Calotropis gigantea (L.) Dryand – A review update

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ABSTRACT

Calotropis gigantea (L.) Dryand (Giant milk weed; family Asclepiadaceae) has been traditionally used in the treatment of bronchitis, asthma, leprosy, eczema and elephantiasis. This review emphasizes on ethnopharmacology, chemical constituents and pharmacology of *C. gigantea*. The available information on *C. gigantea* was collected through electronic search of major scientific databases. A survey of literature revealed that cardenolides, flavonoids, terpenoids, glycosides, steroids and nonprotein amino acid constitute major groups of chemical constituents in *C. gigantea*. The plant has been evaluated for varied pharmacological activities, and reported to exhibit analgesic, antimicrobial, antioxidant, anti-pyretic, anti-inflammatory, insecticidal, cytotoxic, hepatoprotective, pregnancy interceptive, procoagulant and wound healing activities. Further, thorough scrutiny of literature revealed a startling fact that clinical reports are not available on the plant. The pharmacological work carried out on the plant for validation of its traditional claims is not convincing as crude extracts used in experimental studies have not been characterized. It is concluded that *C. gigantea* is a medicinally promising plant, which needs to be exploited systematically. The plant could provide therapeutically active constituents, which may be developed as clinically potential drugs.

Keywords: Asclepiadaceae, *Calotropis gigantea*, Cardenolides, Flavonoids, Milkweed.

INTRODUCTION

Medicinal plants are major source of the traditional medicine in India. India is considered as "Botanical Garden of World". A large segment of Indian population use medicinal plants for their health security. India has 15 agroclimatic zones and 17000-18000 species of flowering plants of which 6000-7000 are estimated to have medicinal usage in traditional systems of medicines (Anonymous, 2015). The Medicinal and Aromatic Plants contain a large number of chemical constituents which are the major source of therapeutic agents to cure human discomfort. The World Health Organization has also recognized the role of traditional systems of medicine, which depend largely upon the medicinal plants. The use of Medicinal and Aromatic Plants throughout the world has been increasing by the rate of 7-15 % annually. *Calotropis gigantea* (L.) Dryand is one of such plants, which has long tradition of use in various systems of medicine. Thus, a review has been compiled on ethnopharmacological uses, chemical constituents and pharmacology of *C. gigantea*.

The review has been divided into three major sections such as ethnopharmacology, chemical constituents and pharmacological reports. Under the section ethnopharmacology, the traditional uses of *C. gigantea* have been described. The available information on traditional uses of *C. gigantea* in folk systems of medicine has been collected from old medical texts, books and original articles where medicinal uses of the plant are documented. Various classes of chemical constituents (with structures) isolated from *C. gigantea* have been mentioned in chemical constituents section. Section pharmacological reports describe scientifically reported work on *C. gigantea* for different pharmacological activities. The phytochemical and pharmacological reports on *C. gigantea* were collected from various major databases like Google Scholar, Science Direct, PubMed, SciFinder, AGRICOLA, MEDLINE, Directory of Open Access Journal (DOAJ), Scientific Commons, Open J-Gate, Medicinal and Aromatic Plants Abstract (MAPA), The Wealth of India, Glossary of Indian Medicinal Plants, Flora of Different states, World Cats, US Dispensatory, King American Dispensatory, various traditional books and chemical abstracts, searched in the month of March, 2015.

Kadiyala et al. (2013) have compiled reports of phytochemical and pharmacological studies on *C. gigantea*. But thorough scrutiny of available literature reveals that afore-mentioned review on *C. gigantea* need to be updated by incorporating ethnopharmacological, phytochemical and pharmacological reports which have not been covered. The references covered by Kadiyala et al. (2013) have not been included in this article. The present review article contained 109 references.

The present work has been undertaken with following objectives:

- To evaluate whether traditional claims of *C. gigantea* have been validated scientifically by pre-clinical and clinical studies.

- To evaluate whether rational methods have been adopted to isolate bioactive chemical constituents from *C. gigantea* following bioactivity-directed-fractionation.
- To evaluate whether mode of actions of bioactive extract or fraction of *C. gigantea* have been established.
- To evaluate whether any structure activity relationship studies have been carried out on chemical constituents isolated from *C. gigantea*.

***Calotropis gigantea* L. [Synonym Giant milkweed; Family Asclepiadaceae]:** The plant is commonly known as Milkweed, Akand, Bowstring Hemp, Akado, Ark, Arka, Erukku, Lal akra, Akondo, Moto-aak, Verukku and Jilledu belonging to family Asclepiadaceae (Gupta and Sharma, 2007). The plant is distributed throughout India, mostly in Andaman Island upto 900 m altitude in hills. The plant is also abundant in Cambodia, Indonesia, Malaysia, Philippines, Thailand, Sri Lanka, India and China. The plant is a large shrub or small tree, about 4 m in height. The stems are erect and milky. The leaves are broadly elliptical to oblong-obovate in shape but subsessile. Sepal lobes are broadly egg-shaped. The sepal and petal clusters in flowers that are either white or lavender in color. The flower consists of five pointed petals and a small crown which holds the stamens. The fruit is a follicle and when dry, seed dispersed in air by wind. It grows especially in the region of sandy soil and dry uncultivated land. The root, root-bark, leaves and flowers are basically used in traditional system of medicine (Agharkar, 1991; Gupta and Ali, 2000).

Ethnopharmacology: The plant is traditionally used in Indian systems of medicine for the treatment of various ailments which are discussed in table 1.

