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REVIEW ARTICLE

Desmodium adscendens (Sw.) DC.: A magnificent plant with biological and pharmacological properties

Maria Giulia Manzione[1] | **Jesús Herrera-Bravo**[2,3] | **Javad Sharifi-Rad**[4] | **Dorota Kregiel**[5] | **Mustafa Sevindik**[6] | **Emre Sevindik**[7] | **Zeliha Salamoglu**[8] | **Wissam Zam**[9] | **Sara Vitalini**[10,11] | **Christophe Hano**[12] | **Wirginia Kukula-Koch**[13] | **Wojciech Koch**[14] | **Raffaele Pezzani**[1,15]

[1]Phytotherapy Lab, Endocrinology Unit, Department of Medicine (DIMED), University of Padova, Padova, Italy

[2]Departamento de Ciencias Básicas, Facultad de Ciencias, Universidad Santo Tomas, Santiago, Chile

[3]Center of Molecular Biology and Pharmacogenetics, Scientific and Technological Bioresource Nucleus, Universidad de La Frontera, Temuco, Chile

[4]Facultad de Medicina, Universidad del Azuay, Cuenca, Ecuador

[5]Department of Environmental Biotechnology, Lodz University of Technology, Lodz, Poland

[6]Department of Food Processing, Bahçe Vocational School, Osmaniye Korkut Ata University, Osmaniye, Turkey

[7]Department of Agricultural Biotechnology, Faculty of Agriculture, Adnan Menderes University, Aydin, Turkey

[8]Department of Medical Biology, Faculty of Medicine, Nigde Omer Halisdemir University, Nigde, Turkey

[9]Department of Analytical and Food Chemistry, Faculty of Pharmacy, Al-Andalus University for Medical Sciences, Tartous, Syria

[10]Department of Agricultural and Environmental Sciences, Università degli Studi di Milano, Milan, Italy

[11]Phytochem Lab, Department of Agricultural and Environmental Sciences, Università degli Studi di Milano, Milan, Italy

[12]Laboratoire de Biologie Des Ligneux Et Des Grandes Cultures (LBLGC), INRA USC1328 Université d' Orléans, Orléans Cedex 2, France

[13]Department of Pharmacognosy with Medicinal Plants Garden, Medical University of Lublin, Lublin, Poland

[14]Department of Food and Nutrition, Medical University of Lublin, 4a Chodźki Str., Lublin 20-093, Poland

[15]AIROB, Associazione Italiana per la Ricerca Oncologica di Base, Padova, Italy

Correspondence
Javad Sharifi-Rad, Facultad de Medicina, Universidad del Azuay, Cuenca, Ecuador.
Email: javad.sharifirad@gmail.com

Sara Vitalini, Department of Agricultural and Environmental Sciences, Università degli Studi di Milano, Via G. Celoria 2, 20133, Milan, Italy.
Email: sara.vitalini@unimi.it

Christophe Hano, Laboratoire de Biologie Des Ligneux Et Des Grandes Cultures (LBLGC), INRA USC1328 Université d' Orléans, 45067 Orléans Cedex2, France.
Email: hano.christophe@gmail.com

Abstract

Desmodium adscendens (Sw.) DC. is a plant of the Fabaceae family especially rich in flavonoids but also in alkaloids, terpenoids, steroids, phenols, phenylpropanoids, glycosides, and volatiles. This herb has been traditionally used in numerous countries all over the world for its pharmacological and biological properties (i.e., it has been used for the treatment of diarrheas, fever, epilepsy, asthma, leishmaniasis, gastroduodenal ulcer, diabetes, hepatic diseases, etc.). Given the wide uses of *D. adscendens*, this review summarizes all recent data on *D. adscendens* evaluating its phytochemistry as well as its ethno-traditional and pharmacological properties. In addition, an association between the phytocompounds of this plant and its potential mechanism of action in cell

Raffaele Pezzani, Phytotherapy Lab, Endocrinology Unit, Department of Medicine (DIMED), University of Padova, via Ospedale 105, Padova, 35128, Italy.
Email: raffaele.pezzani@unipd.it

Sara Vitalini and Raffaele Pezzani are co-last authors.

and animal models has been investigated, focusing with a special emphasis on human experiments.

KEYWORDS
clinical trial, *Desmodium adscendens*, pharmacological properties, phytochemistry, preclinical studies

1 | INTRODUCTION

According to World Health Organization https://www.who.int/health-topics/traditional-complementary-and-integrative-medicine, the term "traditional medicine" is defined as the sum of knowledge, skills, and practices based on different culture-specific theories, beliefs, and experiences to protect and improve health. The use of traditional medicine since ancient times is shared in different countries, and its knowledge has been transmitted for generations (Leonti, 2011). Plants (fruits, vegetables, herbs) can contain many active ingredients, such as vitamins, terpenoids, phenolic compounds, nitrogen compounds (alkaloids, amines, and betalains), and other metabolites with interesting antioxidant potential (Muanda et al., 2011; Serafini & Peluso, 2016; Traka & Mithen, 2011). *Desmodium adscendens* (Sw.) DC., abbreviated "DA", is a perennial medicinal plant from the *Fabaceae* family found in tropical and subtropical areas of the world which contains numerous bioactive compounds (Magielse et al., 2013). This herbaceous plant (Figure 1) is used since ancient times for different diseases, including muscle cramps, tendinitis, spinal pain, epilepsy, jaundice, hepatitis, bronchitis, asthma, allergic reactions, and eczema. It has also antispasmodic and antihypertensive properties (Seriki et al., 2019). Of note that diverse ethnotraditional medicines in the world used DA for the treatment of different diseases. For example, in the American continent, it is valued for the treatment of gonorrhea, diarrheas, body aches, excessive urination, ovarian inflammations, fever, and epilepsy, while in Africa it cures smooth muscle contraction and asthma (Taylor, 2005; Gyamfi et al., 1999). In India, *D. adscendens* has been reported to possess antileishmanial, antioxidant, immunomodulatory, antiulcer, cardio-protective, antidiabetic, anti-amnesia, antiviral, and hepatoprotective activities (Ma et al., 2011; Rastogi et al., 2011). In Europe, the plant is commonly used as a food health supplement for its hepatoprotective action even if EFSA (European Food Safety Authority, the agency of the European Union that provides scientific information on potential risks associated with the food chain and botanicals) still needs to confirm this supposed effect (Botanicals On-hold – EFSA https://www.efsa.europa.eu › *sites* › *default* › *files* 371, M-2008-1061, *EFSA*-Q-2008-3268, 2535 – *Desmodium*).

