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Traditional uses, phytochemistry and pharmacology of *Clerodendron glandulosum* Coleb – a review

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ABSTRACT

Present review for the first time provides a complete botanical description and information on ethnomedicinal uses of *Clerodendron glandulosum.*Coleb (CG; Fam, Verbenaceae). Recent studies conducted from our laboratory provide pharmacological evidence for its anti-hypertensive, anti-diabetic and anti-obesity potentials. Further, its beneficial potential in preventing *in vitro* and *in vivo* non-alcoholic steatohepatitis and atherosclerosis and potent hepatoprotective and free radical scavenging abilities along with its acute and sub-chronic toxicological evaluations are also reported from our laboratory. In keeping with its traditional uses, CG extract was capable of ameliorating experimentally induced hypertension, diabetes and obesity. Its beneficial potential against NASH induced oxidative stress and atherosclerosis can be attributed to its potent free radical scavenging potential. Non-toxic nature of CG leaf extract further provides added merit to its reported pharmacological properties. The present review summarizes the pioneering scientific evidence for the pharmacological effects of CG against related metabolic disorders like hypertension, diabetes and obesity along with anti oxidant potential and beneficial effects against non alcoholic steatohepatitis.

1. Introduction

The genus *Clerodendrum* L. (*Verbenaceae*) is very widely distributed in tropical and sub-tropical regions of the world and is comprised of small trees, shrub sand herbs. This genus, with about 560 taxa, is the largest in the *Verbenaceae* and is taxonomically complex. Term *Clerodendrum* was named by Linnaeus in Species *Plantarum* in 1753[1]. The name is derived from two Greek words, *kleros*, meaning "chance or fate" and *dendron*, "a tree"[2]. The name so derived (*Clerodendrum*) has apt relevance to the considerable variation reported of its usefulness in medicine[3]. After a decade later, Adanson (1763) changed the Latin name "*Clerodendrum*" to its Greek form "*Clerodendron*"[4]; in Greek Klero means "chance" and *dendron* means "tree" *i.e.* chance tree, which means the tree that does not bring good luck. The reason for the genesis of the name to the genus is obscure but may well have relevance to the ancient belief that some species exhibited healing properties while, others had exactly opposite effects. Later, after a span of about two centuries Moldenke (1942)[5] readopted the Latinized name '*Clerodendrum*', which is now commonly used by taxonomists for the classification and description of the genus and species[4,5,6].

2. Botanical description

*Clerodendron glandulosum.*Coleb (CG; Family: *Verbenaceae*) is a shrub or a small tree, perennial, and wild or cultivated (Figure 1). Stem quadrangular, branches robust and sparsely pubescent with corky internodes. Young stem is shiny but turns light gray on maturity. Leaves are (1.5-28 cm) opposable, decussate, petiolate and long with prominent scars. Each leaf is broadly ovate, sub truncate or chordate at base, apex acute to acuminate, simple margin entire to slightly undulate, disagreeable small lateral veins

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(6–9) with few glands clustered at the petiole and scattered beneath. Inflorescence is terminal, compact and corymbose cymes (30–60 cm long and up to 5 cm in diameter). Peduncles are robust, cylindrical (5–20 cm long), minutely pubescent and hollow. Flowers (0.4–2 cm) are pediculate, numerous, bracteates, white in colour and pedicelate (2–4 cm). Bracts are lanceolate or narrowly ovate, caduceus at the time of flowering. One bract is present for each flower and glands are present on the lower surface. Calyx are gamosepalous, persistent, sepaloid, pubersent, campanulate with several peltate glands, sepals 5 (up to 0.4 cm long) and glandular. Teeth triangular, less than 0.1 cm, fruiting calyx, reddish purple (0.5–1 cm), corolla gamopealous, hypocrateri forms tube slander. Petals 5, white in colour, limps oblong or obovbate and acute at apex [0.5 cm × (0.25–0.3 cm)]. Tube nearly glabrous (2.5–3 cm), stamen 4, didynamous, filiform, epipetalous exerted, glabrous and white (upto 1.5 cm). Anthers are reddish or maroon, introse and 0.2 cm long. Gynoecium (1.5 cm long) has exerted style and shorter than stamen with 4 loculi (due to the presence of false partitions). One locule is ovate in each loculus. Fruit is drupe, subglobose, glossy and bluish green in colour that turns black on drying[7].

