Indian Journal of Biochemistry & Biophysics
Vol. 59, June 2022, pp. 611-618

A Review

Phytochemistry and Pharmacology of *Calotropis gigantea* — An update

Meenakshi Sharma[1], Anil Kumar Delta[1] & Prashant Kaushik[2]*

[1]Department of Chemistry, Ranchi University, Ranchi-834 001, Jharkhand, India

[2]Instituto de Conservación y Mejora de la Agrodiversidad Valenciana, Universitat Politècnica de València, Valencia-46022, Spain

Received 05 November 2021; *revised 20 December 2021*

Calotropis gigantea is a perennial herb known for its applications in traditional medicine. It has been efficiently used in Ayurveda, Unani, and Siddha medicinal systems for years. All the plant parts have been used as medicine owing to its analgesic, anthelmintic, astringent, anti-inflammatory, wound healing, sedative, anti-asthmatic, antimicrobial, antioxidant, procoagulant, hepatoprotective, hypoglycemic, and pregnancy interceptive properties. For instance, the leaves, latex, flowers, stem bark, root of the plant are used as expectorant, depilatory, in leprosy scabies of the scalp, eruptions on the body, piles, asthma, liver and spleen enlargement, and painful joint swellings. Moreover, the plant is beneficial for the treatment of various diseases including tumors, ulcers, and piles thereby providing great opportunity to be used in pharmaceutical industry for modern drug synthesis. Phytochemical constituents of the plant responsible for its pharmacological activities include alkaloids, triterpenoids, flavonoids, saponins, steroids, alcohol, fatty acids, esters of calotropeols, glycosides and proteases. Besides, there is a strong correlation between the chemical structures and therapeutic activity of *C. gigantea*. Therefore, present review tries to give a brief description of its phytochemical composition, ethnobotanical characteristics, and pharmacological activity.

Keywords: *Calotropis*, Ethnobotanical, Geographical, Phytochemical, Pharmacology

Introduction

Medicinal plants represent the traditional source of medicines for prevention and control of diseases, particularly in underdeveloped countries where the modern treatments and therapies are not accessible[1,2]. The plants capable of naturally synthesizing and accumulating secondary metabolites, like glycosides, alkaloids, tannins, steroids, and rich in vitamins and minerals are used for their medicinal properties. Every part of the medicinal plant shows distinct characteristics which are employed for different purposes[3]. Based on the integrative drug development approach, a large variety of medicinal plants have successfully been analyzed. *Calotropis gigantea*, also called giant milk weed, is one such plant belonging to the *Asclepiadaceae* family[4,5]. It is a native plant of continental Asia and south-east Asia found in Bangladesh, India, China, Indonesia, Philippines, Malaysia, Myanmar, Pakistan, Thailand, and Sri Lanka[6,7]. The major significance of *C. gigantea* lies in its properties of simple cultivation methods, drought resistance and salt tolerance to a considerable extent[8,9]. Although a common weed found in wasteland, *C. gigantean* has numerous applications in traditional system of medicine. Moreover, it has scientifically been recognized for its exceptional therapeutic properties[10]. For instance, analgesic, antimicrobial and cytotoxic properties of flowers[11]; anti-diarrheal and antioxidant properties of leaves[12]; antipyretic, cytotoxic, insecticidal, and wound healing properties of roots[13]; purgative and procoagulant properties of the latex[14]; and hepatoprotective effects of stems[4]. In fact, all of the plant parts are considered significant owing to their medicinal properties and are used for the treatment of ailments like epilepsy, fever, gout, hysteria, inflammation, leprosy, muscular spasm, snakebites, warts, and cancer[15]. Owing to its exceptional healing properties, various indigenous tribes in India use the different plant parts as traditional medicine, for example, they treat skin infections using the latex[16]. Also, the bark is used as diaphoretic and expectorant[17]; fruit pulp as abortive[18]; and fresh leaves for treatment of convulsions and fits in children[19]. Like other medicinal plants, the presence of bioactive compounds such as, alkaloids, flavonoids, and terpenoids in *C. gigantea* is responsible for its medicinal properties. For instance, Madhavan *et al*., evaluated α-Amylase inhibition and antioxidant activity of Nepalese originated *C. gigantea* (L.) along

*Correspondence:
E-mail:prakau@doctor.upv.es

with its phytochemical analysis[20]. α-Amylase inhibition is known for treatment of health disorders related to carbohydrate uptake, including diabetes, dental caries, periodontal diseases, and obesity[21].

