals, which are responsible for the emergence of diseases such as cancer (Greenwell and Rahman, 2015; Zhang et al., 2015; Khurana et al., 2018). Despite the promising therapeutic potential, 10% of the research raise concerns regarding toxicity in some species. The aerial portions of plants, particularly the leaves, are the most often utilized in folk medicine and, as a result, the most studied in pharmacological investigations (Fig. 2).

Antioxidant properties

Sida alnifolia L. aqueous extract. The antioxidant activity of the leaves was substantial (Attanayake et al., 2015). Nwankpa et al. (2015) found that an ethanolic extract of Sida acuta leaves alleviated the effects of oxidative stress in rats. Muneeswari et al. (2016, 2019) used 2,2-Diphenyl-1-picrylhydrazyl (DPPH), nitric oxide (NO), hydroxyl radical (OH), and ferric reducing antioxidant power (FRAP) tests to validate the antioxidant capacity of various extracts of Sida acuta aerial parts. The ethanolic extract of Sida acuta leaves dramatically decreased monosodium glutamate-induced oxidative stress in rats, returning it to normal levels (Owoeye and Salami, 2017).

Some extracts, particularly the ethyl acetate extract of Sida rhombifolia, demonstrated antioxidant activity in DPPH and FRAP experiments in the research by Mah et al. (2017). Similarly, Arciniegas et al. (2017)

demonstrated the antioxidant activity of Sida acuta and Sida rhombifolia hexanic, methanolic, and acetonic extracts, as well as isolated components. Ferro et al. (2019) also validated Sida rhombifolia's antioxidant properties.

Siddiqui et al. (2016) evaluated Sida cordifolia's antioxidant activity using DPPH and superoxide anion radical (O2—) tests. This species' ethanolic extract decreased alcohol-induced oxidative stress in the liver (Rejitha et al., 2015). Gupta et al. (2016) demonstrated this antioxidant activity in rats utilizing chronic and acute oxidative stress paradigms. The tests revealed that it is a non-toxic antioxidant capable of counteracting the harmful effects of oxidative stress in animals. Ankad et al. (2015) investigated the antioxidant activity of eight Sida species using root extracts and discovered substantial findings, with Sida cordifolia having the highest activity. Sri-Nithya et al. (2016) synthesized silver nanoparticles from Sida cordifolia leaf extract and discovered that it had higher free radical scavenging activity than traditional medicines. DPPH tests show that Sida cordifolia is a natural source of antioxidants (Zaman and Khalid, 2015; Mahato and Banerjee, 2017).

Antimicrobial activity

Some Sida species are particularly notable for their antibacterial properties. Infusions of Sida tuberculata leaves and roots, for example, demonstrated substantial clinical outcomes against Candida krusei, with MICs ranging from 3.9 to 62.5 mg/mL for leaves and 1.95 to 31.25 mg/mL for roots (Rosa et al., 2015).

Halilu et al. (2016) discovered antibacterial activity of Sida cordifolia against Staphylococcus aureus and Bacillus subtilis, correlating with prior research on the species (Mahesh and Satish, 2008). Sida cordifolia had considerable antibacterial efficacy as well as antifungal activity against the pathogenic fungus C. albicans (Venkatachalam and colleagues, 2019).

Bora (2016) recently shown the antifungal activity of Sida carpinifolia L.f. (synonym of Sida acuta) against three Candida species. Das et al. (2016) found pentyl-10,12-dimethyl-11-hydroxyxioleate to be responsible for antifungal activity against Fusarium oxysporum in a series of tests using chemicals isolated from Sida glutinosa. Rai et al. (2017) discovered that a chloroform extract of Sida rhombifolia aerial parts has antifungal activity against Aspergillus niger.

Anti-inflammatory properties

Tanumihardja et al. (2016) discovered that Sida rhombifolia has an anti-inflammatory impact on periapical lesions in rats. Sida rhombifolia extracts, notably n-hexane extract, also shown anti-inflammatory efficacy, with an IC50 of 52.16 in a NO test and 146.03 mg/mL in a protein denaturation inhibition model (Mah et al., 2017). Sida rhombifolia also shown anti-inflammatory effects by inhibiting the enzymes cyclooxygenase (COX-1 and COX-2). According to Azad et al. (2017), a dose-dependent antiinflammatory activity of Sida rhombifolia methanolic extract leads to decreased levels of blood sugar, inflammation, and discomfort in produced mice paw edema. Acetone extracts of Sida rhombifolia and Sida acuta were also discovered to have moderate anti-inflammatory action (Arciniegas et al., 2017).