The nonflowering aerial parts including leaves and stems are the medicinal parts that have been extensively studied over the past few decades (Ma, Zheng, Hu, Rahman & Qin, 2011; Rastogi, Pandey & Rawat, 2011). These organs contain flavonoids, isoflavonoids, alkaloids, terpenoids, steroids, phenols, phenylpropanoids, glycosides, and volatile molecules (Ma et al., 2011). In vitro and in vivo works based on crude extracts, fractions, or isolated components of DA have been shown to provide scientific evidence for their conventional uses. The aim of this review is to provide comprehensive information on botany, phytochemistry, traditional uses, preclinical and clinical pharmacological research, and the toxicology of DA and to explore its therapeutic potential and future perspectives. This work was prepared by researching articles, papers, and books from different databases (Embase-Elsevier, Google Scholar, Ovid, PubMed, Science Direct, Scopus, Web of Science) using a combination of different keywords, that is, *Desmodium*, *Desmodium adscendens*, pharmacology, ethnopharmacology, phytochemicals, antioxidant, antimicrobial, anti-asthmatic, immunomodulatory, antiulcer, cardioprotective, antidiabetic, anti-amnesia, antiviral, hepatoprotective. Only sources written in English from any country were included.

2 | PHYLOGENY, BIOGEOGRAPHY, AND CHARACTER EVOLUTION

Fabaceae (Leguminosae), the third largest family within the Angiosperms, includes 946 genera and over 24,500 accepted species (The Plant List, http://www.theplantlist.org/browse/A/Leguminosae/). There are commonly three subfamilies—Caesalpinioideae, Mimosoideae, and Papilionoideae—that have been recently split into six subfamilies, namely Caesalpinioideae, Cercidoideae, Detarioideae, Dialioideae, Duparquetioideae, and Papilionoideae. The Legume Phylogeny Working Group (LPWG) provided key and taxonomic descriptions to exemplify the diversity of flowers and fruits in these subfamilies (Azani et al., 2017). The Phaseoloid clade is one lineage within Papilionoideae, which comprises the Phaseoleae *sensu lato* (s.l.) clade, Desmodieae, and Psoraleeae. The clade shows a multifaceted phylogenetic association among and within tribes. Indeed Desmodieae and Psoraleeae can be considered monophyletic groups that are nested within the paraphyletic Phaseoleae *s.l.* group (Jin et al., 2019).

The tribe Desmodieae (Benth.) Hutchinson comprises 32 genera and ca. 530 species used for medicine and forage (Jabbour et al., 2018). They largely grow in warm-temperate regions, even if a small group has adapted to cool-temperate and boreal regions of North America. This tribe is commonly represented by herbs or shrubs, while not often by trees. Legumes or loments (a single carpel that disarticulates into single-seeded segments when ripe) are the classical forms of fruits. Bryinae, Desmodiinae, and Lespedezinae are the three subtribes of Desmodieae. Of note that Desmodiinae possesses great generic diversity in tropical South and South-East Asia, while species of the subtribe Lespedezinae are found in temperate East Asia and North America. The tribe was further circumscribed into three groups based on an analysis of the chloroplast gene rbcL: the Lespedeza group (three

FIGURE 1 Flowering stem and developing seedpods of *Desmodium adscendens* (Sw.) DC. plant

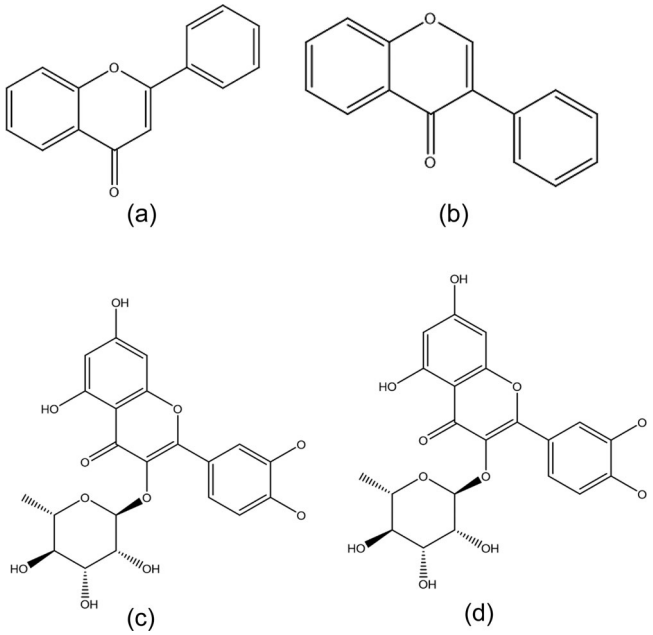

FIGURE 2 Chemical structures of flavonoids (a) and isoflavonoids (b). Chemical structure of isovitexin-2″-*O*-xyloside. (c) Chemical structure of quercitrin dehydrate (d)

genera) corresponding to the Lespedezinae subtribe, the Phyllodium (12 genera), and Desmodium (17 genera) groups, together corresponding to the Desmodiinae subtribe (Jabbour et al., 2018; Jin et al., 2019). Jabbour et al. obtained chloroplast (rbcL, psbA-trnH) and nuclear (ITS-1) DNA sequences to evaluate the molecular phylogeny and historical biogeography of Desmodieae (Jabbour et al., 2018). The results obtained from wide molecular analysis suggested that the hypothetical common ancestor of Desmodieae was dated to the Middle Oligocene and was likely an Asian shrub or tree producing indehiscent loments. While America has been suggested to be colonized once, with the development of *Desmodium intortum* (Mill.) Urb. and *Desmodium adscendens* (Sw.) DC., Oceania, and Africa were populated several times. Jin and co-workers investigated the plastome evolution and analyzed phylogenetic signaling by sequencing six complete plastomes from representative members of *Desmodieae* (Jin et al., 2019). The phylogenetic analysis showed that the tribe Desmodieae was probably a monophyletic group nested within the paraphyletic Phaseoleae, as reported in former works.

