Journal of Medicinal Plants Studies

www.PlantsJournal.com

ISSN (E): 2320-3862
ISSN (P): 2394-0530
NAAS Rating: 3.53
JMPS 2019; 7(3): 112-116

Received: 24-03-2019
Accepted: 26-04-2019

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Crescentia genus of medicinal plants: A review

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Abstract
Plants have always been a source of drugs possibly from the advent of human beings. Even in recent times, many important allopathic drugs have been discovered from plants. All plants produce secondary metabolites, which metabolites can have a diverse range of pharmacological activities. Recent times are witnessing not only emergence of new diseases like bird flu, Nipah, Ebola to name only a few, but also emergence of drug-resistant vectors of old diseases like common cold, enteric diseases, and parasitic diseases. At the same time, diseases like diabetes mellitus, cardiovascular disorders and Alzheimers have started to reach or have already reached endemic proportions. The *Crescentia* genus is a less studied genus and has only a few species within the genus. Nevertheless two of the species, namely *Crescentia cujete* and *Crescentia alata* have been found to have a diverse range of bioactive phytochemicals. This review attempts to collate various traditional uses of the two plants, their reported phytochemicals and the pharmacological activity studies of the two plants and plant parts with a view to spur scientific interest in this genus leading to novel drug discoveries.

Keywords: *Crescentia*, phytochemicals, antimicrobial, antioxidant, anti-inflammatory, acaricidal, anthelmintic

Introduction
Medicinal plants have been used since pre-historic times to treat different diseases all over the world, especially in Asia. According to World Health Organization (WHO), 20,000 medicinal plants are used globally, and these plants are teeming with versatile phytochemicals. Approximately 2000 drugs are used from these plant sources [1]. Among Colombian medicinal plants *Crescentia cujete* is considered to have antitumor and antiviral activity [2, 3]. The genus *Crescentia* belongs to the Bignoniaceae family and is indigenous to tropical America, Asia and Malaysia. The *Crescentia* genus comprises 7 species such as *Crescentia cujete*, *Crescentia amazonica*, *Crescentia plectantha*, *Crescentia alata*, *Crescentia linearifolia*, *Crescentia portoricensis* and *Crescentia latifolia*, and some of these species are considered to have medicinal values [4, 5]. Among these, *C. cujete* and *C. alata* are well known for their therapeutic uses in traditional medicines. These two plants are also planted in various regions of India as they have ornamental values [6]. This review shall attempt to summarize the various traditional uses of *Crescentia* genus plants, bioactive phytochemicals known to be present in the plants, pharmacological activities of whole plant and plant parts, and potential of drug discovery from plants of this genus. Search of the relevant scientific literature has been made in various abstracting bodies like PubMed, SCOPUS and Google Scholar. No time limits were set for the searches.

Botanical description
Crescentia plants exist in dry tropical meadow systems [7, 8]. The height of *C. cujete*is 6 to 12 meters (m) tall and leaves are spoon shaped, 5 to 18 cm long and 2 to 5 cm broad, which are arranged in clusters with the stout twigs. Flowers are light green bell-shaped and 5 to 6.5 cm long. It produces very large and oval green or brown fruits which are 10 to 30 cm in diameter [9]. It is also a perennial species which is dispersed in the tropical lowlands of Mesoamerica. It also grows in savannahs and semi-evergreen tropical forest. It has two generic categories according to Maya and Spanish which are known as *uas*and*luch* that distinguish wild and domesticated varieties [10].
On the other hand, *C. alata* Kunth can grow up to 8m tall. Leaves are dark green in color with length up to 20cm. Flowers are ball-shaped, yellow-green to maroon color and with a length of

about 6cm. This plant is grown as an ornamental in India. The pectoral fruits are considered medicinal, being used for colds and kidney diseases [11].