Chemical constituents: *C. gigantea* consists of a wide range of constituents such as cardenolides, oxypregnane –oligoglycosides, triterpenoids, terpenes, terpenes esters, flavonoids, sterols, proteinases, cardiac glycosides, aromatic product, carbohydrate, resin, fatty acids and nonprotein amino acids etc. Kadiyala et al. (2013) have reported the presence of phytoconstituents such as 19-nor-10-hydrocalactinic acid methyl ester, uzarigenin, calactinic acid methyl ester, 19-carboxyl- calactinic acid methyl ester, 18,20-epoxycalotropin, calactin, calotropin, 15*β*-hydroxycalotro- pin, 2*α*,15*β*-dihydroxy-19-oxo-uzarigenin, 19-nor-2*α*,10,15*β*-trihydroxyuzarigenin, 19-nor-10-hydroperoxy-2*α*, 15*β*-dihydroxyuzarigenin, 15*β*-hydroxycalactinic acid, 16*α*-hydroxycalac- tinic acid methyl ester, 16*α*-hydroxycalotropagenin, calactinic acid, 12*β*-hydroxycoroglauci- genin, calotropagenin, frugoside, 6'-*O*-(*E*-4-hydroxycinnamoyl)desglucouzarin, coroglauci-genin, calotoxin, 16*α*-hydroxycalotropin, 9,12,13-trihydroxyoctadeca-10(*E*),15(*Z*)-dienoic acid, *R*-(-)-mevalonolactone, calotroposide A, calotroposide B, calotroposide C, calotroposide D, calotroposide E, calotroposide F, calotroposide G, calotropisesquiterpenol, calotropisesterter- penol, γ-taraxasteryl acetate, giganticine, calotropbenzofuranone and calotropnaphthalene. Other reported chemical constituents from *C. gigantea* are depicted in table 2. Figure 1 shows structures of chemical constituents.

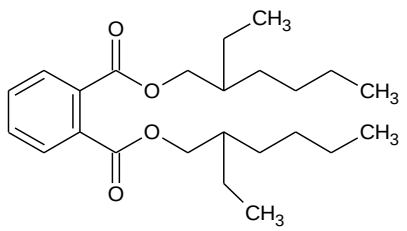
Pharmacological reports: *C. gigantea* has been reported to possess pharmacological activities including analgesic, antipyretic, larvicidal, antiarthritic, antidiabetic, antihyperlipidemic, antibacterial, anti-inflammatory and anticancer. Unexplored crude extracts of the plant have been employed for most of pharmacological studies. The pharmacological reports of *C. gigantea* have been presented in table 3. The information covered in table 3 includes pharmacological activity, plant part used, extract/fraction/isolate, doses tested and route of administration, bioactive dose, positive control, negative control, animals used, experimental studies and parameters assessed, mechanism of action and inference in concern with activity. The pharmacological reports compiled by Kadiyala et al. (2013) for analgesic, anthelmintic, antianxiety, anti-arthritic, anti-asthmatic, antibacterial, anticonvulsant, anti-diabetic, antidiarrheal, antifungal, anti-inflammatory, antimicrobial, antioxidant, anti-pyretic, antitumor, cytotoxic, hepatoprotective, locomotor, pregnancy interceptive, skeletal muscle relaxant and wound healing activities of *C. gigantea*, have not been included in present review article.

Table.1.Traditional uses of *Calotropis gigantea*

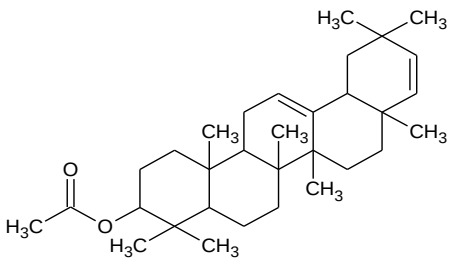
Plant part	Traditional use	Reference
Whole plant	Treatment of bronchial asthma	Shankara, 1979
	Treatment of cholera	Jain and Tarafder, 1970
	Treatment of convulsions	
	Treatment of pneumonia	
	Treatment of ringworm infection	
	Treatment of small pox infection	
	Treatment of toothache	
	Treatment of epilepsy	
	Treatment of fever	Pal et al., 1999; Kumar et al., 2003
	Treatment of leprosy	Iyengar et al., 1986
	As purgative	Deka et al., 1984
	Treatment of rheumatism	Subramaniam, 1999; Katiyar and Kolhe, 2000-2001
	As wound healer	Singh and Pandy, 1980
Flower	As antirabic	Mishra and Naquvi, 1995
	Treatment of asthma	Jha, 2001
	Treatment of catarrh	Yoganarasimhan et al., 1982
	Treatment of cold	Ahluwalia, 1968; Raj and Patel, 1978; Kapoor and Kapoor, 1980; Singh et al., 1998
	Treatment of cough	Suresh et al., 1995; Verma et al., 1995; Kothari and Londhe, 1999
	As digestive	Banerjee and Banerjee, 1986
	Treatment of dog bite infection	Girach et al., 1998
	Treatment of inflammation and tumours	Tiwari and Majumder, 1996
	Treatment of mental disorder	Upadhye et al., 1994, 1997; Borthakur et al., 1996; Katewa et al., 2003
	Treatment of snake bite infection	Natarajan et al., 1999
	Treatment of tuberculosis	Topno and Ghosh, 1999
	As wound healer	Reddy et al., 1988; Rao et al., 2000
Fruit	Treatment of leucoderma	Iyengar et al., 1986
Seed	Treatment of earache	Banerjee, 1999
	Treatment of cold, cough and chest pain	
	Treatment of blood clots	Chelvan, 1998
	Treatment of body pain and fractures	Rao and Jamir, 1990
	Treatment of eye inflammation	Sudhakar and Rao, 1985; Singh and Maheshwari, 1994; Singh, 2000-2001
	Treatment of tonsillitis	Basak, 1997
	Treatment of insect bite infection	Rosakutty et al., 1999
	Treatment of malaria	Maikhuri and Gangwar, 1993
Leave	Treatment of pneumonia	Girach et al., 1997
	Treatment of stomach pain	Brahma and Boissya, 1996
	As vermicide	Tarafder, 1984
Aerial part	Treatment of congestion and asthma	Kshirsagar et al., 2003
	Treatment of toothache, cold, cough and chest pain	Banerjee, 1999
Latex	Treatment of abortion	Natarajan et al., 1999
	As anthelmintic	Iyengar et al., 1986
	As irritant	Kapoor and Kapoor, 1980
Wood	Treatment of asthma	Shah, 1982
	Treatment of bleeding	Dash and Mishra, 1999
	Treatment of enlargement of liver	Gogoi and Borthakur, 2001
	As expectorant	Iyengar et al., 1986
	Treatment of joint pain	Iman et al., 1997
	Increase breast milk	Saren et al., 1999
	Treatment of jaundice	Yadav and Patil, 2001
	Treatment of leprosy	Shah and Joshi, 1971
	Treatment of migraine	Hemadri and Rao, 1990
	Mother and child health care	Goel and Rajendran, 1999
	Treatment of piles	Nayak et al., 2004
	Treatment of swelling	Maheshwari et al., 1986
	Treatment of toothache	Shah, 1982
Root	Antidote in snake venom	Murthy et al., 1986
	Antidote to rat bite	Barua et al., 1999
	Treatment of cancer	Singh, 2000-2001
	Treatment of cuts and boils	Kumar et al., 2003
	As diaphoretic	Kapoor and Kapoor, 1980
	Treatment of diarrhoea	Nayak et al., 2004
	Treatment of dog bite infection	Topno and Ghosh, 1999; Rao and Jamir, 1990
	Treatment of dysentery	Shah and Gopal, 1982
	Treatment of joint pain	Iman et al., 1997
	Treatment of leprosy and eczema	Banerjee and Banerjee, 1986
	Treatment of malaria	Kshirsagar et al., 2003
	Treatment of menstrual disorders	Rao et al., 1999
	Treatment of skin diseases	Jamir, 1990
	Treatment of worms infection	Shah et al., 1983
	Treatment of ulcer	Deka et al., 1984
	As carminative	
Stem	Treatment of epilepsy	Jain and Sikarwar, 1998