Furthermore, the development of functional foods involves enhancement of bioactive components of plants to provide vital nutrition along with medicinal effects against chronic illnesses[22,23]. As another example, oxidative stress is considered a significant factor leading to various life-threatening diseases, from cardiovascular diseases to cancer[24]. The antioxidant activities of medicinal plants can be helpful in this regard to develop substitute drugs or to preserve food quality[25–27]. Since, *C. gigantea* is known to possess numerous protective and healing properties, it offers a number of opportunities to be used for treatment of serious illnesses. It has also been analyzed for antiproliferative activities on cancer cells[28–30]. However, the main challenges encountered in developing herbal medicine are the stability and efficiency of herbal products. Accordingly, it becomes necessary to carefully evaluate the biochemical composition of the medicinal plant including phytochemicals and explore its potential therapeutic effects. Therefore, the main focus of the review is to present the utilities of *C. gigantea* for developing effective therapeutic compounds based on its biochemical composition and future aspects for advanced scientific research. The literature was reviewed systematically on the basis of PRISMA (Preferred Reporting Items for Systematic Meta-Analysis) approach[31]. For this review, articles published from 2010-2021 were analyzed with the help of scientific search engines, particularly, Google scholar using the keywords: Calotropis; ethnobotanical features; geographical distribution; phytochemical constituents; pharmacology and all the relevant studies published in peer-reviewed journals were considered.In total, 110 documents were evaluated, out of which 60 papers were found relevant for the manuscript (Fig. 1). Finally, the research papers published in journals which have an impact factor were selected and their observations are reported in this review.

Ethnobotanical description

C. gigantea is an erect and branched shrub generally 1-5 M in height[32]. The plant possesses oval-shaped light green leaves, and clusters of waxy white or lavender colored flowers. Leaves are generally concentrated around the emerging tips[33]. Further, it has cylindrical roots about 90 cm long and 2-10 cm in diameter which are tortuous and often branched[32]. The root in its transverse section shows the occurrence of cork in the outermost layer, systematically arranged with 15-20 rectangular cell layers with no intercellular spaces. The cells present in the cortex region contain ample of starch grains. These cells are consisted of parenchymatic cells and laticiferous tubes[34]. Root bark is generally short and curved with quilled pieces, 2-5 mm in thickness and 3-5 cm in breadth, distinctly sticky and bitter in taste.

Leaves of the plant are decussated, sub-sessile, and exstipulate[7,13]. The blades are elliptical or oblong and have a short pointed to blunt apex with an almost clasping heart-shaped base. They are about 3-8 inches in length and 2-5 inches in width[33]. The transverse section of leaves through midrib shows a single-layered epidermis covered with thick striped cuticle externally, and some epidermal cells on both the surfaces of leaves elongated to form a series of 2-3 celled trichomes. Flowers are actinomorphic, bisexual, bracteate, hypogynous, pentamerous, and pedunculate; calyx contains five sepals and a lobe, shortly joined at the base; corolla composed of united petals[6]. Each flower of the plant contains five pointed petals with a small "crown" holding the stamens arising from its center. The latex contains cardiac glycosides, calcium oxalate and volatile fatty acids[33]. Furthermore, fruits are fleshy, inflated, and sub-globose to implicitly ovoid in shape. They contain green spongy follicles, ovoid in shape up to 15cm long and 10cm wide and release plumed and papery light brown seeds[10]. Seeds are flattened or compressed with silky white pappus, about 6×5 mm dimensions.

Phytochemical composition

Earlier investigations on *C. gigantea* have reported the presence of wide range of phytochemicals in different plant parts[35–37]. Alkaloids, triterpenoids, flavonoids, saponins, steroids, alcohol, fatty acids,

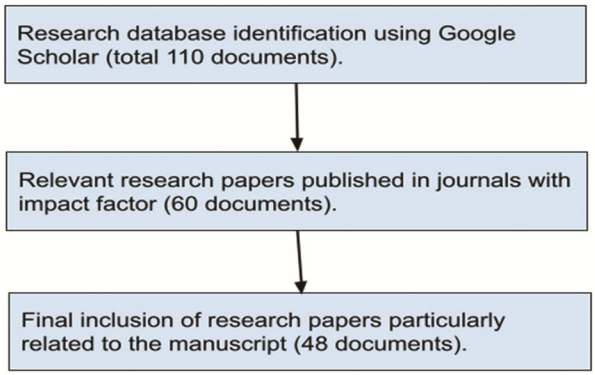

Fig.— 1 The methodological framework of research analysis

esters of calotropeols, glycosides and proteases have been extracted from various plant parts. The leaves and latex of *C. gigantean* contain cardiac glycosides, various among which have been isolated and studied[38]. The Calotropis laticifer fluid is known to have significant proteolytic activity catalyzed by aspartic proteinase and cysteine proteinase enzymes.

The latex is abundant in calotropin, calotoxin, lupeol, and the latex protein uscharidin[6]. The leaves of the plant primarily contain glycosides, alkaloids, and the active constituent mudarine. Further, the flowers possess α- and β-calotropeol, amyrin, mudarine, cardenolide glycoside asclepin, akundarin, and calotropin[38]. Table 1 the roots are also found to contain a number of cardiac glycosides which include calotropogenin, calactin, calotoxin, calotropin, coroglaucigenn, uscharin, frugoside, and 4β-D-glucofrugoside in addition tooxypregnane-oligoglycosides[39]. Root bark of the plant possesses β- amyrin, giganteol, isogiganteol, and cardenolides. Besides, giganticine (a non-protein amino acid) has also been isolated from a methanolic root bark extract of *C. gigantea*[38,40]. The seed oil contains palmitic acid, oleic acid, linoleic acid, and linolenic acid, and the unsaponifiable part contains stigmasterol, phytosterol, and melissyl alcohol[32,41].