Sida cordifolia has a high anti-inflammatory action. The activity under consideration was the suppression of mediators that typically rise during anti-inflammatory activity (as byproducts of the arachidonic acid metabolism pathway). Leaf extracts were shown to be capable of inhibiting the release of these mediators, resulting in strong anti-

inflammatory efficacy (Martins et al., 2018). Anti-inflammatory, antioxidant, and anti-arthritic properties were also shown by an indigenous formulation of Sida cordifolia extracts (Ratheesh et al., 2017).

Toxicity

Sida tuberculata leaf and root extracts were shown to be non-toxic to Artemia salina (Rosa et al., 2016). Silver nanoparticles made from Sida cordifolia extract were shown to be less hazardous than commercial medications (Srinithya et al., 2016).

The hexanic extract of Sida rhombifolia was highly poisonous to A. salina, while the methanolic and ethanolic extracts demonstrated only mild action (Mah et al., 2017). Sida acuta has cytotoxic action as well (Kanthal, 2017). Nwankpa et al. (2018) discovered that Sida acuta extracts were harmful to rat kidneys and had the potential to cause renal failure.

Sida carpinifolia, which grows in humid and shaded places across Brazil, is responsible for the poisoning of goats, horses, cattle, and cervids (Reis et al., 2019).

Antiparasitic activity

Jatsa et al. (2015) discovered that the aqueous extract of Sida pilosa, particularly the n-butanolic fraction, displayed potent antiparasitic activity against Schistosoma mansoni, with a median-lethal concentration (LC50) of 1.25 mg/mL. After just 24 hours of exposure, the remaining fractions exhibited 100% mortality. In other studies (Jatsa et al., 2016, 2018), the authors discovered that an aqueous extract of Sida pilosa significantly reduced the concentration of Sida mansoni eggs in infected mice's liver and intestine, indicating the species as a promising source of bioactive compounds against Sida mansoni.

Anticancer properties

The anticancer efficacy of Sida cordifolia was shown to be promising utilizing an in silico strategy targeting Bcl-2 and VEGFR2 (Muthuraman et al., 2017). Silver nanoparticles derived from Sida cordifolia leaves were shown to be anticancer in Ehrlich ascites carcinoma (EAC) and HT-29 cell lines (Srinithya et al., 2016). In an in vivo model, Sida acuta shown strong anticancer capabilities (Thon-dawada et al., 2016), and its chloroform extract demonstrated anticancer activity against human A-431 squamous cell carcinoma and HeLa cervical carcinoma cell lines (Kanthal et al., 2017).

Hypoglycemic response

The ethanolic extract of Sida rhombifolia leaves inhibited a-amylase and a-glucosidase in a dose-dependent manner, increasing glucose absorption and lowering blood glucose levels in rats (Bati et al., 2018). Sida cordifolia also demonstrated anti-diabetic effects in vitro (Siddiqui et al., 2016). Arciniegas et al. (2017) evaluated the antihyperglycemic efficacy of Sida acuta and Sida rhombifolia methanolic, hexanic, and ethyl acetate extracts against yeast and mammalian a-glucosidase enzymes. According to these scientists, the acetone extract inhibited the yeast enzyme more effectively, but there were no significant findings in the inhibition of the enzyme in humans.

Possibility of healing

In diabetic rats, a methanolic extract of Sida cordifolia aerial portions greatly accelerated wound healing (Pawar et al., 2016). Sida rhombifolia has also been shown to improve wound healing (Francis et al., 2018). Sida cordifolia ethereal, acetate, methanolic, and aqueous extracts enhanced wound healing in mice, lending credence to its traditional usage (Kumar et al., 2019).