Table.2.Various chemical constituents isolated from *C. gigantea*

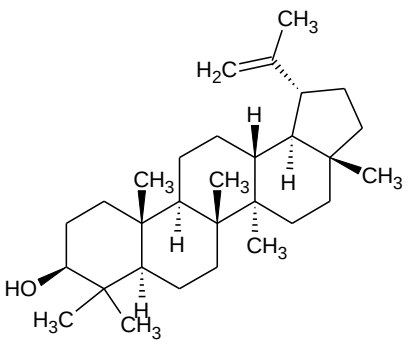
Class of chemical constituent	Name of chemical constituent	Plant part used	Extract taken	Reference
Triterpenoids	Di-(2-ethylhexyl) Phthalate	Flowers	Ethyl acetate extract	Habib and Karim, 2009, 2012
	Anhydrosophoradiol-3-acetate			
	Lupeol	Aerial parts	Latex	Anjaneyulu and Row, 1968
	α –Taraxerol	Root bark	Ethyl acetate extract	Anjaneyulu and Row, 1968; Mohaimenul et al., 2012
Triterpene esters	γ-Taraxasterol	Aerial parts	Hexane and methanol soluble extract	Thakur et al., 1984
	Lupenyl-1-acetate	Root bark	Petroleum ether extract	Anjaneyulu and Row, 1968
Flavonol	Isorhamnetin	Aerial parts	Methanol extract	Heneidak et al., 2006
Cardiac glycosides	Calotropone	Roots	Ethanol extract	Wang et al., 2008
	Gofruside			
Steroids	Stigmasterol	Root bark	Methanol extract	Basu and Nath, 1934
	β-Sitosterol			
	β–Sitosterolacetate		Ethyl acetate extract	Mohaimenul et al., 2012
Resin	*β*-Amyrin	Root bark	95 % Alcohol extract	Murti, Seshadri, 1945
	β-Amyrin acetate			
Fatty acids	Isovaleric acid	Root bark	95 % Alcohol extract	Murti and Seshadri, 1945
Miscellaneous	Asclepin	Roots	Latex	Singh and Rastogi, 1972