Structure-Activity Relationship (SAR) of the chemical compounds

Various studies have demonstrated the dependence of pharmacological activities of *C. gigantea* on the structural characteristics of chemical compounds isolated. In a study conducted by Parhira *et al*., uscharin and its stereoisomer 2′-epi-uscharin were isolated from latex of *C. gigantea*. Both the cardenolides showed inhibitory effects on HIF-1transcriptional activity, however with different magnitudes. Uscharin displayed much more inhibitory effects than digoxin (a positive control) at 100 nM concentration, while 2′-epi-uscharin showed comparable effects with digoxin at 200 nM concentration. The bio-active discrepancy observed between the two compounds indicated that β-configuration of 2′-hydroxy group is required for HIF-1 transcriptional activity inhibition. The results suggested uscharin and 2′-epi-uscharin to be potential HIF-1 inhibitors which may display their anti-cancer mechanism and provide a rational design for effective anticancer drug development[42].

Table 1 — Biochemical composition of different plant parts of *C. gigantea*

Plant part	Chemical constituents
Root	Cardiacglycosides, calotroposides A-G (oxypregnane-oligoglycosides), calotropnaphthalene, calotropisesquiterpenol, calotropisesterterpenol, calotropbenzofuranone[32]
Root Bark	β-amyrin, giganteol, isogiganteol, and cardenolides.[40]
Flower	α- and β-calotropeol, amyrin, glycosides, mudarine, asclepin, akundarin[38]
Leaves	Sapogenins, calotropin, uscharin, calotoxin,alkaloids, and mudarine[38]
Latex	Calotoxin, calactin, calotropin,uscharin, α- and β-calotropeol, β-amyrin and calcium oxalate[6]
Seed	Palmitic acid, oleic acid, linoleic acid and linolenic acid,stigmasterol, phytosterol, melissyl alcohol[41]
Stem Bark	α- and β- calotropeol, β- amyrin, and giganteol[14]

Parhira*et al*., in another study isolated (+)-pinoresinol 4-O-[6″-O-vanilloyl]-β-D-glucopyranoside, 6′-O-vanilloyltachioside and 6′-O-vanilloylisotachioside from the latex of *C. gigantea*. These three compounds and (+)-pinoresinol 4-O-β-D-glucopyranoside were examined for anti-influenza activity using CPE assay. The study revealed that (+)-pinoresinol 4-O-[6″-O-vanilloyl]-β-D-glucopyranoside exhibited significant anti-influenza activitywhile the other three isolates showed no such activity against influenza virus strain A/PR/8/34 (H1N1). The discrepancyin anti-influenza activities of these compounds revealed the vanilloyl moiety in (+)-pinoresinol 4-O-[6″-O-vanilloyl]-β-D-glucopyranoside responsible for its anti-influenza virus activity[43].

You *et al*. evaluated the cardenolides isolated from root bark of *C. gigantea* for their anti-proliferative effects on human A549 and Hela cell lines (with bufalin as positive control). The active cardenolides displayed higher cytotoxicity against A549 cell lines than Hela cell lines. The study revealed that 19-dihydrocalactin, calactin, and calotropin indicated significantly higher inhibitory activity against A549 and Hela cell lines. The bioassayresults on A549 and Hela cell lines implied that both of the C-10 formyl and hydroxymethyl groups helped enhance cytotoxicity of these compounds. Also, the 4′β-OH or 16α-OH group reduced the cytotoxicity to different extents. Further it was observed that the double linked six-membered sugar units were essential lor enhanced antiproliferative effects[44].

Geographical distribution

C. gigantea is native to India, Malaysia, China and distributed almost all around the world[45]. In general, it is found in tropical and sub-tropical areas of the

world. In India, it is found mainly in Himalayas, Punjab, Assam, Bengal, and Madras. *C. gigantea* can grow up to 900 m and generally prefers the rough sandy soils receiving annual rainfall of about 300-400 mM[46]. It is frequently dominant in parts of uncontrolled cultivation and therefore, assumed an indicator of abandoned cultivation. Some of the major features of *C. gigantea* include cultivation in different conditions of environment, no requirement of cultivation practices, and drought tolerance[6]. These features make it the forerunner vegetation in desert soils and xerophytic adaptations due to occurrence of latex, expansively branched root structure, and wax-coated thick leaves. It prospers on poor soils especially where there is no competition from native grass due to over-grazing.

Pharmacological properties

Antimicrobial effects

The aqueous, methanolic, and ethanolic leaf extracts of *C. gigantea*are reported to have anti-Candida property against clinical isolates of *Candida albicans*, *C. krusei*, *C. parapsilosis*, and *C. tropicalis*[5]. Further, the aqueous leaf extracts are known to possess anti-bacterial property against *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsella pneumonia, Pseudomonas aeruginosa*, and *Micrococcus luteus*[18]. Besides, *C. gigantean* shows anti-fungal activity against several plant-pathogenic fungi like *Fusarium mangiferae*. The ethanolic leaf extracts of *C. gigantea* showed anti-fungal activity against *Aspergillus niger* with minimum inhibitory concentration (MIC) of 7.5 mg/mL. The inhibitory action of the plant extracts against bacteria and fungi, the causative agents of numerous diseases such as dermal infections, diarrhoea and respiratory tract infections suggests *C. gigantea* as a capable antimicrobial agent[47].