Traditional uses

In Mexico, *C. alata* plays a leading role during dry season which provides fiber, energy and protein to sheep [12]. The inhabitants of Colombia have been using various medicinal plants for curing different diseases including *Crescentia* genus plants. In the northern part of Bolivia, the plant *C. cujete* is known as Totumo. Decoction of the interior part of this plant is used for the treatment of flu among the native people of Bolivia [13]. Various formulations of *C. cujete* are used by Haitian immigrants and their descendants in the Province of Camaguey, Cuba for medicating different ailments, which encompasses catarrh, asthma, stomach pain, intestinal parasites, cold uterus and female infertility [14]. Leaves are used in Trinidad and Tobago in order to treat hypertension [15]. *C. alata* is an herbaceous plant cultivated in Central America, particularly in Mexico and Guatemala. The leaves of this plant are used in different health disorders such as ulcers, boils, skin lesions, rheumatism, and as a febrifuge [16]. In the Yucatan area, as well as in the Antilles, Mexico and through Central and South America, leaves and fruit pulp of *C. cujete* are also used for internal abscesses, to expedite delivery and respiratory ailments among the Zapotec and the Mixe communities [17, 18]. Conventional physicians in north-western Colombia use the unripe fruit of *C. cujete* for snakebites patients; the fruits have measurable and extreme neutralizing capacity against *Bothrops atrox* venom, which causes hemorrhage [19].

Phytochemicals

A number of phytochemicals have been reported from *C. cujete* and *C. alata*. Reportedly, leaves were found to contain naphthoquinones [20], iridoid glycosides, aucubin, plumieride, asperuloside and 6-*O*-*p*-hydroxybenzoyl-10-deoxyeucommiol, 6-*O*-benzoyl-10-deoxyeucommiol, 6-*O*-benzoyl-dihydrocatalpolgenin, ningpogenin and 6-*O*-*p*-hydroxybenzoyl-aucubin [21, 22]; cardenolides and hydrogen cyanide have been reported in fruits of *C. cujete* [23]. The methanolic extract of fruit was shown to contain a number of compounds including aucubin, 6-*O*-*p*-hydroxybenzoyl-6-epiaucubin, agnuside, 5,7-bisdeoxycynanchoside, ajugol, 6-*O*-*p*-hydroxybenzoylajugol, and ningpogenin. Other studies have discovered five iridoids known as crescentins I, II, III, IV, and V, and three other previously unreported iridoid glucosides known as crescentosides A, B and C in fruits [24].

Various compounds were found in the fractionated methanolic extract of *C. cujete*, which are identified as (2*S*,3*S*)-3-hydroxy-5,6-dimethoxydehydroiso-α-lapachone, 2-(1-hydroxyethyl)naphtha[2,3-*b*]furan-4,9-dione, 5-hydroxy-2-(1-hydroxyethyl)naphtha[2,3-*b*]furan-4,9-dione, 2-isopropenylnaphtho[2,3-*b*]furan-4,9-dione and 5-hydroxydehydroiso-α-lapachone [25]. 3-hydroxymethylfuro [3, 2-b]naphtho[2,3-d]furan-5,10-dione, a compound found in *C. cujete* has also been synthesized [26].

Anthracene derivatives, coumarins, lignans, mono and diterpenes, anthraquinones [27], triterpenes and steroids were obtained from the methanolic extract of leaves of *C. cujete* [28].

A comprehensive study showed that the fruit of *C. cujete* gave twelve compounds of which four compounds were identified as acanthoside D (9), *β*-D-fructofuranosyl benzoate (10), (*R*)-1-*O*-*β*-D-glucopyranosyl-1, 3-octanediol (11), and *β*-D-fructofuranosyl 6-*O*-(*p*-hydroxybenzoyl)-*α*-D-glucopyranoside (12). Of the other eight partially identified compounds, compound 1 ($C_{11}H_{22}O_7$) was a *β*-glucopyranoside of 2, 4-pentanediol, compounds 2, 3, 6 and 7 ($C_{17}H_{32}O_{12}$, $C_{16}H_{30}O_{11}$, $C_{17}H_{32}O_{12}$, $C_{20}H_{38}O_{12}$) were obtained as oils, compounds 4, 5 and 8 as powders ($C_{11}H_{20}O_7$, $C_{17}H_{30}O_{12}$, $C_{13}H_{16}O_8$). Compound 12 has been previously been obtained from alkaline hydrolysis of tenuifoliside A, and but not found in nature [29].