Figure 1. Classification and digital photograph of CG taken from Imphal district, Manipur, India.

3. Traditional medicinal uses

The term "*Kuthap*" is a combination of "Ku" meaning a "wooden coffin" and "Thap", "distant", which literally means that a person using the plant as food or medicine is shielded or kept away from ills and ailments. It has a long association with the culture and tradition of Manipur since early 16th century[8]. The plant is used on many occasions by the people living both in the valley and hills. One such occasion is the *Sajibu cheiraoba*, the New Year day in Manipur calendar, in which the "*kuthap*" is an important ingredient used in the preparation of a special menu called "uti", a naturally carbonated mixed vegetable pourice. Belief has it that, one taking uti on the first day of a year will endure long without any ailments until the end of the year. At the time of childbirth, the tribals use kuthap along with another plant called "*kokan*" to insure easy parturition for mother. The decoction of *kuthap* is soaked in a piece of cotton and inserted into the rectum of a child to expel worms out of the body. In other cases, *kuthap* finds usage in the preparation of natural hair care remedy locally known as *chinghi*, to kill lice. From the ancient times, belief has it that, a twig of *kuthap* hung on the wall of a room can protect from bugs carried in by bats. Traditionally, *kuthap* finds usage as medicine for lowering hypertension and for curing many skin diseases. Now, local markets sell *kuthap* for various purposes including household consumption as a food additive[9,10].

Leaves of CG are used by *Apatani* and *Nyishi* tribes of North-East India as a therapeutic agent against hypertension[11,12] while, the tender shoots are used by the Debaru tribe for antipyresis[13]. Rural and urban people of Manipur (India) routinely grow CG in the kitchen garden with the leaves often sold in the market. Traditionally, cross sections of people across Manipur consume decoction of CG leaves for treating diabetes, obesity and hypertension[14].

4. Phytochemical constituents

Phytochemical analysis of methanolic extract of CG revealed presence of phenols, steroids, alkaloids, anthraquinones, flavonoids and polyphenols while, tannins and terpenoids were absent[15]. Further, GC-MS analysis of CG hexane extract has demonstrated presence of 28 compounds. Strongyloster, lupeol, *n*-hentriacontane and hexacosane represented 7%–13% each in hexane extract whereas, palmitic acid, vitamin E, 2-pentadecyn-1-ol, norolean-12-ene and octacosane were present in < 2%.

5. Pharmacology

5.1. Antioxidant and free radical scavenging activity

Reactive oxygen species and free radical-mediated reactions are known to be involved in degenerative or pathological processes such as aging, cancer, coronary heart disease and Alzheimer's disease[16]. Natural antioxidants have gained wide popularity in lieu of its synthetic counterparts[17]. Methanolic extract of CG leaves (MECG) was assayed for its qualitative and quantitative phytochemical constituents as well as free radical scavenging potential using different in vitro assays for hydrogen peroxide, hydroxyl, superoxide, DPPH, nitric oxide, peroxynitrite, singlet oxygen and hypochlorous acid radicals. Its lipid peroxidation inhibitory activity, metal chelating activity and reducing power were also assayed. Qualitative phytochemical screening of MECG showed presence of polyphenols, steroids, flavanoids and saponins. Quantitative phytochemical analysis revealed (34.3±0.89) mg/mL gallic acid equivalent-polyphenols, (46.1±1.00) mg/mL quercetin equivalent-flavanoids and (53.36±0.93) mg/mL ascorbic acid per 100 mg MECG. The MECG scavenges hydrogen peroxide [IC_{50} (120.23±1.53) μg/mL], hydroxyl [IC_{50} (70.23±1.36) μg/mL] superoxide [IC_{50} (80.36 ±1.36) μg/mL], DPPH [IC_{50} (50.11±1.36 μg/mL) and nitric oxide [IC_{50} (90.11±1.55) μg/mL] radicals in a dose dependent manner. The IC_{50} values for peroxynitrite, singlet oxygen and hypochlorous acid were (48.41±1.72), (62.15± 1.69) and (136.69±2.01) μg/mL respectively. MECG also inhibited lipid peroxidation [IC_{50} (150.56±3.02) μg/mL] and promoted metal chelation [IC_{50} (50.29±2.00) μg/mL] in dose dependent manner. Assay of reducing capacity

of MECG showed a dose dependent response. This report suggests strong antioxidant activity of a methanolic extract of CG leaves against all known radicals and hence worthy of consideration as a natural antioxidant[15].