Desmodium is a genus with more than 46 species and is considered a curative plant in Africa (Central African Republic, Gabon, Ghana, Cameroon, Congo, Ivory Coast, Equatorial Guinea, Senegal, Sierra Leone, Benin, and Togo), in South America (Peru, Bolivia, Ecuador, Brazil, Venezuela, Guyana, Guyana, Nicaragua), in Southeast Asia (Japan, Burma, Indonesia, Malaysia, Philippines, Cambodia, Vietnam), India, Indian Ocean (Rodrigues, Mauritius), in Pacific (Vanuatu, New Caledonia, Guadalcanal, Salomon, Palau), Taiwan, and China (Farid et al., 2018) and North-East America (Parker et al., 2015).

3 | PHYTOCHEMISTRY OF *DESMODIUM* SPECIES

Different parts of *Desmodium* species possess mixed groups of bioactive compounds. They are rich in flavonoids (flavones, 7, 8-prenyl-lactone flavonoids, flavonols, flavan-3-ols, and flavanonols) and especially isoflavonoids (isoflavones, isoflavanones, pterocarpans, and coumaronochromones) (Figure 2a,b). Indole alkaloids, phenylethylamine alkaloids, pyrrolidine alkaloids, amide alkaloids, and simple alkylamine were the main alkaloids found in *Desmodium*. In addition, numerous terpenoids, steroids, phenols, phenylpropanoids, glycosides, and volatile oils have been isolated and characterized in the genus (Ma et al., 2011).

Some studies evaluated methanolic crude extracts of DA reporting the presence of polyphenols and particularly flavonoids, found mainly in the leaves rather than in stems (Konan et al., 2012; Mamyrbékova-Békro et al., 2008). In the past decade, Baiocchi and collaborators were able to quantify saponins and alkaloids using high-resolution mass spectrometry (Baiocchi et al., 2013). Of note that plants grown in Africa were quantified for flavonoids by high-performance liquid chromatography (HPLC) with a diode array detector, mass spectrometry, and multidimensional nuclear magnetic resonance spectroscopy (Zielinska-Pisklak et al., 2015). Chemical characterization of DA plant material identified the isovetixin-2″-*O*-xyloside (flavone C-glycosides) (Figure 2c) as the main compound in an ethanol extract (Muanda et al., 2011). Munda and collaborators isolated and identified five main phenolic compounds from DA leaves, namely caffeic acid, quercetin, *p*-coumaric acid, epicatechin, and rutin as well as other compounds such as phenylethylamines, indole-3-alkyl amines, tetrahydroiso-quinolones, and triterpenoid saponins (Muanda et al., 2011).

The volatiles extracted from the leaves included phytone (14.72%), caryophyllene oxide (11.32%), eudesma (7.41%), geraniol (5.42%), linalool (5.33%), palmitic acid (5.06%), α-caryophyllene (4.76%), scytalone (3.83%), β-ionone (3.47%), 2,2-dimethyl-hexanale (3.37%), pelargonaldehyde (3.26%), hyperforine (3.27%), 2-pentyl furan (2.71%), oleic acid (2.68%), and 4-azidoheptane (2.02%) (Ayoola et al., 2018) In another study, phytochemical investigation of a DA

decoction resulted in the identification of flavonoids such as vicenin-2, isoschaftoside, schaftoside, 2″-*O*-xylosylvitexin, 2″-*O*-pentosyl-chexosylapigenin, and an *O*-hexosyl-*C*-hexosyl-apigenin, tentatively identified as 2″-*O*-glucosyl-vitexin (van Dooren et al., 2018). In addition, DA decoction possessed vitexin and isovitexin glycosides at high concentration: vitexin and the C-glycosides thereof were investigated for their interaction at the gastrointestinal level (with simulation test) reporting the stability of the molecules (van Dooren et al., 2018). Muanda et al. evaluated the total phenolic profile in DA leaves which were found to be a rich source of flavonoids with 12.8 mg of catechin equivalent (CE)/g dry weight (dw) (Muanda et al., 2011). The amount of total polyphenols was 11.1 mg of gallic acid equivalent (GAE)/g dw while that of total anthocyanin and total tannin compounds was not elevated, equal to 0.0182 mg CE/g dw and 0.39 mg CE/g dw, respectively. Finally, HPLC analyses revealed that the main phenolic compound identified in the methanol–water extract was quercetin dihydrate (2.11 mg/mL) (Figure 2d). The compounds identified in DA are listed in Table 1. Recently, also seeds of *D. gangeticum* (L.) DC. were evaluated and their content (oil and fatty acids) was examined. The yield of crude oil was found to be 4.39%. Among the identified fatty acids, oleic acid (38.7%), linoleic acid (35.4%), palmitic acid (11.2%), behenic acid (8.0%), and stearic acid (4.5%) were the main constituents (Manivel et al., 2018).