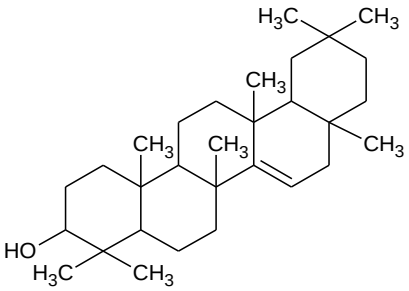
Di-(2-ethylhexyl) Phthalate



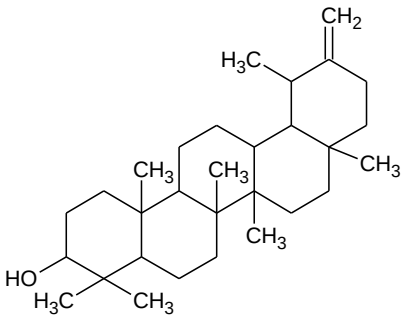
Anhydrosophoradiol-3-acetate



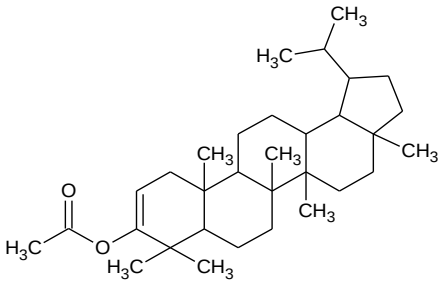
Lupeol



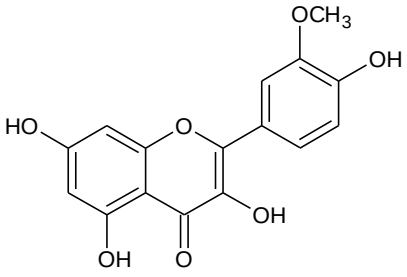
α –Taraxerol



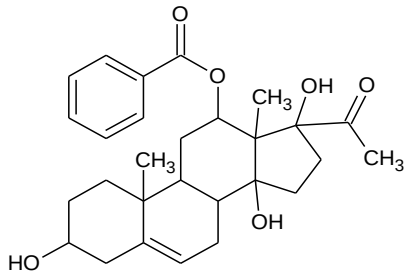
γ-Taraxasterol



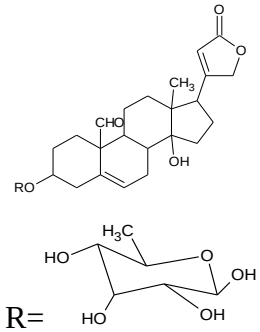
Lupenyl-1-acetate



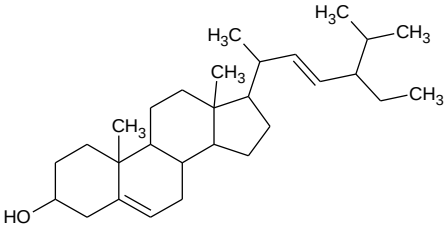
Isorhamnetin



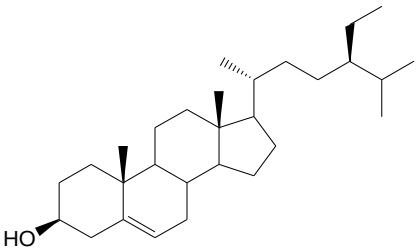
Calotropone



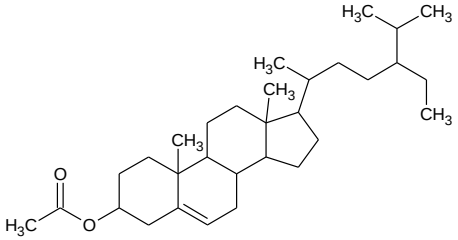
Gofruside



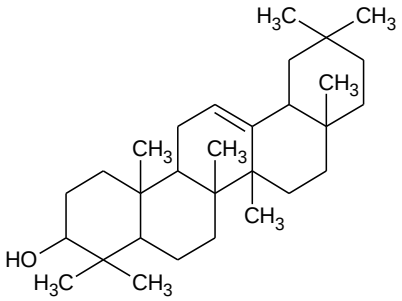
Stigmasterol



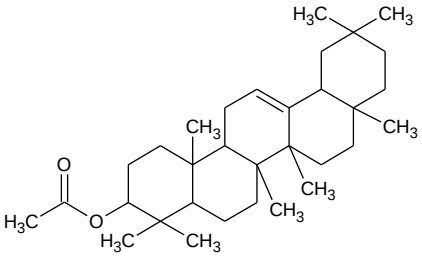
β-Sitosterol



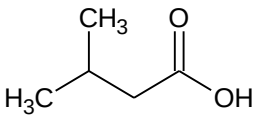
β−Sitosterolacetate



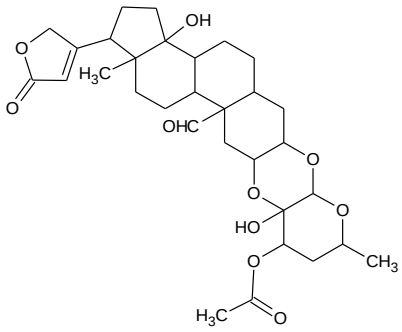
β-Amyrin



β-Amyrin acetate



Isovaleric acid



Asclepin

Figure.1.Chemical structures of various chemical constituents isolated from *C. gigantea*

Table.3.Pharmacological activities reported for *C. gigantea*

Pharmacological Activity	Plant Part	Extract/Fraction/ Isolate	Doses tested/ Route of administration	Bioactive dose	Positive control	Negative control	Animals	Experimental studies and parameters assessed	Mechanism of action	Inference in concern with activity	Reference
Analgesic activity	Roots	Methanol extract Ethyl acetate fraction	200 or 400 mg/kg, *p.o.* 25 or 50 mg/kg, *p.o.*	200 or 400 mg/kg, *p.o.* 25 or 50 mg/kg, *p.o.*	Morphine (5 mg/kg, *i.p.*)	2 % Tween 80 in distilled water	Laca mice	Tail immersion test	Involvement of $GABA_A$ receptor, monoamine inhibitory activity, chloride ion channel complex and 5-hydroxytryptamine1A	Showed mild analgesic activity	Kaur et al., 2014
Antianxiety activity	Roots	Methanol extract Ethyl acetate fraction	200 or 400 mg/kg, *p.o.* 25 or 50 mg/kg, *p.o.*	200 mg/kg, *p.o.* 25 or 50 mg/kg, *p.o.*	Diazepam (2 mg/kg, *i.p.*)	2 % Tween 80 in distilled water	Laca mice	Elevated plus maze model	Involvement of $GABA_A$ receptor, monoamine inhibitory activity, chloride ion channel complex and 5-hydroxytryptamine1A	Showed significant anxiolytic activity	Kaur et al., 2014; Kumar and Kumar, 2014
	Leaves	Ethanol extract	400 mg/kg, *p.o.*	400 mg/kg	Diazepam (1 mg/kg, *i.p.*)	1 % Tween 80 in distilled water	Male Swiss albino mice	Elevated plus maze model	Involvement of GABA receptor transmission and chloride ion channel complex opening	Showed significant anxiolytic activity	Khan et al., 2014
Antibacterial activity	Leaves	Aqueous, methanol and ethanol extracts	--------	--------	Vancomycin, tobramycin, streptomycin and amikacin	--------	*In vitro; Staphylococcus epidermidis, Proteus vulgaris, Proteus mirabilis, Serratia marcescens, Klebsiella pneumoniae , Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* cultures	Agar diffusion method or Kirby-Bauer disc diffusion method	--------	Showed mild activity against bacterial strain	Wasnik and Tumane, 2011
	Leaves and latex	Methanol and ethyl acetate extracts	1, 2, 4 or 8 mg/ml	8 mg	Ciprofloxacin, tetracycline and Polymyxin (10 µl/disc)	--------	*In vitro; Micrococcus luteus, Bacillus subtilis, P. aeruginosa, Serratia marcescens* cultures	Disc diffusion method; Mueller Hinton agar medium	--------	Showed activity against bacterial strains	Murugan, 2012
	Flowers	Ethyl acetate extract Di-(2-ethylhexyl) phthalate and anhyrosophoradiol-3-acetate isolated from ethyl acetate extract	30, 60 or 90 µl/disc	Dose dependent activity	Kanamycin (30 µl/disc)	Blank disc with respective solvent	*In vitro; S. aureus, Bacillus megaterium, B. subtilis, Sarcina lutea, E. coli, Shigella sonnei, Shigella shiga, Shigella dysenteriae* cultures	Disc diffusion method; Mueller Hinton agar medium	--------	Showed activity against bacterial strains	Habib and Karim, 2009
	Latex	Chloroform, ethyl acetate, hexane, methanol and aqueous extracts	100 mg	-------	Ampicillin (10µg/ml)	Organic solvent	*In vitro; Actinomyces viscosus, Lactobacillus acidophilus, Lactobacillus casei, Streptococcus mitis*	Agar diffusion method and minimum inhibitory concentration (MIC)	-------	Showed activity against bacterial strains in chloroform extract	Ishnava et al., 2012