Cytotoxic effects

Cardenolide glycosides extracted from the roots of *C. gigantea* carry significant cytotoxic activity against numerous human cell lines. Calotropin, frugoside and 4'–O-β-D-glucopyransylfrugoside are the major active constituents[5]. Ethanolic root extracts of *C. gigantean* show inhibitory effects to chronic myelogenous leukemia (K562 cell line) and human gastric cancer (SGC-7901 cell line)[48]. Moreover, treatment with anhydrosophoradiol-3-acetate (A3A) obtained from the flower extract of *C. gigantean* reduced the tumor cells, changed the hematological and biochemical parameters consequently increasing the life-span of Ehrlich's ascites carcinoma affected mice[10].The ethanolic leaf extracts, dichloromethane and ethyl acetate fractions of *C. gigantea* significantly decreased the cell viability of WiDr cells (human colon cancer) in a concentration-dependent manner[49]. The silver nanoparticles biosynthesized from aqueous latex extract when tested for their potent cytotoxicity against HeLa cancer cell lines, induced cytotoxicity in a dose-dependent manner. Moreover, significant cytotoxicity was observed in biosynthesized silver nanoparticles than the crude aqueous latex extract with respective LC_{50} values of 91.3 µg and 311 µg[50].

Insecticidal and ovicidal activity

The methanolic root bark extracts of *C. gigantean* showed significant insecticidal activity against *Tribolium castaneum* when evaluated against its larvae and adult[12,51]. Prabhu *et al*. evaluated different plant parts including leaves, flower, stem, and roots at different concentrations for ovicidal activity against *Helicoverpa armigera*[52]. It was observed that leaf extract produced 100% inhibition of hatching ability of egg while flower extract produced 90% inhibition. Further, it was found that inhibition in egg hatchability increases with the dosage and the early stages of eggs (24-48 h) were highly susceptible at all the tested concentrations. These results indicated the insecticidal and ovicidal properties of *C. gigantea* plant which could be potentially used for control and management of insects like *T. castaneum and H. armigera*. Further, the aqueous leaf extracts of *C. gigantean* when analyzed for their larvicidal, mosquito repellent and ovicidal activity against *Culex gelidus* and *Culex tritaeniorhynchus* mosquitoes, displayed dose-dependent larvicidal activity with LC_{50} value of 137.90 against *C. gelidus* and 110.05 against *C. tritaeniorhynchus*[53].

Antioxidant effects

The antioxidant activity of leaf extracts of *C. gigantean* has been shown through the DPPH radical scavenging activity, nitric oxide scavenging activity, and reducing power activity of hydroalcoholic leaf extract of *C. gigantea*[4]. The extract revealed maximum DPPH radical scavenging activity of 85% at 400 µg/mL concentration, nitric oxide scavenging activity of 54% at 100 µg/mL concentration, and reducing power increased with the concentration of the extract. Further, the *in vitro* antioxidant activity of root extracts of *C. gigantea* were investigated by DPPH and fluorescence recovery after photo-bleaching method[54]. Both the

methods demonstrated high antioxidant activity of extract as compared to the standard ascorbic acid possibly due to presence of high phytochemical content. Besides, the investigation of antioxidant potential of leaf and flower extracts of *C. gigantean* revealed that the acetone and chloroform extracts displayed free radical scavenging activity of only 30% and 37% respectively, while the methanolic extract displayed significant free radical scavenging activity of 64%[55].

Procoagulant effects

The latex of *C. gigantean* is known to exhibit significant procoagulant activity. The crude extract of latex contains highly basic proteins which exhibit strong proteolytic activity[38].The latex hydrolyzed casein, human fibrinogen along with crude fibrin clot depending upon dosage[14]. Proteins found in the *C. gigantea* latex due to their proteolytic nature are responsible for the procoagulant activity. The extract hydrolyses the fibrinogen subunits, alpha subunit gets hydrolyzed first then beta and gamma subunits[12].The gamma subunit being highly resistant gets hydrolyzed at either higher protein concentrations or takes longer incubation time[38]. The crude extract hydrolyses the crude fibrin clot relatively more strongly as compared to papain and trypsin. Further, the crude extract is found to be hemorrhagic which induces skin hemorrhage at about >75 microns and promotes blood coagulation[38].

Hepatoprotective effects

The ethanolic stem extracts of *C. gigantean* displayed hepatoprotective properties against liver damage induced by carbon tetrachloride in male Wistar rats. The protective effects of the extract were compared with standard drug, silymarin. Biochemical parameters such as alanine amino transferase (ALT), aspartate amino transferase (AST), glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), lipid peroxide (LPO), and glutathione peroxidase (GPx) were evaluated. It was observed that the extract was quite effective in liver protection and reported significant decrease in AST, ALT and lipid peroxide levels[56]. Besides, the methanolic and chloroform leaf extracts have also reported hepatoprotective activity against acetaminophen induced hepatic damage in experimental animals[57]. The liver damage can also be adjudged by evaluating the serum parameters (like SGOT, SGPT, ALP and BLN). The serum level of enzymes increases due to cellular leakage and anti-hepatotoxic agents tend to decrease the increased serum level of these enzymes. The serum parameters were significantly reduced in the animals which were treated with alcoholic flower extracts of *C. gigantean* as compared to the toxicant, showing its hepatoprotective activity. Further, the flower extracts were found to be more efficient than the standard drug, silymarin[58].