5.2. Hypolipidemic potential

Saturated fats and/or cholesterol rich diet contribute to hypercholesterolemia and hypertriglyceridemia that progress to cardiovascular disorders[18]. Epidemiological and experimental studies have established the role of elevated plasma cholesterol in the development of atherosclerosis and other cardiovascular diseases[19]. In recent times, therapeutic approach for treatment of hyperlipidemia has shifted towards a combination therapy with synthetic drugs (*i.e.* niacin extended lovastatin release tablet), as cholesterol lowering drugs are having a moderate effect on triacylglyceride levels[20]. Another drawback of synthetic drugs is their inability to increase HDL levels[21]. Viewed in this context, the hypolipidemic potentials of medicinal plants need critical study. Several plant species with anti-hypercholesterolemic potentials have found recognition[19]. Studies on the efficacy of aqueous extract of CG leaves on alteration in lipid and cholesterol metabolisms in high fat diet fed hyperlipidemic rats were undertaken. Rats were orally administered with CG extract (200, 400 or 800 mg/kg bodyweight) and fed with a standard laboratory diet (SLD) or high fat diet (HFD) for 6 weeks. Alterations in the plasma and hepatic lipid profiles, lipid and cholesterol metabolizing enzymes in target tissues, faecal total lipids and bile acid contents were evaluated in all the experimental groups. The results were compared with that of the synthetic hypolipidemic drug lovastatin. Results clearly indicated no alteration of any of the parameters tested in control rats for all the doses of CG employed. However, CG extract significantly prevented increment in plasma and tissue lipid profiles in HFD fed rats. Feeding with CG extract significantly suppresses activity levels of HMG CoA reductase (Hepatic) and cholesterol ester synthase (Hepatic and intestinal) and increases the activity levels of plasma lecithin cholesterol acyl transferase and lipoprotein lipase (plasma, hepatic and adipose). Further, feeding of HFD rats with CG extract increased excretion of triglycerides, cholesterol and bile acids through faeces. These results suggest reduced absorption, effective elimination and augmented catabolism of lipids and cholesterol, possibly accreditable to high content of saponin and phytosterols in CG. Therapeutic potential of CG extract against hypercholesterolemia and hypertriglyceridemia was projected for the first time through the data published in this report[22].

5.3. Prevention of metabolic syndrome

A conglomerate of glucose intolerance, dyslipidemia and hypertension is known as metabolic syndrome (MetS)[23]. Of late, MetS has become one of the major public health challenges worldwide[24]. Feeding rats with fructose (FRU) rich diet is known to develop experimental hypertension accompanied by the metabolic abnormalities of hyperinsulinemia, insulin resistance and hyperlipidemia[25], which has led to consideration of this as an ideal experimental model for pre-clinical evaluation of various therapeutic agents against MetS[26]. Protective effect of an aqueous extract of CG leaves against FRU induced metabolic syndrome was evaluated in male *Charles foster* rats. Experimental metabolic syndrome was induced by feeding with 60% FRU rich diet. Changes in bodyweight, food and fluid intake, plasma glucose, insulin, fasting insulin resistance index (FIRI), plasma total lipid profile, free fatty acids (FFA), oral glucose tolerance (OGTT), blood pressure and vascular reactivity were all investigated in Control (rats fed with laboratory chow for 8 weeks), FRU (rats fed with FRU rich diet for 8 weeks) and FRU+CG (rats fed with FRU rich diet and orally administered with 200 or 400 mg/kg of CG extract for 8 weeks) groups. FRU+CG groups recorded significant decrement ($P<0.05$) in plasma glucose, insulin, FIRI and lipid profile while, plasma HDL level was significantly increased ($P<0.05$) along with an efficient clearance of glucose as revealed by tolerance curve and area under the curve value. FRU+CG groups also recorded significantly decreased ($P<0.05$) mean arterial blood pressure along with decreased vasoconstriction and increased vasorelaxation in response to administration of various pharmacological agents. These results were comparable with those of metformin treated rats. This report surmises the role of CG extract in ameliorating experimentally induced insulin resistance and hypertension and provides the first pharmacological evidence for protective role of CG leaves against experimentally induced metabolic syndrome[27].