							and Streptococcus mutans cultures				
	Leaves	n-Hexane, ethanol, methanol, chloroform, water and ethyl acetate extracts	20 µl	-------	-------	Dimethyl sulfoxide	*In vitro*; *B. cereus, B. subtilis, E. coli, K. pneumoniae, S. aureus, Salmonella typhi and M. luteus* cultures	The Kirby's Disc Diffusion method	-------	Showed activity against bacterial strains in ethyl acetate extract	Ishnava et al., 2011
Anticonvulsant activity	Roots	Methanol extract Ethyl acetate fraction	200 or 400 mg/kg, *p.o.* 25 or 50 mg/kg, *p.o.*	200 or 400 mg/kg, *p.o.* 25 or 50 mg/kg, *p.o.*	Phenytoin (20 mg/kg, *i.p.*)	2 % Tween 80 in distilled water	Laca mice	Maximal electro shock test	Involvement of $GABA_A$ receptor, monoamine inhibitory activity and 5-hydroxytryptamine1A	Showed mild activity against convulsions	Kaur et al., 2014
		Aqueous extract	100 or 200 mg/kg, *p.o.*	200 mg/kg	Valproic acid (40 mg/kg, *i.p.*)	Gum acacia	Laca mice	Pentylenetetrazole and maximal electro shock induced convulsions model	Involvement of GABA aminergic mechanism	Showed significant activity	Kalabharathi et al., 2013
Antidepressant activity	Roots	Methanol extract Ethyl acetate fraction	200 or 400 mg/kg, *p.o.* 25 or 50 mg/kg, *p.o.*	200 or 400 mg/kg, *p.o.* 25 or 50 mg/kg, *p.o.*	Imipramine (15 mg/kg, *i.p.*)	2 % Tween 80 in distilled water	Laca mice	Forced swim test	Involvement of $GABA_A$ receptor, monoamine inhibitory activity, chloride ion channel complex and 5-hydroxytryptamine1A	Significantly decreased the duration of immobility in mice	Kaur et al., 2014
Antidiarrheal activity	Roots	50 % Ethanol extract	200, 300 or 400 mg/kg, *i.p.*	200 or 400 mg/kg, *i.p.*	Loperamide (3 mg/kg, *p.o.*)	2 % Tween 80 saline	Wistar albino rats	Castor oil induced diarrhea	Inhibit the liberation of ricinoleic acid from castor oil involved in the prostaglandins and autocoids production	Significant increase in percent inhibition of defecation	Pratap et al., 2010
Antifungal activity	Leaves	Chloroform, ethanol and aqueous extract	200 µl	200 µl	--------	--------	*In vitro; Colletotrichum falcatum* cultures	Agar diffusion method; Potato dextrose agar medium	--------	Showed activity against fungal strain	Prince, and Prabakaran, 2011
	Leave, stem, flower, fruit and seed	Hexane, methanol and methanol-water (70:30) extracts	--------	--------	--------	Water	*In vitro; Fusarium mangiferae* cultures	Disc diffusion method; Murashige and Skoog medium	--------	Showed activity against fungal strain	Usha et al., 2009
	Leaves and latex	Methanol and ethyl acetate extracts	1, 2, 4 or 8 mg/ml	Dose dependent activity	Ciprofloxacin, tetracycline and Polymyxin (10 µl/disc)	--------	*In vitro; Aspergillus niger, Aspergillus flavus, Alternaria spp., Fusarium spp., Penicillium spp., Rhizopus spp.* cultures	Disc diffusion method; Mueller Hinton agar medium	--------	Showed activity against fungal strains	Murugan, 2012
	Flowers	Ethyl acetate extract Di-(2-ethylhexyl) phthalate and anhyrosophoradiol-3-acetate isolated from ethyl acetate	100, 200 or 400 µl/disc	Dose dependent activity	Nystatin (100 µl/disc)	Blank disc with respective solvent	*In vitro; A. niger, A. flavus, A. fumigates, Fusarium spp.*, cultures	Disc diffusion method; Mueller Hinton agar medium	--------	Showed activity against fungal strains	Habib, and Karim, 2009