Pregnancy interceptive effects

The root extracts of *C. gigantean* in different organic solvents were evaluated for their pregnancy-interceptive effects in rats. The extract showed 100% pregnancy-interceptive activity at 100 mg/kg dose. Also, the extract exhibited 100% efficacy when administered in the days 1-5 and 1-7 postcoitum schedules at 12.5 mg/kg of dose[38].

Anti-asthmatic effects

Furthermore, *C. gigantea* showed remarkable activity against ova albumin (OVA)-induced asthma in rats. The activity on different body cells, various enzymes, and histopathological changes was observed. *C. gigantean* reported significant reduction in neutrophils, eosinophils, lymphocytes, and total leukocytes in bronchoalveolar lavage fluid at 200 and 400 mg/kg[59]. These observations suggested the potential of plant to be used as a therapeutic drug for treatment of asthma due to its anti-inflammatory, antioxidant, and anti-lipoxygenase activities. The aqueous flower extracts of *C. gigantean* significantly affected the cough induced by ammonia and sulfurdioxide in mice at doses of 250 mg and 500 mg per kg of body weight for anti-tussive effect when compared with the control. The aqueous extracts also affected cough induced by citric acid in guinea pigs (250 mg/kg and 500 mg/kg body weight), exhibited considerable anti-tussive effect. Further, the anti-asthmatic effects in guinea pigs, as compared with the control, were also significant in aqueous extract at doses of 250 mg/kg and 500 mg/kg[60].

Hypoglycemic effects

The leaf and flower extracts of *C. gigantean* in chloroform were evaluated for hypoglycemic activity in streptozotocin induced diabetes in rats, glibenclamide was used as standard drug. The leaf and flower extract were found to be effective in reducing serum glucose level or blood sugar level in normal rats[61]. In addition, oral glucose tolerance was also improved after treatment with the test drug. Besides, the chloroform and ethyl acetate extracts of *C. gigantea* white flowers produced significant hypoglycemic

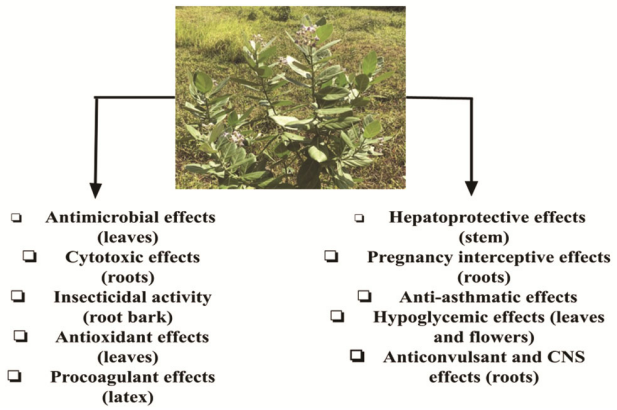

Fig. 2 — Pharmacological properties of different parts of *C. gigantea* plant

activity in alloxan-induced diabetes in rats and had beneficial effects on blood sugar levels[62]. The *C. gigantean* leaf extracts presented hypoglycemic effects in normal as well as alloxan induced diabetic rats after both oral as well as intra-peritoneal administration which were comparable to that of metformin and glibenclamide taken at 11.3 mg/kg and 0.13 mg/kg concentrations, respectively. Regarding the mechanism of its action, it could be speculated that the hypoglycemic activity has resulted from the enhanced peripheral glucose metabolism. Also increased release of insulin cannot be excluded[63].

Anticonvulsant and central nervous system (CNS) effects

The alcoholic root extracts of *C. gigantea* were evaluated for CNS activity orally in albino rats. It revealed prominent analgesic activity in Eddy's hot plate method and acetic acid-induced writhings[18]. Further, significant anticonvulsant activity was observed due to delayed onset of pentylenetetrazole-induced convulsions and decreased severity[12,14]. A decrease in locomotor activity along with decrease in fall-off time (motor coordination) was also observed. Moreover, a potentiation in pentobarbitone induced sleep owing to sedative effect of the extracts was reported[38]. Further, the anticonvulsant and sedative activity of the ethanolic extracts of *C. gigantea* were evaluated with strychnine and electroshock induced convulsions (Fig. 2). The animals treated with extract showed significant anti-convulsant activity against highest electroshock induced convulsions, but produced no marked effect against strychnine convulsion model. Also, the extracts showed significant muscle relaxant activity and decreased motor coordination[64]. These results indicated the analgesic, anticonvulsant, and sedative effects of the *C. gigantea* extracts.

Conclusion

The plant *C. gigantea* growing in almost all types of soil and environment conditions and demanding no cultivation practices, comes with many curative properties and economic values. Pharmacological screening of *C. gigantea* through various studies have indicated its therapeutic potential and rendered it an important medicinal plant. The medicinal potential of *C. gigantean* may be exploited for controlling various diseases owing to its antimicrobial, cytotoxic, antioxidant, anticonvulsant, antiasthma, hypoglycemic, hepatoprotective, and procoagulant activities. Accordingly, different plant parts *viz*. roots, root bark, flower, leaves, seeds, and stem are used as remedy for various human ailments. However, it is required that its medicinal values be scrutinized at molecular level using biotechnological tools and techniques. Advanced research needs to be conducted for elucidation of interactive mechanism of the drugs derived from this plant with humans at molecular level.