The analysis of *C. alata* is limited and few chemicals have been determined from the fruit. On the basis of IR, UV, 1H and 13C, NMR, DEPT, COSY, HSQC, HMBC, MS and X-ray data, four new compounds were identified in the fruit. The compounds are 6*β*,7*β*,8*α*,10-tetrahydroxy-*cis*-2-oxabicyclo[4.3.0]nonan-3-one, 6*β*,7*β*,8*α*,10-tetra-*p*-hydroxybenzoyl-*cis*-2-oxabicyclo[4.3.0]nonan-3-one, 1*β*,6*β*,7α,8α,10-pentathydroxy-*cis*-2-oxabicyclo[4.3.0]nonane, and 6*β*-hydroxy-2-oxabicyclo[4.3.0]-δ-8-9-nonen-1-one [30].

C. alata was found to contain 27 volatile compounds in raw and roasted fruit, of which ethyl-2-methylbutyrate was the important aromatic compound [31]. A study published showed that the dry pulp of *C. cujete* fruit contained different nutritive and anti-nutritive compounds such as crude fiber, ash, crude protein, and carbohydrate; riboflavin, niacin and thiamin were present in high levels [32]. Different minerals were also present in pulp like Ca, Mg, Na, K, Fe, Mn, Cu, Zn, and PO_4. The minerals are important for maintenance of electrolyte balance in the body such as Ca and P ratio, Na and K ratio, etc [33].

Leaves of *C. cujete* were reported to contain many volatile compounds in essential oil obtained from leaves, which were identified as hexadecane, 1,1-dimethyl-3-hexyl-cyclopentane, 4-methyl-2-heptanone, *tran*s-pinane, selina-4(15),6-diene, *allo*-aromadendrene, globulol, neophytadiene, hexadecanal, kaur-16-ene, phytol, and (*Z*)-9,17-octadecadienal; limonene (16.7%) was the only terpene found mainly in the oil sample.

C. cujete furthermore reportedly contained phytochemicals such as β-D-glucopyransoyl benzoate, (2*R*,4*S*)-2, 4-pentanediol, (*R*)-4-hydroxy-2-pentanone, (*R*)-1, 3-octanediol, 3-hydroxymethylfuro[3, 2-b]naphtha [2,3-d]furan-5,10-dione, 9-hydroxy-3-hydroxymethylfuro[3,2-b]naphtho[2,3-d]furan-5,10-dione, 3-hydroxyoctanol glycosides, 2,4-pentanediol glycosides, 4-hydoroxy-2-pentanone glycosides, 6-Op-hydroxybenzoylajugol, aucubin 6-Op-hydroxybenzoyl-6-epi-aucubin, 1-dehydroxy-3, 4-dihydroaucubigenin, benzoic acid glucosyl ester, 5-hydroxymethylfurfural, 6-*O*-benzoyl-dihydrocatalpolgeninningpogenin, 6-*O*-*p*-hydroxybenzoylaucubin, crescentins I-V, crescentosides A,B and C, 5,7-bisdeoxycynanchoside, 6-*O*-*p*-hydroxylbenzoylaucubin, 3,3'-bisdemethylpinoresinol, (22*E*,24*R*)-ergosta-6,22-dien-3β-ol, ergosta-4,6,8(14),22-dien-3-one, cerevisterol, 5α,8α-epidiory-(22*E*,24*R*)-ergosta-6,22-dien-3β-ol, β-sitosterol, daucosterol, 3β,5α,9α-trihydroxyergosta-7,22-dien-6-one, ergosta-7,22-dien-3-one, sesquiterpene, 4-hydroxybenzoicacid, benzoicacid, p-hydroxybenzylethanol, *p*-hydroxybenzylalcohol, D-allitol, 5-hydroxymethyl-2-furancarboxaldehyde, dimethyl disulphide, dimethyl trisulfide, and dimethyltetrasulphide [34]. The structures of some of the phytochemicals present in the plants are shown in Fig 1.