Analgesic action

Sida rhombifolia leaves exhibited analgesic efficacy, lowering acetic acid-induced pain in rats in a dose-dependent manner (Azad et al., 2017). Rosa et al. (2018) demonstrated that Sida tuberculata leaves had antinociceptive effects, lowering acetic acid-induced abdominal contractions in rats by around 70%.

Other Activity

A recent research found that combining Sida rhombifolia extract with the medication meloxicam is an effective therapy for osteoarthritis (Sari and Marpaung, 2019). Shahed-Al-Mahmud et al. (2018) offered evidence to support the ethnomedicinal usage of Sida cordifolia for diarrhea control. The hydroalcoholic extract of roots, according to these investigators, offered considerable and dose-dependent protection against castor oil- and magnesium sulfate-induced diarrhea in rats. Shah et al. (2017) found Sida cordata to be protective in the kidneys of rats with induced nephrotoxicity.

The extracts of Sida acuta displayed sedative, hypnotic, and anxiolytic effects, indicating that this species may produce changes in the central nervous system, lending credence to its traditional usage to treat nervous system illnesses (Benjumea et al., 2016). The hexanic extract of Sida rhombifolia demonstrated anti-cholinesterase action as well as a vasodilator impact (Mah et al., 2017).

Sida corymbosa shown a hypolipidemic effect, affecting cholesterol levels and therefore having the potential to reduce cardiovascular disease (Chukwuemeka et al., 2018). The species is also antihemorrhagic (John-Africa and Aboh, 2015).

The photoprotective capability of Sida galheirensis Ulbr. was looked into, but no noteworthy findings were discovered. The lack of action is thought to be owing to the low level of flavonoids in the species' ethanolic extract (Nunes et al., 2018).