4 | TRADITIONAL USE OF GENUS *DESMODIUM*

Ethnobotany describes relationships between humans and plants and searches for traditional botanical knowledge. Ethnobotanical studies explore the profound interaction between plant diversity, social, and cultural systems to understand and develop knowledge of valuable region-specific plants (Amjad et al., 2017; Baydoun et al., 2015). Among these, *Desmodium* spp. were frequently reported as ethnomedicinal plants. In particular, DA is the most known and used plant, also called beggar-lice, beggar weed, tick clover, or tick trefoil (Rastogi et al., 2011). The simple use of DA by decoction (the act of placing a plant or its part in hot water and the possibility to be administered orally or topically) led to the wide diffusion of this plant (Baydoun et al., 2015). In Brazil, this species is without difficulty collected in the Northeast, Center West, and Southeast regions (Rastogi et al., 2011). In Mato Grosso, the plant is known as "amores do campo" or "carrapichinho" and in São Paulo and Rio Grande do Sul as "pega-pega" (Santos et al., 2013). Its leaves are commonly collected to treat leucorrhea, gonorrhea, diarrheas, body aches, excessive urination, hepatic infections, and ovarian inflammations (Rastogi et al., 2011). In France and Belgium, this plant is traditionally used as a food health supplement for its hepatoprotective effects (Muanda et al., 2011). DA is a woody stem climbing plant that also grows in fallow land on the west coast of Africa, frequently found in Nigeria, Cameroon, and Zimbabwe. This perennial herb produces numerous light-purple flowers and green fruits in small, beanlike pods (Adeniyi et al., 2013). It is a solitary hedgerow growing in humid lands, and it is widespread in savannas and forests (Azani et al., 2017). In Africa, plants of the *Desmodium* genus are extensively used to heal asthma and smooth muscle spasms (Muanda et al., 2011). In China, the use of *Desmodium* spp. for ethnomedicinal purposes dates back as far as 3000 years ago. They were mainly used to treat fever, block pain, restore blood circulation, counteract toxins, remove cough, and relieve dyspnea. Ethnopharmacological studies on DA in India showed a broad spectrum of activities including antileishmanial, antiviral, antioxidant, immunomodulatory, antiulcer, cardio-protective, antidiabetic, and anti-amnesia, and hepatoprotective (Rastogi et al., 2011). Currently, in Chinese and Indian medicines, *Desmodium* species are used to approach with fever, rheumatism, hemoptysis, abscess, common cold, wounds, icteric hepatitis, pharyngitis, infantile malnutrition, dysentery, urinary diseases, parotitis, cholecystitis, malaria, and epidemic encephalitis (Ma et al., 2011; Rastogi et al., 2011).

D. gangeticum, another recognized and used plant of the same genus commonly known as 'Salpan', 'Salpani' in Hindi and 'Shalparni' in Sanskrit, is used in Ayurveda, Siddha, and Unani systems of medicine either as a single drug or in combination with other drugs. *D. gangeticum* is an accepted source of Shaliparni as per the Ayurvedic Pharmacopeia of India (Vaghela et al., 2012). This plant with bitter tonic, febrifuge, digestive, anticatarrhal, and antiemetic properties, is used in inflammatory conditions of the chest and other cases due to "vata" disorder (in Ayurveda, vata is one of the three principles of energy associated with movement). The roots have been used as an expectorant and in snake bites and scorpion stings. It is an ingredient of Ayurvedic preparations like "Dashmoolarishta" and "Dashmoolakwaath" recommended for postnatal care to avoid secondary complications (Rastogi et al., 2011).

Desmodium species that form a nitrogen-fixing symbiosis with rhizobia play an important role in sustainable agriculture (Delamuta et al., 2015; Xu et al., 2016). They are very effective in suppressing weeds while improving soil fertility. In addition, these plants provide high-value animal fodder and forage, inducing milk production and expanding farmers' income sources (Khan et al., 2014; Thomas & Sumberg, 1995). In general, soil microedges provide an ecological niche for *Desmodium* spp. (Kowalski & Henry, 2019). Furthermore, DA has been used as a ground cover in post-mining lands. It was documented that this plant is an important instrument in soil conservation and rehabilitation, especially in degraded soils (Tambunan et al., 2017).

In addition, a very recent work analyzed the effects of DA and *Arachis repens* as cover crops on banana plantations (Reine Kosso Boka et al., 2022). The authors showed that only *Arachis repens* (and not DA) were able to enrich the biological soil fertility because it increased arbuscular mycorrhizal fungal spores at a different time of analysis (6 and 12 months).

5 | PHARMACOLOGICAL PROPERTIES OF *DESMODIUM ADSCENDENS*

The pharmacological properties of DA have been widely explored during the past decades (Rastogi et al., 2011). In the following sections, we summarize the scientific evidence of the therapeutic potential of DA obtained from preclinical experiments and clinical trials (Table 2).

TABLE 1 Chemical compounds from leaves of *D. adscendens*

Source	Compounds	References
	Alkaloids	
Aqueous extract, ethanol 70%	Dimethyltryptamine, dimethyoxyphenylethylamine, salsoline, hordenine, tyramine, gramine	Baiocchi et al. (2013), Addy and Schwartzman (1995)
	Flavonoids	
Decoction, ethanol 70%, methanol 50%, methanol 70%	6*C*,8*C*-Dihexosyl-kaempferol, 5-*O*-hexosyl-apigenin, 6-*C*,8-*C*-dihexosyl-apigenin, 6-*C*-pentosyl-8-*C*-hexosyl-kaempferol, 6-*C*-hexosyl-8-*C*-pentosyl-kaempferol, 5-*O*-hexosyl-kaempferol, 6-*C*-hexosyl-8-*C*-pentosyl-diosmetin, 6-*C*-pentosyl-8-*C*-hexosyl-kaempferol, 6-*C*-pentosyl-8-*C*-hexosyl-apigenin, 8-*C*-hexosyl-kaempferol, 6-*C*-pentosyl-8-*C*-hexosyl-kaempferol, 6-*C*-pentosyl-8-*C*-hexosyl-apigenin, 6-*C*-hexosyl-8-*C*-rhamnosyl-kaempferol, 6-*C*-hexosyl-8-*C*-pentosyl-apigenin, 5-*O*-pentosyl-1,6-rhamnosyl-kaempferol, saponarin (6-*C*-hexosyl-7-*O*-hexosyl-apigenine), 7-*O*-pentosyl-1,6-rhamnosyl-kaempferol, 6-*C*-hexosyl-8-*C*-pentosyl-apigenin, vitexin (8-*C*-hexosyl-apigenin), 5-*O*-rhamnosyl-(1-6)-hexosyl-apigenin, 5-*O*-pentosyl-(1-6)-hexosyl-apigenin, 6-*C*-hexosyl-8-*C*-pentosyl-kaempferol, astragalin (3-*O*-hexosyl-kaempferol), 6-*C*-hexosyl-8-*C*-rhamnosyl-apigenin, 5-*O*-pentosyl-(1,6)-hexosyl-diosmetin, 6-*C*-hexosyl-8-*C*-pentosyl-apigenin, 6-*C*-rhamnosyl-8-*C*-hexosyl-apigenin, 6-*C*-hexosyl-7-*O*-rhamnosyl-apigenin, 7-*O*-rhamnosil-quercetin, 6-*C*-rhamnosyl-8-*C*-hexosyl-apigenin, 7-*O*-hexosyl-kaempfero, 1,6-rhamnosyl-7-*O*-hexosyl-7-apigenin, 7-*O*-hexosyl-apigenin, 7-*O*-pentosyl-1,6-hexosyl-diosmetin, isovitexin 2″-*O*-xyloside, vitexin 2″-*O*-xyloside, vitexin, isovitexin, 2″-*O*-glucosyl-vitexin, vicenin-2, schaftoside, isoschaftoside, 2″-*O*-xylosylvitexin, 2″-*O*-pentosyl-*C*-hexosyl apigenin, epicatechin, rutin, quercetin, quercetin glucosyl, quercetin dehydrate	Muanda et al. (2011), Baiocchi et al. (2013), Zielinska-Pisklak et al. (2015) Van dooren et al. (2018)
	Phenolic acids	
Methanol 50%, methanol 70%	Caffeic acid, *p*-coumaric acid, gallic acid, protocatechuic acid, chlorogenic acid, cinnamic acid	Muanda et al. (2011)
	Saponins	
Ethanol 70%	Soyasaponin I, soyasaponin III, dehydrosoyasaponin I, and soyasapogenol B and E	Baiocchi et al. (2013)
	Terpenoids	
Essential oil	α-Terpinene, α-terpinolene, linalool, geraniol α-caryophyllene, caryophyllene oxide, epoxide II humulene eudesma	Muanda et al. (2011)
	Fatty acids	
Essential oil	Margaric acid, oleic acid, palmitic acid	Muanda et al. (2011)
	Others	
Essential oil	2-Pentyl furan, 1-methyl silabenzène, azido-4 heptane, 2-(*N*-methyl pyrrolidine) methenamine, 3-hexen-1-ol, 2,2- dimethyl-hexanal, 3-octenol, pelargonaldehyde, methyl benzoate, perillardehyde, mandelic acid, b-ionone, ol-13 8-cedrene, 3-(2-pentyl) 1,2,4- cyclopentanetrione, oleic acid, phytone, scytalone, hyperforin, palmitic acid, margaric acid, α-isomethyl ionone, linoleic acid, 4,6,9- nonadecatriene, cetanole	Muanda et al. (2011)