Pharmacological activity

Antimicrobial

According to different studies, the genera *Crescentia* shows more antimicrobial activity compared to others. In a study, *C. alata* was triply extracted with methanol to obtain methanol extract (ME); ME was further fractionated with hexane (HF), chloroform (CF) and ethyl acetate (EAF). The HF of *C. alata* showed significant antibacterial activity. The experimental result showed that the minimal inhibitory concentration (MIC) of HF fraction was 3mg/ml for the tested bacteria (*Escherichia coli*) [35]. Chloroformic extracts of *C. alata* inhibited one type of yeast namely *Candida albicans*; methanolic extract of *C. alata* were active against *Streptococcus pneumoniae and Streptococcus pyogenes*. In the case of *C. cujete*, alkaloids, flavonoids and tannins present in the plant reportedly have antimicrobial property [36]. Fabrication of silver nanoparticles (CCAgNPs) was made by using the extract of the leaves of *C. cujete* which was found to have excellent bacterial activity against human pathogens *Bacillus subtilis, Staphylococcus epidermidis, Rhodococcus rhodochrous, Salmonella typhi, Mycobacterium smegmatis, Shigella flexneri* and *Vibrio cholera* [37].

Antioxidant

Plants are excellent sources for antioxidant compounds, which can combat against reactive oxygen species (ROS) responsible for many health disorders such as anemia, cardiovascular disease, cancer, inflammation, ageing, diabetes, degenerative disease and ischemia [38]. Phenolic and flavonoids compounds present in plants are good antioxidants [39]. Phenolic and flavonoids compounds from the ethanol extract and fractions of *C. cujete* leaves have capacity to scavenge free radicals rather than stem and bark [40].

Anti-inflammatory

The crude ethanol extract of leaves and bark of *C. cujete* revealed greater anti-inflammatory activity than the chloroform fraction of the plant. This activity was examined by red blood cell membrane stabilization [41]. The methanolic extract of *C. alata* showed good anti-inflammatory result by reducing the expression of nitric oxide synthesis in J774.A1 macrophage cell line [42].

Acaricidal activity

Assessment of acaricidal activity was determined with fruit pulp of *C. cujete* on *Rhipicephalus microplus*. Benzoic acid and cinnamic acid present in the extract of fruit pulp reportedly was responsible for the acaricidal activity [43].

Anthelmintic activity

It has been reported that *C. cujete* is enriched with different phytochemicals such as alkaloids, flavonoids, tannins, cardiac glycosides, phytosterols, terpenoids and saponins. Tannins and flavonoids present in the plant have been hypothesized as responsible for the observed anthelmintic effects [44, 45].

