Cadamba: A miraculous tree having enormous pharmacological implications

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ABSTRACT

The *Cadamba* is one of the important medicinal plants belonging to the *Rubiaceae* family. It is crucially significant as it has the largest number of phytochemicals and secondary metabolites (*viz*., cadambagenic acid, cadamine, quinovic acid, *β*-sitosterol, cadambine, etc.) having pharmacological and biological properties. It can be used as an alternative to various synthetic chemical compounds in the prevention as well as the treatment of several incurable diseases. More than 100 years of research has been done to discover various phytochemicals and their implications. Very few of them, i.e. ≤2% have been commercialized due to the lack of a suitable model system as well as various associated controversial issues. The solubility of phytochemicals is another major concern: Further response that will be generated due to the solvent used is also unpredictable. Moreover, the *Cadamba* is one of the ornamental plants with religious significance. Here we have made an effort to summarize all the phytochemicals and their significance to render the interest that would help in their commercialization.

Key words: Anticancer, antioxidant, *Cadamba*, pharmacology, phytochemical

INTRODUCTION

There is a number of flora in use for medicinal purposes over the past several centuries. Countries such as China, India, and Egypt are well known for the active usage of medicinal plants in the treatment of various incurable diseases. India is the largest producer of medicinal herbs in the world due to which it is often called a botanical paradise. Ayurvedic science is deeply rooted in India and its neighboring countries. It was developed even before the medieval period, when people had little knowledge of science. There is a number of ancient therapeutic measures based on medicinal plants that have been developed in India.[1-3] They can cure several diseases and ailments such as diabetes, cardiovascular disorders, cancer, and liver damage.[4-6] A variety of plants is used for medicinal treatments; either whole or in specific part/s (bark, root, leaves, fruit, flowers, seeds), in the dried state. These are consumed using water, sugar, salt, honey, etc. Now they are formulated into suitable preparations such as tablets, pills, extracts, tinctures, lotions, ointments, and creams.[6,7]

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The *Cadamba* is commonly known as "Kadamba" in Sanskrit and Hindi and as "Kodom" in Bengali. It is an evergreen tropical tree found in different parts of India, Bangladesh, Nepal, Myanmar, Sri Lanka, Cambodia, Laos, Philippines, Malaysia, Indonesia, Papua New Guinea, and Australia. The other names of the plant are *Neolamarckia cadamba, Nauclea cadamba* (Roxb.), *Anthocephalus cadamba* (Roxb.) Miq., *Samama cadamba* (Roxb.) Kuntze, *Anthocephalus morindifolius* Korth., *Nauclea megaphylla* S. Moore, *Neonauclea megaphylla* (S. Moore) S. Moore, etc. The species has been widely but incorrectly called *Anthocephalus chinensis* as it has scented orange flowers present in dense globe-shaped clusters, which are used in the preparation of perfumes. It is an ornamental plant that is also used for timber- and paper-making. It has crucial significance in Indian mythology and religion. Various religions in India have strongly believed that God lives inside a *Cadamba* tree based on its enormous significance to humankind. It has been said in the Sanskrit shloka,"*Ayi Jagadamba Mad-Amba Kadamba Vana-Priyavaasini Haasa-Rate*," that is, Goddess Durga likes to live in the forest of *Cadamba* trees.

The *Cadamba* is a large tree with height of ~ 45 m with a broad umbrella-shaped crown and straight cylindrical bole. It grows very

quickly in length but takes 6-8 years to increase its girth. Its trunk has a diameter of 100-160 cm, while the leaves are 13-32 cm long. Flowering usually begins when the tree is 4-5 years old. The fruits of the *Cadamba* are small, containing fleshy capsules packed closely together to form a yellow-orange infructescence. The *Cadamba* has been known to cure a number of diseases; particularly, the extract prepared from the bark and leaves is crucial.[8] Various researchers across the world have focused their studies on discovering a number of phytochemicals as well as secondary metabolites (saponins, indole and quinoline alkaloids, secoiridoids, and triterpenes) with pharmacological significance from the *Cadamba*.[9-12] The present review is based on the significance of the *Cadamba* and its derived products to humankind.