Ethnomedicinal studies, in recent years, have received considerable attention for the development of new drugs from natural sources especially plants owing to their medicinal properties. Since *C. gigantean* is known to possess great potential to cure various human ailments, it can be used effectively as a remedy in the form of drugs. Pharmaceutical property of this plant lies in the secondary metabolites which act as prototypes for the synthesis of new drugs. Further, the therapeutic activity of different bioactive compounds isolated from this plant greatly depends upon their structural features. The variations in therapeutic activities owing to different configurations may provide the rational design for drug synthesis. Therefore, the present review attempts to describe the morphological characteristics, therapeutic value, and the pharmacological importance of *C. gigantea* along with its phytochemical composition in order to explore its applications in pharmaceutical industry.

Conflict of interest

All authors declare no conflict of interest.

References

1 Sarkar S, Pal A, Chouni A & Paul S, A novel compound β-sitosterol-3-O-β-D-glucoside isolated from *Azadirachta indica* effectively induces apoptosis in leukemic cells by targeting G0/G1 populations. *Indian J Biochem Biophys*, 57 (2020) 22.

2 Uttam D, Tanmay S, Rita G & Das SK, *Trianthema portulacastrum* L.: Traditional medicine in healthcare and biology. *Indian J Biochem Biophys*, 57 (2020) 127.

3 Sharma A, Sah VK, Yadav V & Kaushik P, Effect of poplar and eucalyptus based agroforestry system on soil biochemistry. *Indian J Biochem Biophys*, 59 (2022) 126.

4 Biswasroy P, Panda S, Das D, Kar DM & Ghosh G, Pharmacological investigation of *Calotropis gigantea*: A benevolent herb of Nature. *Res J Pharm Technol*, 13 (2020) 461.

5 Kumar G, Karthik L & Rao KVB, A review on pharmacological and phytochemical profile of *Calotropis gigantea* Linn. *Pharmacologyonline*, 1 (2011) 1.

6 Kumar PS, Suresh E & Kalavathy S, Review on a potential herb *Calotropis gigantea* (L.) R. Br. *Sch Acad J Pharm*, 2 (2013) 135.

7 Negi D & Bisht AS, A Review on Brief Study of *Calotropis gigantea* Linn. *J Drug Del Therap*, 11 (2021) 224.

8 Yadav VK, Jha RK& Kaushik P, Biochemical composition of potato biowaste of popular North Indian cultivars. *Indian J Biochem Biophys*, 58 (2021) 100.

9 Tang J, Ge L, Ma H, Liu H & Zheng Y, Anatomical structures of roots, stems and leaves of *Calotropis gigantea* in dry-hot valley. *J South Agric*, 47 (2016) 251.

10 Sarkar S, Chakraverty R & Ghosh A, *Calotropis gigantean* Linn.-a complete busket of Indian traditional medicine. *Int J Pharm Res Sci*, 2 (2014) 7.

11 Punia G, A review on varieties of arka -*Calotropis procera* (aiton) dryand and *Calotropis gigantean* (L.) dryand. *Global J Res Med Plants & Indigen Med*, 2 (2013) 392.

12 Joseph B, George J, Jeevitha MV & Charles S, Pharmacological and biological overview on *Calotropis gigantea*: A comprehensive review. *Int Res J Pharm App Sci*, 3 (2013) 219.

13 Gharge VG, Ghadge DM, Shelar PA & Yadav AV, Importance of pharmacognostic study of medicinal plants *Calotropis gigantea* (Linn.): A review. *Int J Pharmacognosy*, 4 (2017) 363.

14 Mishra P, Yadav KS & Shrivastava P, An updated Review on Phytochemistry, Pharmacological activity and Medicinal uses of *Calotropis gigantea* R. Br. *Res J Pharm Phyto*, 9 (2017) 135.

15 Julius OO, Oluwasusi VO, Ibiyemi MF & Oluwatobi FB, Antibacterial Activities and Phytochemical Screening of Crude Extracts of *Calotropis gigantea* (Giant Milk Weed). *South Asian J Res Micro*, 22 (2021) 24.

16 Seniya C, Trivedia SS & Verma SK, Antibacterial efficacy and phytochemical analysis of organic solvent extracts of *Calotropis gigantea*. *J Chem Pharm Res*, 3 (2011) 330.

17 Rahman MS, Moly NN & Hossen MJ, Antimicrobial, cytotoxic and antioxidant activity of the exudate of *calotropis gigantea*. *Int J Pharm Sci Res*, 4 (2013) 745.

18 Kadiyala M, Ponnusankar S & Elango K, *Calotropis gigantiea* (L.) R. Br (Apocynaceae): A phytochemical and pharmacological review. *J Ethno*, 150 (2013) 32.

19 Timilsina H, Modi B & Basnyat R, Phytochemical, antimicrobial and ethnobotanical study of *calotropis gigantean*. *J Health Alli Sci*, 10 (2020) 23.

20 Madhavan SA, Vinotha P & Uma V, Phytochemical screening and comparative gc–ms analysis of bioactive compounds present in methanolic leaf and latex extract *Calotropis gigantea* (L). *Asian J Med Sci*, 7 (2020) 1.