TABLE 2 Preclinical and clinical pharmacological properties of *D. adscendens*

Types of samples administrated	Results	References
Aqueous or alcoholic extracts of DA	Decrease in the anaphylactic contraction of ileal pieces from sensitized guinea pigs	Addy and Awumey (1984)
Oral administration of the extracts	Reduction in the sensitivity of trachea-bronchial smooth muscle to histamine and decreased the amount of muscle stimulating substances released from the lungs	Addy (1992)
DHS-I purified from crude extracts of DA	Activation of maxi-K which regulates bronchospasms	McManus et al. (1993)
n-butanol fraction of DA	Increase in prostaglandin synthesis	Addy and Schwartzman (1995)
Intraperitoneal administration of the plant extract	Hypothermia, a reduction of acetic acid-induced writhes and climbing activities, analgesic properties, and a delay in the onset of clonic PTZ convulsion	N'Gouemo et al. (1996), Amoateng et al. (2017)
Leaf extracts	Antioxidant and antiradical activities	Muanda et al. (2011)
Hydroalcoholic extract of DA	Cytoprotective effects in human kidney LLC-PK1	François et al. (2015)
D-pinitol isolated from aqueous decoction of DA	Hepatoprotective properties	Magielse et al. (2013)
Lisosan® Reduction	Hypocholesterolemic and hepatoprotective effects	Russo et al. (2019)
Hexane/methanol extract of DA	Antimicrobial effects against *Staphylococcus aureus* SA1199 and *Candida albicans* ATCC 90029 strains	Adeniyi et al. (2013)
Silver nanoparticles	Antimicrobial effects against *Escherichia coli*	Thirunavoukkarasu et al. (2013)
DA decoction	Vitexin and C-glycosides were stable during their passage in the gastrointestinal tract, while the O-glycosidic bonds of O-glycosides of vitexin were metabolized by the colon bacteria. The flavonoid fraction and D-pinitol were both stable.	Van Dooren et al. (2018)
DA combined with *Lithotamnium calcareum*	Patients with head and neck cancer were concomitantly treated with standard chemotherapy. ECOG and GPS scores were found to be stable throughout the study. Moreover, both pain and fatigue significantly improved at a later stage of the therapy.	Imperatori et al. (2018)

5.1 | Preclinical experiments

5.1.1 | Anti-asthmatic properties

In 1984, Addy and Awumey performed the first preclinical study to evaluate the effects of DA extracts on anaphylaxis in guinea pigs (M. E. Addy & Awumey, 1984). For this purpose, animals were sensitized with egg albumin (antigen) to provoke an allergic reaction and bronchial smooth muscle contractions. Guinea pigs were then divided into three groups. One group was treated with water (control), one with aqueous, and one with alcoholic extract of DA (DAE). Extracts were administered orally. Anaphylaxis was assessed by determining the contractions of the ileal pieces. The study revealed that animals receiving an aqueous or alcoholic extract of DA had less than 50% bronchial contractions compared to control animals. Histamine content of lung tissues of guinea pigs treated with plant extracts was reduced by more than 50% compared to animals treated with water. The authors proposed that DAE probably interfered with the release of inflammatory mediators. Nevertheless, they did not isolate the active components responsible for the anti-inflammatory action and the work did not compare the use of DA with standard pharmacological therapy (i.e., prednisolone, chlorpheniramine, ketotifen, etc.) for anaphylaxis in experimental models. Subsequent studies identified triterpenoid saponins, β-phenylethylamines, and tetrahydroisoquinolines in DA as the main effectors of the potential anti-asthmatic activity of DA (M. E. Addy & Schwartzman, 1995). In vitro experiments using microsomes from the human kidney, cortex showed that two phenylethylamines found in DA, tyramine, and hordenine, activated the NADPH-dependent cytochrome P450 monooxygenase and increased the levels of prostaglandin E2 (PGE2). Salsoline, a tetrahydroisoquinoline derivative found in DA, inhibited P450 monooxygenase and decreased the levels of PGE2 (M. E. Addy, 1992). In 1993, McManus et al. (1993) purified dehydrosoyasaponin I (DHS-I), a triterpene glycoside, from crude extracts of DA. When applied to bovine tracheal smooth muscle membranes, DHS-I could activate reversibly and, with high-affinity, calcium-dependent potassium channels (maxi-K) by partially inhibiting the binding of monoiodotyrosine charybdotoxin (125I-ChTX) to receptor sites (K_i = 120 nM, 62% maximum inhibition) (McManus et al., 1993). Maxi-K channels regulate the muscle tone of lung airways and the release of substances that causes bronchoconstriction and inflammation. These results suggest that different classes of bioactive molecules found in DA may have anti-asthmatic properties. However, in vivo studies are needed to compare the beneficial effects of the phytochemicals found in DA with the effects of chemically