		extract									
	Healthy plant tissue	Endophytic fungi was isolated from plant tissue	------	-------	-------	Sterile paper disc	*In vitro*; *A. niger*, *Colletotrichum gloeosporioides*, *Fusarium* spp., *Phytophthora nicotianae*, *Scopulariopsis* spp., *Trichoderma viride* and *Verticillium* spp. culture	Disc diffusion method; Mueller Hinton agar medium	------	Showed activity against fungal strains	Li, 2005
Anti-inflammatory activity	Leaves	60 % Hydro ethanol extract	600 mg/kg, *p.o.*	600 mg/kg, *p.o.*	Ibuprofen (25, 50, 100, 150 and 200 mg/kg, *p.o.*)	NaCl (0.9 %) for standard drug Distilled water for extract	Male and female albino rats	Carrageenan induce paw oedema in rats (intradermal injection of carrageenin 5% in gum acacia)	Inhibit the cyclooxygenase involved in the prostaglandin synthesis	Significantly reduced the paw oedema with respect to standard drug	Awasthi et al., 2009
	Leaves	Petroleum ether (60-80^{0}C), chloroform, ethyl acetate, n-butanol, ethanol and distilled water extracts	200 mg/kg, *p.o.*	Only ethanol and distilled water extracts of leaves showed activity at 200 mg/kg, *p.o.*	Paracetamol (200 mg/kg, *p.o.*)	Distilled water	Female albino wistar rats	Carrageenin induce paw oedema in rats (injection of 1 % Carrageenin-0.1 ml/gm in distilled water)	--------	Significantly reduced the paw oedema with respect to standard drug in case of ethanol and distilled water extract	Usman et al., 2012
	Leaves	Petroleum ether (60-80^{0}C), chloroform, ethyl acetate, 1-butanol, ethanol and distilled water extracts	200 mg/kg	200mg/kg	Ibuprofen (100 mg/kg)	Di methyl formamide	*In vitro* assay	Inhibition of albumin denaturation technique	Inhibition of release of inflammatory mediators	Significantly reduced the inflammation	Jagtap et al., 2010
Antimicrobial activity	Latex	Methanol extarct	0.125, 0.25, 0.50, 1 or 2 µg/ml	2 µg/ml	Amoxicillin (10 µg/ml) Amphotericin (10 µg/ml)	--------	*In vitro*; **(Bacteria)** *S. aureus, B. cereus, Methicillin Resistant S. aureus, P. aeruginosa, E. coli* **(Fungi)** *C. albicans, Trichophyton rubrum, A. flavus* cultures	Disc diffusion method; Mueller Hinton agar medium	--------	Showed activity against bacterial and fungal strains	Alluri and Majumdar, 2014
	Leaves	Hexane, carbon tetrachloride, chloroform, ethanol and water extract	400 µg/disc	400 µg	Kanamycin (30 µg/disc)	Blank sterile filter paper disc	*In vitro*; **(Gram positive bacteria)** *B. sereus, S. aureus, B. megaterium, B. subtilis, S. lutea* **(Gram negative bacteria)** *E. coli , Pseudomonas aureus ,*	Disc diffusion method; Mueller Hinton agar medium	--------	Showed activity against bacterial and fungal strains	Hossain et al., 2012a

							S. typhi , *Vibrio mimicus, Shigella boydii* , *S. dysenteriae* , *Salmonella paratyphi* , *Vibrio parahemolyticus,* **(Fungi)** *Saccharromyces cerevaceae* , *Candida albicans* , *A. niger cultures*				
	Flower	Ethyl acetate, ethanol and water extract	2.5–1000 µg/disc	Dose dependent activity	Gentamicin, Streptomycin and Tetracycline (10µg/disc) Fluconazole and Ketoconazole (10µg/disc)	Blank sterile filter paper disc	*In vitro*; *B. subtilis* , *E. coli* , *S. aureus, P. aeruginosa* *In vitro*; *C. albicans, Tinea capitis* cultures	Disc diffusion method; Mueller Hinton agar medium	--------	Showed activity against bacterial and fungal strains	Patil and Saini, 2012
	Leaves	Aqueous and ethanol extract	-----	-----	Ciprofloxacin and Nystain	-----	Various gram positive and gram negative bacteria	Disc diffusion method; Mueller Hinton agar medium	-----	Showed significant antimicrobial activity against *Proteus mirabilis* in case of aqueous extract and *K. pneumoniae* in case of ethanol extract	Kumar and Kashyap , 2012
	Aerial parts	Aqueous and ethanol extract	50, 100, 150 and 200 mg/ml	-----	Ofloxacin and NorfloxTZ (50, 100, 150 and 200 mg/ml)	-----	*In vitro; S. aureus, V. cholerae* culture	Disc diffusion method; Mueller Hinton agar medium	-----	Showed significant activity against microbial strain	Kumar and Kashyap , 2012
Antioxidant activity	Root	Methanol extract	100, 200 and 300 µg/ml	300 µg/ml	Ascorbic acid	-------	*In vitro* assay	DPPH Free Radical Scavenging activity Ferric Reducing Ability Plasma method	Free radical scavenging	Significantly reduces the free radical	Elakkiya and Prasanna, 2012
	Whole plant	Ethanol extract	25-250 µg/ml	------	Ascorbic acid Curcumin	Methanol	*In vitro* assay	DPPH Free Radical Scavenging activity Nitric Oxide scavenging	Free radical scavenging	Significantly reduced the free radical	Joshi et al., 2010