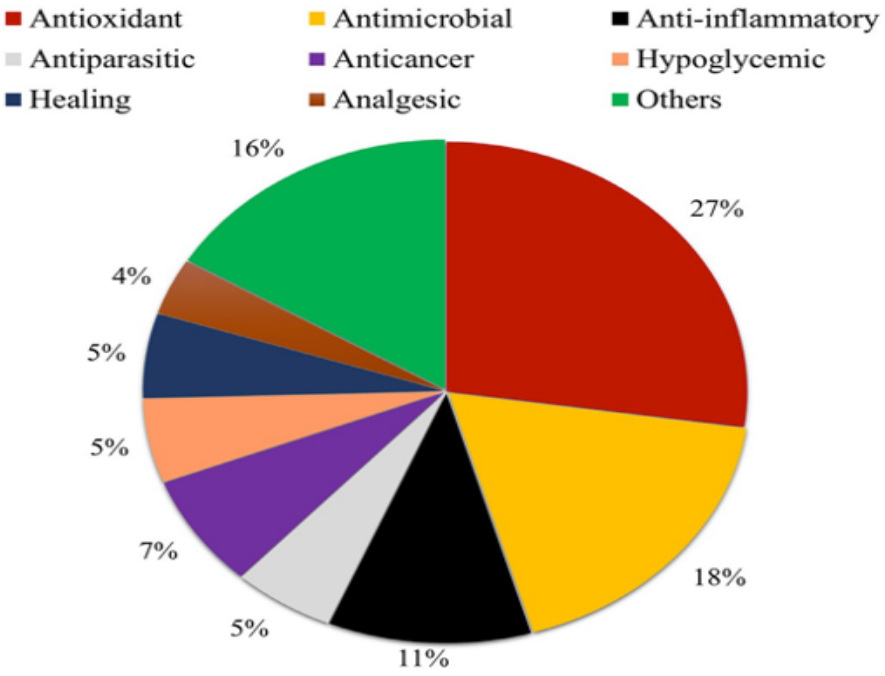

Figure 1: Pharmacological activities reported for *Sida* species

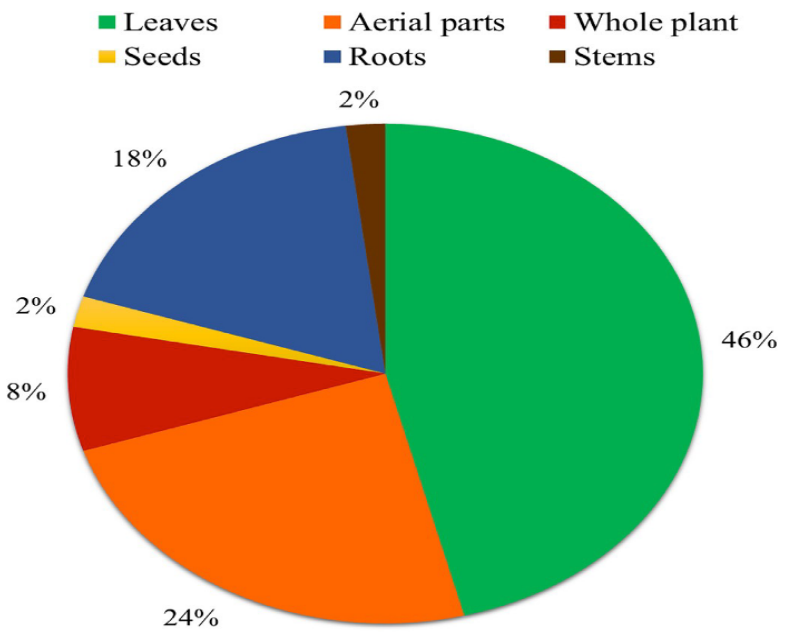

Figure 2: Plant Parts used in studies on biological and pharmacological activities reported for *Sida* species in the last five years (2015—2019). Aerial parts are not specified by the authors of the studies.

Chemistry of the genus *Sida*

A total of 142 chemical constituents had been identified in the genus *Sida* until 2015. Our study presents an update of the list of substances by including data published since the last review by Dinda *et al.,* (2015).

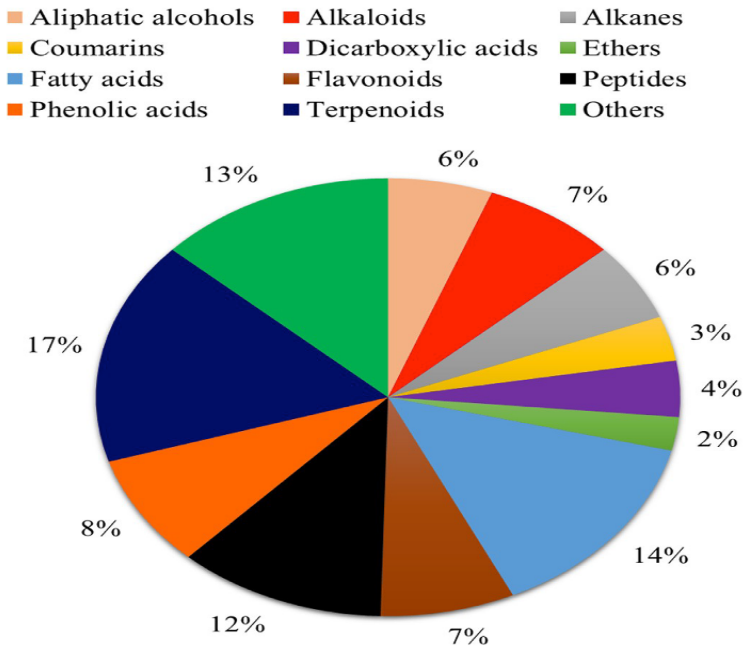

Figure 3: Percentage of the main chemical classes found in species of the genus *Sida*

Conclusion

Our review compiled information on ethnomedicinal uses, pharmacological activities and phytochemistry of species of the genus *Sida* from 2015 to present date. *Sida* is a genus of great importance worldwide, whose ethnomedicinal uses have been supported by several pharmacological studies, through in vitro and in vivo assays. The studies have focused on some species of the genus, such as *S. acuta, S. cordifolia* and *S. rhombifolia*, while few works have been dedicated to other species such as *S. gal- heirensis. Sida* species are traditionally used for the treatment of various health conditions, especially ulcers, asthma, fever, pain, rheumatism and diarrhea. Phytochemical investigations have demonstrated the potential of this genus as a source of bioactive substances. The new substances discovered over the last few years further reinforce the medicinal importance of *Sida* species.

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