related molecules found in other natural sources. For example, soya saponins extracted from soya beans have promising anti-inflammatory activities in mice (Kang et al., 2005). Saponins content of soya beans is also higher compared to the percentage of soyasaponins found in DA (0.43–0.76% in soya beans compare to 0.003–0.03% in DA) (M. E. Addy, 1992), and, therefore, it should be carefully evaluated which plant source is more convenient to use for future therapeutic application. Moreover, a comparison with a standard therapy would be helpful to uncover the alleged benefits of DA or other medicinal plants.

5.1.2 | Neurological effects

In 1996, the neuropharmacological profile of DAE in rodents was examined (N'Gouemo et al., 1996). Intraperitoneal administration of the plant extract at doses of 1000 mg/kg caused abdominal contractions, decreased spontaneous motor activity, and exploratory behavior. Moreover, administration of DAE (300 mg/kg) caused a significant fall in body temperature ($p < 0.05$) compared to untreated animals. Injection of 109.89 mg/kg of DA inhibited acetic acid-induced writhes by 50% compared with injection of the vehicle. In addition, pretreatment with 300 mg/kg DAE inhibited tonic pentylenetetrazole (PTZ) induced convulsions and significantly ($p < 0.05$) postponed the onset of clonic PTZ convulsion (N'Gouemo et al., 1996). The authors suggested that DA at 300 mg/kg could have depressant activity on the central nervous system, together with anticonvulsant and analgesic effects in mice. More recently, a similar study investigated the antipsychotic-like properties of DAE in mice (Amoateng et al., 2017). Animals were orally pretreated with 30, 100, 300, 1000, and 3000 mg/kg DAE or vehicle. The effects on spontaneous motor activity and general anesthetic effects (Irwin's test) were measured for 3 h after treatment. Doses up to 300 mg/kg did not cause detectable neurological effects in agreement with the previous observation (N'Gouemo et al., 1996). However, mice pretreated for 15–30 min with 1000–3000 mg/kg of DA were sedated. Locomotor behavior was also evaluated by comparing mice treated with 1000 mg/kg DAE or with 1 mg/kg chlorpromazine, a well-known antipsychotic agent, or water (negative control). The frequency of rearing in mice treated with DAE was significantly decreased ($p \leq 0.001$) by ~ 50% compared to control animals (water). Apomorphine-induced cage climbing was decreased after pretreatment with 300–1000 mg/kg of DAE although the effects were less potent compared to treatment with haloperidol (HAL). The total duration of HAL-induced catalepsy in mice was significantly increased ($p \leq 0.01$) after pretreatment with 1000 mg/kg DA. Overall, these studies suggest that DAE used at 1000 mg/kg has potential sedative and analgesic effects, that need to be further investigated in human studies. Moreover, the authors proposed that the antipsychotic effects were probably due to the presence of flavonoids acting on cholinergic or serotonergic mechanisms. More recently, a survey from Goma city in the Democratic Republic of Congo reported that people from this region made use of different plant extracts including DA for the treatment of different mental disorders (i.e., depression, anxiety, post-traumatic stress disorder, schizophrenia, etc.) (Kyolo et al., 2022). Even if the work investigated the ethnopharmacological use of DA, it has not been possible to conclude the real benefit of DA in these diseases, both of the anecdotic uses and lack of standardization. Clinical trials are necessary to pursue the matter.

In other studies, it has been shown that salsolinol (a tetrahydroisoquinoline derivative), found in DA and other natural sources, showed both neuroprotective and neurotoxic activities in mice (Kurnik-Lucka et al., 2018). Interestingly, salsolinol is also produced endogenously from dopamine, indeed it was first detected in the urine of Parkinsonian patients on therapy with L-DOPA (L-dihydroxyphenylalanine) (Sandler et al., 1973). This suggested a role in Parkinson's pathogenesis as a neurotoxin that can induce apoptosis of dopaminergic neurons due to its structural similarity to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (CNS Neurol Disord Drug Targets, 2020). However, salsolinol can be found in numerous plants and protein-derived foods, that is, bananas, cheese, cocoa, eggs, flour, etc. (Deng et al., 1997) and even if potentially implicated in the disease, up to now it is not possible to determine a clear positive or negative impact of salsolinol on human health. What emerges from different studies is that it colocalizes with dopamine-rich regions not only in the brain but also in the enteric nervous system and gut microbiota (CNS Neurol Disord Drug Targets, 2020). Different aspects of the pharmacological and biological profile of salsolinol still need to be established, but it is tempting to speculate that this molecule can be probably responsible for the neurological effects of DA or can act to enhance the effect of endogenous salsolinol in animal models.