								activity			
	Leaves	Hexane, dichloromethane, and methanol extracts	------	------	Ascorbic acid	Methanol	*In vitro* assay	DPPH Free Radical Scavenging activity	Free radical scavenging	Significantly reduced the free radical	Wong et al., 2011
Antiplasmodial activity	Leaves	Hexane, dichloromethane, and methanol extracts	10 mg/ml	------	Artemisinin and Mefloquine	Dimethyl sulfoxide	Chloroquine resistant K1 and Chloroquine sensitive 3D7 strains of *Plasmodium falciparum*	Lactate dehydrogenase assay	-------	Showed significant antiplasmodial activity	Wong et al., 2011
Antiproliferative activity	Leaves	Hexane, dichloromethane, and methanol extracts	8-25 µg/ml	------	Xanthorrhizol, Curcumin and Tamoxifen	Dimethyl sulfoxide	Human cancer cell lines MCF-7, MDAMB-231, HeLa, HT-29, SKOV-3 and HepG2	Sulphorhodamine B assay	-------	Showed significant activity against human cancer cell lines in case of dichloromethane extract	Wong et al., 2011
Anti-pyretic activity	Leaves	Petroleum ether (60-80^0 C), chloroform, ethyl acetate, n-butanol, ethanol and distilled water extracts	200 mg/kg, *p.o.*	Only chloroform and n-butanol extracts of leaves showed activity at 200 mg/kg, *p.o.*	Paracetamol (200 mg/kg, *p.o.*)	NaCl 0.9 %	Female albino wistar rats	Yeast induced pyrexia method (subcutaneous injection of 15 % aqueous suspension of brewer's yeast-10 mg/kg in 0.9 % saline)	--------	Significantly reduced the rectal temperature with respect to standard drug in case of chloroform and n-butanol extract	Usman et al., 2012
	Leaves	Hydro alcohol extract	160, 320 or 640 µg/ml	640 µg/ml	-------	Physiological saline solution	Wistar albino rats Healthy volunteer	*In vivo*: Oedema forming activity *In vitro*: Haemolysis and Procoagulant activity	Mechanism of action involves inhibition of phospholipase enzyme present in cobra venom	Significant anti toxin activity against cobra venom	Pandey et al., 2011
Antistress activity	Roots	Methanol extract Ethyl acetate fraction	200 or 400 mg/kg, *p.o.* 25 or 50 mg/kg, *p.o.*	200 or 400 mg/kg, *p.o.* 25 or 50 mg/kg, *p.o.*	Diazepam (1 mg/kg, *i.p.*)	2 % Tween 80 in distilled water	Laca mice	Cold swim test	Involvement of $GABA_A$ receptor, monoamine inhibitory activity, chloride ion channel complex and 5-hydroxytryptamine1A	Significantly decreased the duration of immobility in mice	Kaur et al., 2014
Antitumor activity	Healthy plant tissue	Endophytic fungi was isolated from plant tissue	10 µl	-------	-------	-------	Human gastric tumor cell line BGC-823	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a tetrazole (MTT) assay	-------	Showed significant activity against human cancer cell line	Li, 2005
	Flower	Di-(2-ethylhexyl) phthalate isolated from ethyl acetate extract	10, 20 or 40 mg/kg, *i.p.*	Dose dependent activity	Bleomycin (0.3 mg/kg, *i.p.*)	2 % Dimethyl sulfoxide	Male swiss albino mice	Carcinoma cells induced tumour model	--------	Significantly reduced the viable tumour cells in mice	Habib and Karim, 2012

	Root bark	Methanol extract Petroleum ether (40-60^0 C) fraction of methanol extract Chloroform fraction of methanol extract	10 or 20 mg/kg, *i.p.* 40 or 80 mg/kg, *i.p.* 20 or 40 mg/kg, *i.p.*	Dose dependent activity	Bleomycin (0.3 mg/kg, *i.p.*)	2 % Dimethyl sulfoxide	Male swiss albino mice	Carcinoma cells induced tumour model	--------	Significantly reduced the viable tumour cells in mice	Habib and Karim, 2011
	Leaves	Ethanol extract	150 or 300 mg/kg, *p.o.*	Dose dependent activity	Omeprazole (20 mg/kg, *p.o.*)	Distilled water	Male wistar rats	Pyloric litigation induced gastric ulcers Ethanol induced gastric ulcers	Anti-secretory mechanism is involved	Significant reduction in ulcer index, gastric volume, free acidity and total acidity compared with control group Significant increase in percent protection compared to standard drug	Swapna et al., 2009
Antivenome activity	Whole plant	Methanol plant extract	100, 200 or 400 mg/kg, *p.o.*	200 or 400 mg/kg, *p.o.*	Lyophilized polyvalent snake venom antiserum	Saline	Swiss albino mice	*In-vivo* neutralization of lethality method	--------	Significantly reduced the venom effect in rats	Chacko et al., 2009
Antiviral activity	Leaves	Ethanol extract	100 µl	-------	-------	RPMI 1640 medium	Herpes simplex virus type-1 and Vesicular stomatitis virus	Plaque reduction assay	-------	Showed activity against both virus	Ali et al., 1996
Cytotoxic activity	Leaves	Hexane, carbon tetrachloride, chloroform, ethanol and water extract	3.125, 6.75, 12.5, 25, 50, 100 200 µg/ml	Dose dependent activity	--------	Dimethyl sulfoxide	*In vitro;* Brine shrimp nauplii in seawater	Brine shrimp lethality bioassay	--------	Significant cytotoxic activity against brine shrimp nauplii in chloroform fraction	Hossain et al., 2012
	Flowers	Ethyl acetate extract Di-(2-ethylhexyl) phthalate and anhyrosophoradiol-3-acetate isolated from ethyl acetate extract	--------	14.61 µg/ml 9.19 and 15.55 µg/ml	Ampicillin trihydrate	Dimethyl sulfoxide	*In vitro;* Brine shrimp nauplii in seawater	Brine shrimp lethality bioassay	--------	Significant cytotoxic activity against brine shrimp nauplii	Habib and Karim, 2009
	Roots	Ethanol extract	10, 20, 50, 100, 500, 1000, 2000 and 5000 µg /ml	1000 µg/ml	Cyclophosphamide	Artificial sea water	*In vitro;* Brine shrimp nauplii in seawater	Brine shrimp lethality bioassay	--------	Significant cytotoxic activity against brine shrimp nauplii	Ravi et al., 2011