5.4. Amelioration of non alcoholic steatohepatitis

Non-alcoholic steatohepatitis (NASH) is a pathological condition characterized by accumulation of lipids in the liver of non-alcoholic individuals and consequent oxidative stress leading to cirrhosis of liver in the long run[28]. Most of the synthetic lipid lowering drugs are efficient in management of hyperlipidemia and obesity but, are of negligible therapeutic value against NASH[29]. Hence, it is a major challenge for pharmaceutical industry to develop a combination therapy that is effective against NASH in obese and IR individuals. Herbal medicines are becoming increasingly popular and being looked up to for management of hyperlipidemia, obesity and IR, primarily because of their minimal side effects and their multiple modes of action in controlling lipid metabolism[22]. Protective role of aqueous extract of CG leaves against high fat diet/fatty acid induced lipotoxicity in C57BL/6J mice and oleic acid treated HepG2 cells have been used as experimental models of NASH[30]. Plasma lipid profile, markers of hepatic damage, hepatic mitochondrial reactive oxygen species, markers of oxidative stress and antioxidants and histopathological changes were evaluated in CON (mice fed with low fat diet for 16 weeks), NASH (mice fed with HFD for 16 weeks) and NASH+CG1 and NASH+CG3 (mice fed with HFD containing 1 and 3% CG extract(w/w)for 16 weeks). Supplementation of NASH mice with CG extract significantly prevented HFD induced elevation in plasma markers of liver damage, plasma and hepatic lipids, mitochondrial oxidative stress and compromised enzymatic and non-enzymatic antioxidant status and histopathological damage to hepatocytes. Furthermore, results from *in vitro* study indicated attenuation of oleic acid induced lipid accumulation in HepG2 cells in presence of CG extract. Moreover, addition of CG extract (20-200 μg/mL for 24 h) to HepG2 cells significantly minimized lipid peroxidation and cytotoxicity and increased cell viability. These *in vivo* and *in vitro* studies were the first comprehensive experimental evidences that establish the potency of CG extract in preventing high fat/fatty acid induced NASH[30].

5.5. Anti-obesity potential

Obesity, initially thought as a problem of the developed world, has now become a worldwide malady because of increasing prevalence in the developing countries as well[31]. Due to the high costs and the potentially hazardous side-effects of synthetic drugs, the potential of natural products for treating obesity is under exploration currently[32,33]. In this behest, traditional herbal medicines and food ingredients capable of controlling weight gain are *in vogue*[34]. Effects of CG extract on (i) expression of genes regulating visceral adiposity in HFD fed C57BL/6J mice and (ii) *in vitro* 3T3L1 pre-adipocyte differentiation and leptin release were also investigated. Changes in body weight, lee index, plasma lipids and leptin, mRNA expression of peroxisome proliferator-activated receptor gamma isoform 2 (PPAR γ -2), sterol regulatory element binding proteins isoform 1c (SREBP1c), fatty acid synthase (FAS), carnitine parmitoyltransferase-1 (CPT-1) and leptin in epididymal adipose tissue of LEAN (mice fed with LFD for 20 weeks), OB (mice fed with HFD for 20 weeks) and OB+CG (mice fed with HFD containing 1% (w/w) CG extract for 20 weeks) were also investigated. Further assessed was the potential of CG extract on *in vitro* 3T3L1 pre-adipocyte differentiation and LEP release. Supplementation of HFD fed mice with CG extract significantly prevented HFD induced increment in bodyweight, lee index, plasma lipids and LEP, visceral adiposity and adipocyte hypertrophy. Further, supplementation with CG extract resulted in down regulation of PPAR γ -2, SREBP1c, FAS and leptin expressions along with up-regulation of CPT-1 in epididymal adipose tissue compared to HFD fed mice. *In vitro* study recorded significant anti-adipogenic effect of CG extract marked by decreased adipogenesis, TG accumulation, leptin release and Glyceraldehyde 3-phosphate dehydrogenase (G3PDH) activity along with higher glycerol release without significantly altering viability of 3T3L1 pre-adipocytes. This inventory was a profound scrutiny of CG extract and its role in preventing adipocyte differentiation and visceral adiposity by down regulation of PPAR γ -2 related genes and leptin expression. This study validates the traditional therapeutic claim of use of CG extract in controlling obesity[35].