5.1.3 | Antioxidant properties

Muanda and collaborators evaluated the antioxidant properties of DA leaves by measuring the levels of intracellular radical oxygen species (ROS) in mouse granulocytes exposed to hydrogen peroxide (H_2O_2) and treated with DA extracts (Muanda et al., 2011). ROS levels were evaluated by flow cytometry. The results showed that treatment with 25 mg/mL of DA reduced the level of intracellular of 83.2 ± 6.21% of ROS level generated by exogenous H_2O_2. Moreover, HPLC analysis of DAE showed a significant content of phenolic, flavonoids, anthocyanins, and tannins with known antioxidant properties. In a subsequent study, it was shown that treatment of pig kidney (LLC-PK1) cells with 1 mg/mL of DAE significantly improved the viability of LLC-PK1 cells exposed to glucose-induced oxidative stress (Francois et al., 2015). The protective effect of DAE was not dose-dependent since treatment with 30 mg/mL did not restore cell proliferation. These data suggest that DA extract may have antioxidant activity at least in in vitro experiments (Francois, Fares, Baiocchi & Maixent, 2015). Additional in vivo studies are needed to confirm the protective effects of DA in comparison with well-known natural antioxidants such as quercetin, resveratrol, and curcumin (Simioni et al., 2018). Of note that ROS cell levels were decreased by DA leaf aqueous extract, suggesting a scavenging activity capacity of the plant (Muanda et al., 2011). A straight association between phenolic compounds and antioxidant activity ($R^2 = 0.96$) was found, with a concentration-response curve for

reduction of ROS generated by exogenous H_2O_2 in blood cells derived from mice. The author concluded that DA possessed pharmacological activity to be potentially tested in clinical trials; however, no other work followed this suggestion. Consequently, the supposed antioxidant properties of DA are justified only in a preclinical setting and need to be confirmed in human experiments.

5.1.4 | Hepatoprotective properties of D-pinitol isolated from DA

The work of Magielse and collaborators evaluated the protective effect of D-pinitol (or 3-*O*-methyl-D-chiro-inositol) isolated from aqueous decoction of DA against acute liver damage induced by D-galactosamine and chronic ethanol-induced liver damage in rats (Magielse et al., 2013). The authors compared the effects of several dosages of D-pinitol with that of silymarin, a natural compound with known hepatoprotective activity in vivo (Baradaran et al., 2019; Freitag et al., 2015). Oral administration of 5 mg/kg D-pinitol significantly reduced aspartate transaminase (AST) and alanine transaminase (ALT) levels (biomarkers for liver damage) 48 h after galactosamine injection at least in the acute liver damage model. Similar results were obtained with 20 mg/kg of silymarin. However, DA decoction nor pure D-pinitol at doses of 10–20 mg/kg had no hepatocurative effects on the chronic hepatotoxicity model. Thus, it is conceivable that the potential hepatoprotective activity of DA is fundamental in an acute setting, while in the chronic model the plant shows a limiting effect. In addition, the authors used a limited number of animals in ethanol-induced liver damage with a modest increase in serum AST and ALT. Such experimental constraints could distort the real effect of DA in the chronic model and will force the researchers to further deepen the supposed hepatoprotective activity of DA in new experiments.

5.1.5 | Hepatoprotective properties of DA

More recently, the beneficial effects of Lisosan® Reduction, a combination of medicinal plant extracts, were tested in mice high-fat diet (HFD)-fed mice (Russo et al., 2019). The plant mixture, produced from a powder of fermented DA, *Triticum aestivum*, *Malus domestica*, *Picrorhiza kurroa*, and *Hordeum vulgare*, has a polyphenol profile composed of syringic acid, *trans*-sinapic acid, and neochlorogenic acid, followed by vitexin, trans-*p*-coumaric acid, and trans ferulic acid. The study showed that administration of Lisosan® Reduction (60 mg/kg) had hypocholesterolemic and hepatoprotective effects in HFD mice by restoring the levels of total cholesterol, serum triglycerides, and glucose with no toxic effect (ALT and AST levels resulted unaffected by the formulation). Nevertheless, the beneficial effects of Lisosan® Reduction cannot be directly related to the presence of DA, which represented 20% of the total mixture. Among the four most abundant constituents of Lisosan® Reduction, syringic acid (284.69 ± 0.77 mg/kg), *trans*-sinapic acid (117.39 ± 1.07 mg/kg), neochlorogenic acid (115.88 ± 0.28 mg/kg), and vitexin (60.40 ± 1.24 mg/kg), only the last has been identified in DA so far (van Dooren et al., 2018; Zielinska-Pisklak et al., 2015). Syringic acid and *trans*-sinapic are found in *T. aestivum* (Wu et al., 2001), which represents 64% of Lisosan® Reduction while neochlorogenic acid is one of the main polyphenolic compounds in *M. domestica* (Crozier et al., 2006) (10% of Lisosan mixture). Consequently, the real activity of DA in the product Lisosan® Reduction is probably limited and restricted, even if the product showed hypocholesterolemic and hepatoprotective in a mouse model. As mentioned in the previous section, DA still needs to be deeply studied to uncover its hepatoprotective properties.

5.1.6 | Antimicrobial properties

In the study conducted by Adeniyi et al. different concentrations of DA hexane/methanol extract showed a significant antimicrobial effect on *Staphylococcus aureus* SA1199 and *Candida albicans* ATCC 90029 strains (Adeniyi et al., 2013). At the concentration of 0.25 mg/mL, the percentage of *S. aureus* cells death was approximately 100% within 120 min. Comparable results were obtained for *C. albicans*. It has been shown that silver nanoparticles have antimicrobial effects (Cho et al., 2005). Different research groups used the leaf aqueous extract of *Desmodium gangeticum* (L) DC. (abbreviated DG) to synthesize silver nanoparticles (AgNPs) with sizes ranging from 18 to 39 nm (Thirunavoukkarasu et al., 2013; Vasanth & Kurian, 2017). The antibacterial property of the DG-based AgNPs was tested against *S. aureus* (ATCC strain) and *Escherichia coli* (ATCC strain). At a concentration of 2500–5000 μg/mL DG-based AgNPs were highly toxic against *E. coli*, thus suggesting the potential use of *D. gangeticum* in the production of antimicrobials of a new generation. However, another study showed that oral administration of 100 mg/kg, DG-based AgNPs in rats-induced alterations in renal architecture. Moreover, cytotoxicity was observed in LLC PK1 cells when treated for 24 h with 1 mg/mL nanoparticles (Vasanth & Kurian, 2017). These outcomes using DG can be used as a model for future experimentation of DA since the two species belong to the same genus and partially share the antimicrobial effect. Although nanoparticles are known for their easy permeability in tissues and most relevant studies were performed on the DG plant, it is important to optimize the antimicrobial in vitro and in vivo effects of DA for a future and safer administration in higher organisms.