21 Sales PM, Souza PM, Simeoni LA, Magalhães PO & Silveira D, α-Amylase inhibitors: a review of raw material and isolated compounds from plant source. *J Pharm Pharm Sci*, 15 (2012) 141.

22 Yadav VK & Kaushik P, Phytochemicals against COVID-19 and a gap in clinical investigations: An outlook. *Indian J Biochem Biophys*, 58 (2021) 403.

23 Yadav VK, Singh R, Jha RK & Kaushik P, Biochemical variability of eggplant peel among Indian cultivars. *Indian J Biochem Biophys*, 57 (5) 2020 634.

24 Namasivayam SKR, Shivaramakrishnan K & Bharani RSA, Potential antioxidative protein-pigment complex Spirulina platensis mediated food grade phycocyanin C -Extraction, purification, antioxidative activity and biocompatibility. *Indian J Biochem Biophys*, 56 (2019) 230.

25 Kumar NG, Satya Deo P, Mallick S, Kumar GS & Panchanan P, Thiol stabilized copper nanoparticles exert antimicrobial properties by preventing cell division in *Escherichia coli*. *Indian J Biochem Biophys*, 57 (2020) 151.

26 Kumari V & Sangal A, Antimicrobial study of *Arjuna Terminalia* loaded PLGA nanoparticle. *Indian J Biochem Biophys*, 57 (2020) 291.

27 Semerci AB, İnceçayir D, Konca T, Tunca H & Tunç K, Phenolic constituents, antioxidant and antimicrobial activities of methanolic extracts of some female cones of gymnosperm plant. *Indian J Biochem Biophys*, 57 (2020) 298.

28 Hasballah K, Sarong M, Rusly R, Fitria H, Maida DR & Iqhrammullah M, Antiproliferative activity of triterpenoid and steroid compounds from ethyl acetate extract of *calotropis gigantea* root bark against p388 murine leukemia cell lines. *Sci Pharm*, 89 (2021) 21.

29 Priya V, Jain P, Vanathi BM, Raj PV & Kamath BV, Methanolic root extract of *Calotropis gigantea* induces apoptosis in human hepatocellular carcinoma by altering Bax/Bcl-2 expression. *Am J Pharmacol Sci*, 3 (2015) 13.

30 Tripathi PK, Awasthi S, Kanojiya S, Tripathi V & Mishra DK, Callus culture and in vitro biosynthesis of cardiac glycosides from *Calotropis gigantea* (L.) Ait. *In Vitro Cell Devel Bio-Plant*, 49 (2013) 455.

31 Moher D, Shamseer L, Clarke M, Ghersi D & Liberati A, Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Sys Rev*, 4 (2015)1.

32 Jahan N, Mushir A & Ahmed A, A review on Phytochemical and biological properties of *Calotropis gigantea* (Linn.) R. Br. *Disc Phytomed*, 3 (2016) 1.

33 Dutta M, Rej S, Jamal S, Das S & Chatterjee S, Study of phytochemical constituents and antibacterial activity of *Calotropis gigantea*. *Int Sci J*, 1 (2014) 15.

34 Srivastava S, Singh AP& Rawat AKS, Comparative botanical and phytochemical evaluation of Calotropis procera Linn. and *Calotropis gigantea* Linn. Root. *J Appl Pharm Sci*, 5 (2015) 041.

35 Patel HV, Patel JD & Patel B, Comparative efficacy of phytochemical analysis and antioxidant activity of methanolic extract of *Calotropis gigantea* and *Calotropis procera*. *Int J Life Sci Biotechnol Pharm Res*, 5 (2014) 107.

36 Radhakrishnan K, Thangamani P & Balakrishnan V, Antibacterial and phytochemical analysis of stem and root extracts of *Calotropis gigantea* against selected pathogens. *Malaya J Bio*, 1 (2014) 49.

37 Sharma PCDR, Screening for bioactive compounds in different plant parts of *Calotropis gigantea* L. *J Pharm Phyto*, 7 (2018) 1592.

38 Singh N, Gupta P, Patel AV & Pathak AK, *Calotropis gigantea*: A Review on its phytochemical & pharmacological profile. *Int J Pharm*, 1 (2014) 1.

39 El-Seedi HR, Khalifa SA, Taher EA, Farag MA & Saeed A, Cardenolides: Insights from chemical structure and pharmacological utility. *Pharm Res*, 141 (2019) 123.

40 Ali-Seyed M & Siddiqua A, *Calotropis*-A multi-potential plant to humankind: Special focus on its wound healing efficacy. *Biocat Agric Biotechnol*, (2020) 101725.

41 Tiwari DK & Upmanyu N, Phytochemical and Pharmacological activity of Wonder Shrub: *Calotropis gigantia*. *Res J Pharm Phyto*, 12 (2) 2020 106.

42 Parhira S, Zhu GY, Jiang RW, Liu L & Bai LP, 2′-Epi-uscharin from the latex of *Calotropis gigantea* with HIF-1 inhibitory activity, *SciRep*, 4 (2014) 1.