Hepatoprotective activity	Root bark	95 % Ethanol extract	200 or 400 mg/kg, *p.o.*	Dose dependent activity	Silymarin (25 mg/kg, *p.o.*)	06 % carboxymethyl cellulose	Wistar albino rats	D-galctosamine induced hepatotoxicity	Mechanism involves the increase the synthesis of RNA and protein	Significant decrease of ASAT, ALAT, ALP, LDH, γ-GT and bilirubin level	Deshmukh et al., 2008
Insecticidal activity	Roots	Methanol extract and its chloroform and petroleum ether (40-60°C) soluble fractions	25, 50, 100 and 200 mg/kg 5, 10 and 20 mg/ml 5, 10 and 20 mg/ml	------	------	Organic solvent	Several inster of larvae and adults of *Tribolium castaneum*	Residual Film Method of Toxicity Fumigant Toxicity Repellency Test	------	Significant activity against *T. castaneum*	Alam et al., 2009
Larvicidal activity	Leaves and roots	Chloroform, dichloromethane and methanol extracts	10 to 1000 mg/L	Dose dependent activity	-----	Organic solvent	Larvae *Aedes aegypti* and *Anopheles stephensi*	Larvicidal bioassay	-----	Showed moderate activity against both strain	Patil et al., 2010
Leishmanicidal activity	Aerial parts	Methanol extract and its aqueous, methanol, butanol and hexane fraction	0.12, 0.25, 0.50 and 1.0 mg/ml	-----	Amphotericin B(0.5mg/ml)	Dimethyl sulfoxide	*Leismania major* strain MRHO/IR/75/ER	*In vitro* assay for Leishmanicidal activity	-----	Showed significant activity against *Leismania* strain in case methanol and its hexane fraction	Oskuee et al., 2012
Mosquitocidal activity	Leaves	Methanol extract	50, 100, 150, 200 or 250 ppm	250 ppm	Neem Azal (0.046, 0.0208 or 0.866 ppm)	Acetone	*Anopheles stephensi, Aedes aegypti, and Culex quinquefasciatus*	Larval/pupal toxicity test	-------	Showed significant Mosquitocidal activity	Kovendan et al., 2012
Ovicidal activity	Leaves, stem, flowers, roots and whole plant	Aqueous extract	2, 4, 6, 8 and 10 %	-----	-----	-----	*Helicoverpa armigera*	Ovicidal activity	-----	Significant inhibition of *Helicoverpa armigera*	Prabhu et al., 2012
Sedative activity	Roots	Methanol extract Ethyl acetate fraction	200 or 40 mg/kg, *p.o.* 25 or 50 mg/kg, *p.o.*	-------- --------	Thiopentone sodium (80 mg/kg, *i.p.*)	2 % Tween 80 in distilled water	Laca mice	Thiopentone sodium induced sleeping assay	Involvement of $GABA_A$ receptor, monoamine inhibitory activity, chloride ion channel complex and 5-hydroxytryptamine1A	Show mild sedative activity	Kaur et al., 2014
	Leaves	Ethanol extract	400 mg/kg, *p.o.*	400 mg/kg	Thiopentone sodium (40 mg/kg, *i.p.*)	1 % Tween 80 in distilled water	Male Swiss albino mice			Show significant sedative activity	Khan et al., 2014
Wound healing activity	Flower	Ethyl acetate extract	400 or 800 mg/kg/day for 14 days, tropically	800 mg/kg/day for 14 days, tropically	--------	--------	Wistar albino rats	Incision and excision wound model	Wound healing mechanism involves four phases: hemostasis, inflammation, granulation and maturation	Significant increase in percent wound contraction and decrease the epithelization period compared to control	Patil and Saini, 2012b

CONCLUSION

C. gigantea has been traditionally used in the treatment of bronchitis, asthma, leprosy and eczema; pharmacologically reported to exhibit analgesic, antipyretic, larvicidal, antiarthritic, antidiabetic, antihyperlipidemic, antibacterial, anti-inflammatory and anticancer activities; phytochemically reported to contain about 4 major classes of chemical constituents such as cardenolides, oxypregnane -oligoglycosides, terpenoids and flavonoids.

To date, about 53 compounds have been identified from *C. gigantea*; of these about 38% are cardenolides, 11% oxypregnane-oligoglycosides, 4% steroids, 4% flavonoids, 20% terpenoids, 3% cardiac glycosides, 4% resins, 6% proteinases and 10 % miscellaneous compounds. Few compounds present in *C. gigantea* especially flavonoids and steroids possess strong evidences of biological importance, but therapeutic actions of plant due to such bioactive principles have not been discussed. Further, no systematic work has been carried out to estimate content of bioactive constituents so that the plant could be standardized on the basis of bioactive markers. Thorough literature reveals that pharmacological studies of *C. gigantea* have not been correlated to its identified chemical constituents. Few pharmacological reports on *C. gigantea* suggest triterpenoids as potent compounds of the plant. Thus, these constituents are of particular interest not only to reveal their activities, but also to develop safer and effective synthetic analogues by structure-activity relationship studies.

The traditional uses of *C. gigantea* have been given some validation by modern pharmacological studies. For most of pharmacological activities, uncharacterized crude extracts of *C. gigantea* have been employed. Sporadic modern pharmacological studies have been carried out on *C. gigantea* where bioactive principles are isolated. For example, anhydrosophoradiol-3-acetate and di-(2-ethylhexyl) Phthalate have shown antimicrobial and cytotoxic activity, and lupeol exhibited anti-arthritic activity. It is evident from the available literature that *C. gigantea* possesses wide range of biological activities still most of traditional claims of the plant have not been validated by scientific studies. It is suggested that the research is needed: (a) to investigate *C. gigantea* for its traditional claims which have not been validated scientifically, (b) to characterize bioactive crude extracts of *C. gigantea* and (c) to establish mode of actions of bioactive constituents of *C. gigantea*.

The proven pharmacological activities of *C. gigantea* in preclinical studies have not been extrapolated to clinical studies. Therefore, *C. gigantea* needs to be investigated clinically and substantiated clinical data on the plant is required to be generated with a view to develop *C. gigantea* or its constituents as modern medicines. Future research on *C. gigantea* may provide convincing support for their clinical use in modern medicines.

C. gigantea represents a potential source of novel phytochemicals with newer biological activities. Finally, it is anticipated that this review will help researchers throughout the globe to select this plant for detailed pharmacological and phytochemical evaluations. The plant holds a great potential to serve as source of new chemical entities which could be developed as clinically potential drugs.

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