5.6. Prevention of in vitro low density lipoprotein (LDL) oxidation and macrophage apoptosis

During the last decade, LDL oxidation and LDL particle size have received extensive attention for their atherogenic potentials[36]. Secondly, oxidized LDL (Ox-LDL) stimulates endothelium to secrete monocyte chemotactic protein-1 (MCP-1) from endothelial cells, which facilitate infiltration of monocytes into the sub-endothelial space[37]. Oxidized LDL can also induce migration and proliferation of smooth muscle cells and impede endothelial cell migration. Oxidized LDL promotes the differentiation of macrophage colony stimulating factor from endothelial cells and inhibits the motility of resident macrophage[38]. Studies have reported that Ox-LDL is cytotoxic to various cell types present in an artery and can induce macrophage apoptosis after being internalized via scavenger receptors[39]. Protective role of CG extract against *in vitro* LDL oxidation and Ox-LDL induced macrophage apoptosis were studied using various *in vitro* experimental models. Effect of CG extract on cell free (Cu^{2+} mediated) and cell mediated (macrophage) LDL oxidation and formation of various intermediary products were investigated. Ox-LDL induced macrophage apoptosis was evaluated by nuclear condensation, cell cycle analysis, and annexinV-FITC/propidium iodide staining in presence or absence of CG extract. Data shown in this report hints at the protective role of CG extract against LDL oxidation, Ox-LDL induced macrophage oxidative stress, mitochondrial dysfunction and apoptosis. Thus, the modulatory role of CG extract on two key events of atherosclerosis contributing to its anti-atherogenic potential and subsequent use as a possible herbal medicine stand reported[40].

5.7. Amelioration of experimental atherosclerosis

Anti-atherogenic potential of CG leaf extract was evaluated using *in vivo* and *in vitro* experimental models. Serum markers of LDL oxidation, cholesterol, triglycerides, lipoproteins and auto-antibody titter, *ex vivo* LDL oxidation, LDL aggregation, aortic lipids and histopathological evaluations along with immunolocalization of macrophage surface marker (F4/80), vascular cell adhesion molecule-1 (VCAM-1) and P-selectin were all evaluated in CON (rats treated with single dose of saline (*i.p.*) and fed with laboratory chow), ATH (rats treated with single dose of vitamin D3 (600 000 IU, *i.p*) and fed with atherogenic diet) and ATH+CG (rats treated with single dose of vitamin D3 (600 000 IU, *i.p.*), fed with atherogenic diet and simultaneously treated with 200 mg/kg CG extract, *p.o.*) for 8 weeks. Supplementation of atherogenic diet fed rats with CG extract significantly prevented increment in serum cholesterol, triglycerides, and lipoproteins, markers of LDL oxidation, auto-antibody titter and aortic lipids. Moreover, LDL isolated from ATH+CG rats recorded minimal aggregation and susceptibility to undergo *ex vivo* LDL oxidation. Microscopic evaluation of thoracic aorta of ATH+CG rats revealed prevention of atheromatous plaque formation, accumulation of lipid laden macrophages, calcium deposition, distortion/defragmentation of elastin, accumulation of macrophages and, down regulation of cell adhesion molecule (VCAM-1 and *P*-selectin) expression. Further, *in vitro* monocyte to macrophage differentiation was significantly attenuated in presence of CG extract (200 μg/mL). It can be concluded from the p2resent study that, CG extract is capable of controlling induction of experimental atherosclerosis and warrants further scrutiny at the clinical level as a possible therapeutic agent[41-46].