43 Parhira S, Yang Z-F, Zhu GY, Chen QL & Zhou BX, *In vitro* anti-influenza virus activities of a new lignan glycoside from the latex of *Calotropis gigantea*. *PLoS one*, 9 (2014) e104544.

44 You H, Lei M, Song W, Chen H & Meng Y, Cytotoxic cardenolides from the root bark of *Calotropis gigantea*. *Steroids*, 78 (2013) 1029.

45 Phoo ZWMM, Razon LF, Knothe G, Ilham Z & GoembiraF Evaluation of Indian milkweed (*Calotropis gigantea*) seed oil as alternative feedstock for biodiesel. *Ind Crops Prod*, 54 (2014) 226.

46 Chandrawat P & Sharma RA, The genus Calotropis: An overview on bioactive principles and their bioefficacy. *Res J Recent Sci*, 2277 (2016) 2502.

47 Pattnaik PK, Kar D, Chhatoi H, Shahbazi S, Ghosh G & Kuanar A, Chemometric profile & antimicrobial activities of leaf extract of *Calotropis procera* and *Calotropis gigantea*. *Nat Prod Res*, 31 (2017) 1954.

48 Jacinto SD, Chun EAC, Montuno AS, Shen CC & Espineli DL, Cytotoxic cardenolide and sterols from *Calotropis gigantea*. *Nat Prod Commun*, 6 (2011) 1934578X1100600614.

49 Mutiah R, Sukardiman S & Widyawaruyanti A, Cytotoxic effect of crude extract and fraction from *Calotropis gigantea* leaves on human colon cancer widr cell lines, *Int J Pharm Pharm Sci*, 9 (2017) 83.

50 Rajkuberan C, Sudha K, Sathishkumar G & Sivaramakrishnan S, Antibacterial and cytotoxic potential of silver nanoparticles synthesized using latex of *Calotropis gigantea* L. *Spectrochim Acta A Mol Biomol Spectrosc*, 136 (2015) 924.

51 Parvin S, Kader MA, Chouduri AU, Rafshanjani MAS & Haque ME, Antibacterial, antifungal and insecticidal activities of the n-hexane and ethyl-acetate fractions of methanolic extract of the leaves of *Calotropis gigantea* Linn. *J Pharm Phyto*, 2 (2014) 1.

52 Prabhu S, Priyadharshini P & Veeravel R, Effect of aqueous extracts of different plant parts of milkweed plant (*Calotropis gigantea* R. Br.) against ovicidal activity on *Helicoverpa armigera* (Hubner). *Int J Adv Life Sci*, 1 (2012) 18.

53 Kumar G, Karthik L, Rao KB, Kirthi AV & Rahuman AA, Larvicidal, repellent and ovicidal activity of *Calotropis gigantea* against *Culex gelidus* and*Culex tritaeniorhynchus* (Diptera: Culicidae). *Int J Agril Technol*, 8 (2012) 869.

54 Elakkiya P & Prasanna G, Study on phytochemical screening and *in vitro* antioxidant activity of *Calotropis gigantea* L. *Int J Pharm Tech Res*, 4 (2012) 1428.

55 Usmani S, Screening for antioxidant and free radical scavenging potential of extracts of leaves and flowers of *Calotropis gigantea*. *Asian J Pharm Clin Res*, 6 (2013) 97.

56 Verma S, Pharmacological perspectives of *Calotropis giganta* (Asclepiadaceae). *Int J Pharmacog*, 3 (2016) 405.

57 Usmani S & Kushwaha P, Hepatoprotective activity of extracts of leaves of *Calotropis gigantea. Asian J Pharm Clin Res*. 3 (2010) 195.

58 Argal A & Dwivedi A, Evaluation of hepatoprotective activity of *Calotropis gigantea* R. Br. flowers. *Ethnobot Leaf*, 4 (2010) 6.

59 Bulani V, Biyani K, Kale R, Joshi U & Charhate K, Inhibitory effect of *Calotropis gigantea* extract on ovalbumin-induced airway inflammation and Arachidonic acid induced inflammation in a murine model of asthma. *Int J Cur Bio Med Sci*, 1 (2011) 19.

60 Jaliwala YA, Neha C, Bhatt NK, Panda PK & Mohanti PK, Pharmacological evaluation of anti-tussive, anti-asthmatic and expectorant activities of *Calotropis gigantea* R. Br. in experimental animals. *J Pharm Res*, 4 (2011) 3383.

61 Rathod NR, Chitme HR, Irchhaiya R & Chandra R, Hypoglycemic effect of *Calotropis gigantea* Linn. leaves and flowers in streptozotocin-induced diabetic rats. *Oman Med J*, 26 (2011) 104.

62 Manivannan R & Shopna R, Antidiabetic activity of *Calotropis gigantea* white flower extracts in alloxan induced diabetic rats. *J Drug Deli Therapeutics*, 7 (2017) 106.

63 Teotia D, Chakrabar SP & Ajay SS, Impact of *Calotropis gigantean* leaves via different routes of administration in normal and alloxan induced diabetic rats. *Int J Sci Res*, 3 (5) 2013.

64 Bairagi SM, Ghule P & Gilhotra R, Pharmacology of Natural Products: An recent approach on *Calotropis gigantea* and *Calotropis procera*. *Ars Pharmaceutica*, 59 (2018) 37.