5.2 | Clinical data

DA possesses numerous pharmacological properties, and it is popular as herbal tea. Nevertheless, only a few studies investigated the pharmacological properties and/or toxicities of DA in humans. In 2018, van Dooren and collaborators used the in vitro gastrointestinal dialysis model combined with HPLC to investigate the biotransformation of D-pinitol, vitexin, and the flavonoid fraction of DA decoction (van Dooren et al., 2018). The authors found that vitexin and *C*-glycosides were stable during their passage in the gastrointestinal dialysis model, while the *O*-glycosidic bonds of *O*-glycosides of vitexin were metabolized by

the colon bacteria. The flavonoid fraction was stable since no biotransformation occurred in the colon phase. D-pinitol was also very stable during passage through the gastric, small intestine, and colonic phases. Nevertheless, the in vitro model used in this study did not give information about the absorption or the enzymatic reactions occurring in the intestine. Thus, it will be interesting to evaluate these processes in the future, as the DA metabolism is understudied in humans.

In 2019, a single-arm study investigated the therapeutic potential of Desmovit®, a medical device containing 300 mg of DA leaves and 50 mg of *Lithotamnium calcareum* (a red marine algae rich in calcium and magnesium) in patients with head and neck cancer treated with standard chemotherapy (paclitaxel 75 mg/m^2 plus carboplatin or methotrexate 40 mg/m^2) (Imperatori et al., 2018). Twelve patients received an intravenous infusion of paclitaxel or methotrexate and a medical device containing 300 mg of DA leaves and 50 mg of *L. calcareum*. Patients were monitored for 12 weeks by assessing the Glasgow Prognostic Score (GPS), a prognostic score that evaluates the plasma level of C-reactive protein and albumin levels, and by examining the Eastern Cooperative Oncology Group (ECOG) performance status, (used to determine how patients tolerate the therapy) (Oken et al., 1982). Pain and fatigue were also examined. Patients treated with Desmovit® had stable GPS scores throughout the 10 weeks-study with ECOG scores that slightly increased at week 10. Moreover, both pain and fatigue significantly improved at a later stage of the therapy (weeks 8–10). The study could not conclude that the potential beneficial events are exclusively imputable to DA because concomitant administration of *L. calcareum* and/or standard chemotherapy could have played a role. Even if nonexhaustive and preliminary, this clinical trial shed new light on the therapeutic potential of this plant. Undoubtedly, more comprehensive studies and clinical evidence are necessary to expand the use of DA in other human diseases.

6 | TOXICITY

The first in vivo example of acute toxicity was observed after intraperitoneal administration of DA extract in mice (N'Gouemo et al., 1996). Only 25% of mice receiving 300 mg/kg of plant extract showed abdominal contractions, while a dose of 1000 mg/kg was associated with more severe neurological symptoms, such as reduced spontaneous motor activity and exploratory behavior. In 2015, François et al. (2015) evaluated the safety and the protective effect of a hydro-alcoholic extract of DA on the human liver (HepG2) and pig kidney (LLC-PK1) cells (Francois et al., 2015). The authors performed cell viability assays using different concentrations of plant extract (1, 10, or 100 mg/mL). The results showed that treatment of LLC PK1 and HepG2 cells with 100 mg/mL of DA for 24 h reduced cell proliferation by ~35% and ~50%, respectively, compared with control (dimethyl sulfoxide). No toxicity was observed at dosages of 1 and 10 mg/mL. In a topical work, Quaye et al. investigated the effect of DA leaf extract on liver and kidney function in rats (Quaye et al., 2017). The authors recorded the animal mortality after oral administration of various doses of plant extract or 5 mL of standard saline solution as control (acute toxicity study). The mean doses that induced 50% lethality (LD_{50}) were calculated and used for subchronic toxicity studies. The results showed that doses higher than 1122 mg/kg (LD_{50}) caused severe signs such as piloerection of both the fur and the whiskers, shiny eyes, agitation, and diarrhea. On autopsy treated rats had wrinkled lungs, darker-colored liver, and dark spots in kidneys. Biomarkers of liver damage (ALT and AST enzymes) and direct bilirubin concentration were also increased after administration of DA, while other biomarkers (serum creatinine concentration, γ-glutamyltransferase, protein concentration, total bilirubin, and blood urea nitrogen) were not altered. Thus, the authors suggested that low dosages of DA (1–100 mg/kg) could be safely used in animal models, similar to another study in which treatment with 300 mg/kg did not cause significant side effects (Amoateng et al., 2017). Furthermore, even if *D. gangeticum* was used and not DA, administration of DG-based silver nanoparticles in rats altered renal architecture, even though behavioral or physiological changes were absent (Vasanth & Kurian, 2017). Moreover, treatment with DG-based nanoparticles also caused cytotoxicity (cell death augmentation) and mitotoxicity (oxidative stress increase) in LLC PK1 cells as above reported (Vasanth & Kurian, 2017). We can assume that the same effects could be seen with DA, but certainly only in vitro and in vivo data can answer such a hypothesis.

7 | FUTURE PERSPECTIVE AND CONCLUSIONS

In developing countries, plants have been always part of an ethnopharmacological use, given the economic straits of people living in such countries. Recently, it has been observed an increasing trend in consuming plant-derived compounds (supplements, foods, homemade preparations), especially in Western countries. Leaving aside the reasons why humans are paying more interest toward plants, it is undeniable that in the past decade the use of plant extracts or plant-derived compounds has grown exponentially. On the one hand, this fact is certainly positive because it turns attention towards a world away from the spotlight; on the other hand, it favors the use of plants or their derived compounds for which a scientific rational study is not always available. For DA, different studies have been conducted providing evidence of its medical use, essentially derived and based on ethnobotanical use in Africa and India. Rational evidence originates from different preclinical in vitro and in vivo research on DA (Ma et al., 2011; Rastogi et al., 2011) and one clinical trial (Imperatori et al., 2018). These proofs, although of a certain value, cannot clearly and definitely justify the use of DA in humans, lacking a large, randomized, placebo-controlled study. Thus, a well-prepared clinical trial is urgently needed to assess the effectiveness and safety of DA.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

ORCID

Javad Sharifi-Rad https://orcid.org/0000-0002-7301-8151

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