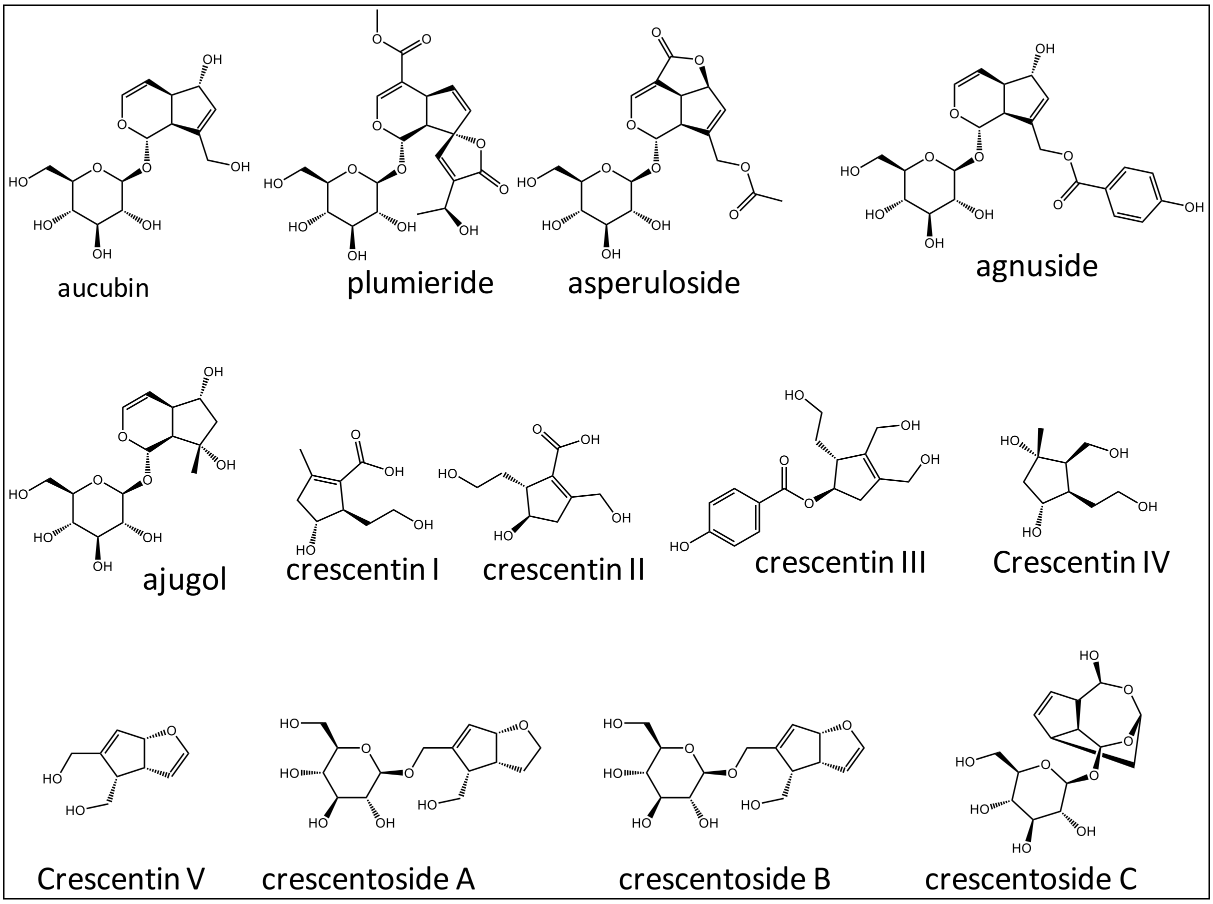

Fig 1: Some Phytochemicals isolated from the *Crescentia* genus of medicinal

Conclusion

Among the various species of the *Crescentia* genus, *C. alata* and *C. cujete* have been documented for their traditional medicinal uses. To our knowledge, there are no traditional medicinal uses for other species of this genus. The present study shows the importance and potential of the *Crescentia* genus as possible sources of new compounds, which can act as lead compounds or new drugs. With the advent and rapid rise in the number of antibiotic-resistant microbial species, the *Crescentia* genus may prove to be novel sources of new compounds against particularly enteric pathogens.

Acknowledgments

The authors are thankful to Khoshnur Jannat for help in preparing the manuscript.

Author Contributions

MMMI and NAS did the search of literature and wrote the first draft under the supervision of MR and ABMAB, TR edited the draft and drew the compound structures. MR corrected and completed the manuscript.

Funding Source

The work was funded by the authors.

Competing Interests

The authors have declared that no competing interests exist.

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