5.8. Hepatoprotective potential

Various hepatic ailments are responsible for billions of deaths worldwide[47]. Further, synthetic therapeutic drug induced hepatic injury is also a serious concern of modern day pharmacists and scientists worldwide. In this behest, use of herbal agents to prevent various hepatic ailments and drug induced hepatotoxicity is *in vogue*. Various herbal extracts in this context have been screened for their possible hepatoprotective potentials. Hepatoprotective potential of CG extract in experimental model of carbon tetrachloride (CCl_4) induced hepatotoxicity in male rats was investigated. Changes in plasma marker enzymes of hepatic damage, total bilirubin content, hepatic lipid peroxidation, enzymatic and non-enzymatic antioxidants and histopatholgical alterations were evaluated in various experimental groups. Rats pre-treated with CG extract

(400 mg/kg for 15 days) followed by administration of CCl_4 (0.5 mL/kg on 16th day) recorded significant decrement in plasma marker enzymes of hepatic damage, total bilirubin content and hepatic lipid peroxidation. In addition, contents of hepatic reduced glutathione, ascorbic acid and plasma total protein and activity levels of superoxide dismutase and catalase showed significant increase in the same animals. Microscopic examination of liver depicted prevention of CCl_4 induced hepatic damage by pre-treatment with CG. In conclusion, this report summarises the potency of CG extract in maintaining cellular integrity of hepatocytes, as denoted by the serum levels markers of hepatic damage, and hence its hepatoprotective efficacy[48].

6. Toxicity evaluation

During the past few decades, use of herbal medicines has witnessed a phenomenal upswing not only in developing countries but also in developed countries[49]. World health organization has also recommended use of herbal medicines against diseases for which synthetic drugs are not available[50]. Further, the awareness of possible multifocal potentials of various herbal drugs has opened a flood gate of investigative therapy against metabolic disorders, where multiple complications coexist[22]. However, use of herbal drugs is still limited because of their consideration as either dietary supplements or as food additives instead of as drugs as per the US-FDA criteria[51] and hence, their rigorous safety evaluation is not a routine practice[48]. Moreover, adverse effects of various herbal extracts have found mention and hence, preclinical toxicological evaluation of herbal extracts is warranted for a better acceptance. Acute and sub-chronic toxicological evaluations of aqueous extract CG leaves were carried out using Swiss albino mice. Acute (single administration of 1 000, 2 000, 3 000, 4 000 or 5 000 mg/kg) and sub-chronic (750, 1 500 or 3 000 mg/kg for 28 days) toxicity tests were performed as per the guideline of Organisation for Economic Cooperation and Development (OECD). No mortality was recorded in animals that were orally administered up to 5 000 mg/kg of extract. There were also no adverse behavioural changes, diarrhoea, salivation or food aversion. Sub-chronic doses of CG extract showed no significant effect on plasma contents of electrolytes, glucose, urea, creatinine, total protein and activity levels of acid phosphatase, alkaline phosphatase, aspartate transaminase and alanine transaminase up to a dose of 3 000 mg/kg bodyweight. Acute and sub-chronic toxicity tests reveal CG extract to be non-toxic with a lethal dose (LD_{50}) value > 5 000 mg/kg bodyweight and no significant alterations in the biochemical profile[48].

7. Conclusion and further scope

To sum up, the review presents an up to date finding providing scientific validity to the traditional practice of using CG as a folklore medicine. The leaf extract is reliably non toxic with strong anti oxidant properties. It shows efficacy against experimentally induced hypertension, insulin resistance and obesity. Besides, it also shows very favourable responses befitting its possible use as a phytotheraputant against NASH.

Based on our detailed study on CG extract reviewed above, future lines of investigation seem appropriate to generate better and focussed understanding of the therapeutant properties of CG. In this behest following investigations should be carried out:

1. Effects of CG extract in amelioration of type I diabetes.
2. To carry forward the finding to its logical conclusion, isolation and characterization of active principles is warranted.
3. In keeping with the folklore usage, its antipyretic and antihelminthic action needs to be ascertained.
4. Molecular mechanism of CG mediated easing of insulin resistance needs to be understood.
5. With effective scientific validation obtained in experimental models, the revealed therapeutic potential of CG extract needs to be carried forward to the level of clinical testing and possible usage as anti- obesity/anti-hypertensive medication.

Conflict of interest statement

Authors declare no conflict of interest.

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