Localization

In India, it is found in the temperate Himalayas (which extend from Kashmir to Bhutan), Garhwal, Himachal Pradesh, Sikkim, Assam, and Manipur. In Garhwal, it is particularly distributed in the temperate zones of Pauri, Tehri, Chamoli, and Uttarkashi districts, while in Himachal Pradesh it is prevalent in the districts of Chamba, Kangra, Manipur, Bilaspur, Kullu, Sirmour, and Simla at the elevation of ~ 2 km. Besides India, the *Cadamba* is found in Nepal, Myanmar, and western China.[13-15]

Composition

- *Heartwood*

Dihydrotectochrysin, dihydrowogonin, pinocembrin, chrysin, naringenin, kaempferol, aromadendrin, quercetin, taxifolin, 7-hydroxy-5, 2´, 4´-trimethoxyflavanone, 2´-hydroxy 2, 4, 4´, 6´- tetramethoxychalcone, 2´, 4´ dihydroxy-2, 4, 6´- trimethoxychalcone [Figures 1-3].[16-19]

- *Stem*

Narigenin, apigenin, β-sitosterol, sakuranetin, prunetin, genkwanin [Figures 1-3].[16-19]

- *Sapwood*

7-O-(β-D-glucopyranosyl)-5-O-methylnaringenin, genistein, prunetin, n-pentacosane, triacontane, noctacosanol, β-sitosterol, ursolic acid, oleic, palmitic, stearic acids, afzelin, kaempteritrin, naringenin, β-sitosterol glucoside [Figures 1-3].[16-19]

- *Stem bark*

Padmakastein and its derivatives, β-sitosterol behenate, tectochrysin, genistein, leucocyanidin, 4´-glucoside of genkwanin, chrysophenol, emodin, 8 β-D glucosides, orientalone, physcion, β-sitosterol glucoside, amygdalin, prunasetin, sakuranetin, puddumetin, flavanone, sakuranetin (5, 4´-dihydroxy-7-methoxy flavone) and its 5-glucoside, neosakuranin (2, 4´-dihydroxy-4-methoxy-6-glucosidoxychalcone), leucocyanidin, puddumin B, naringenin-4´-methylether-7-O-β-D-galactoside), taxifolin [Figures 1-3].[16-19]

- *Root bark*

Ursolic acid, stigmasterol, prunetinoside, glucogenkwanin [Figures 1-3].[16-19]

- *Seed*

Naringenin-5-O-α-L-rhamnopyranoside, 4´-O-methylliquiritigenin -7-O-α-L-rhamnopyranoside, naringenin 4´-methylether 7-xyloside, β-sitosterol-3-O-D-galactopyranoside [Figures 1-3].[16-19]

- *Branches*

Substitute of hydrocyanic acid, amygdalin [Figures 1-3].[16-19]

- *Leaves*

Quercetin-3-rhamnoglucoside, kaempferol [Figures 1-3].[16-19]

- *Commercially available*

Cadambagenic acid, quinovic acid, β-sitosterol, cadambine, cadamine [Figures 1-3].[16-19]

Significance

Astroethnobotanical importance

According to mythology, the whole universe is made of five elements or *panchtatva* (fire, earth, air, soil, and water), including plants and animals. The vast Sanskrit literature has affirmed that not only human beings but even minute creatures,

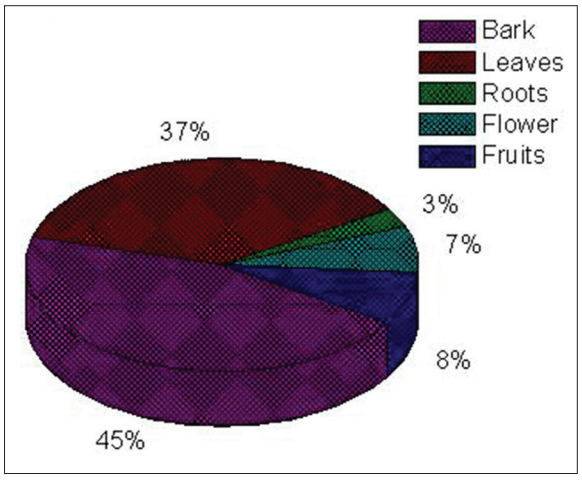

Figure 1: Significance of various parts of *Cadamba*

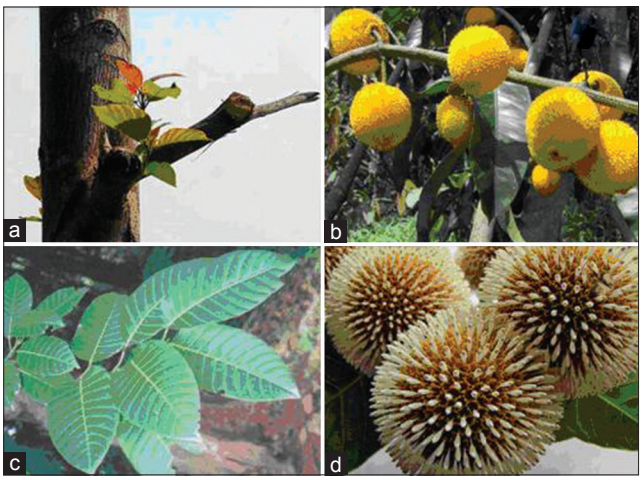

Figure 2: Crucial parts of *Cadamba* secreting important phytochemicals; (a) Stem bark (b) fruits (c) leaves (d) flowers

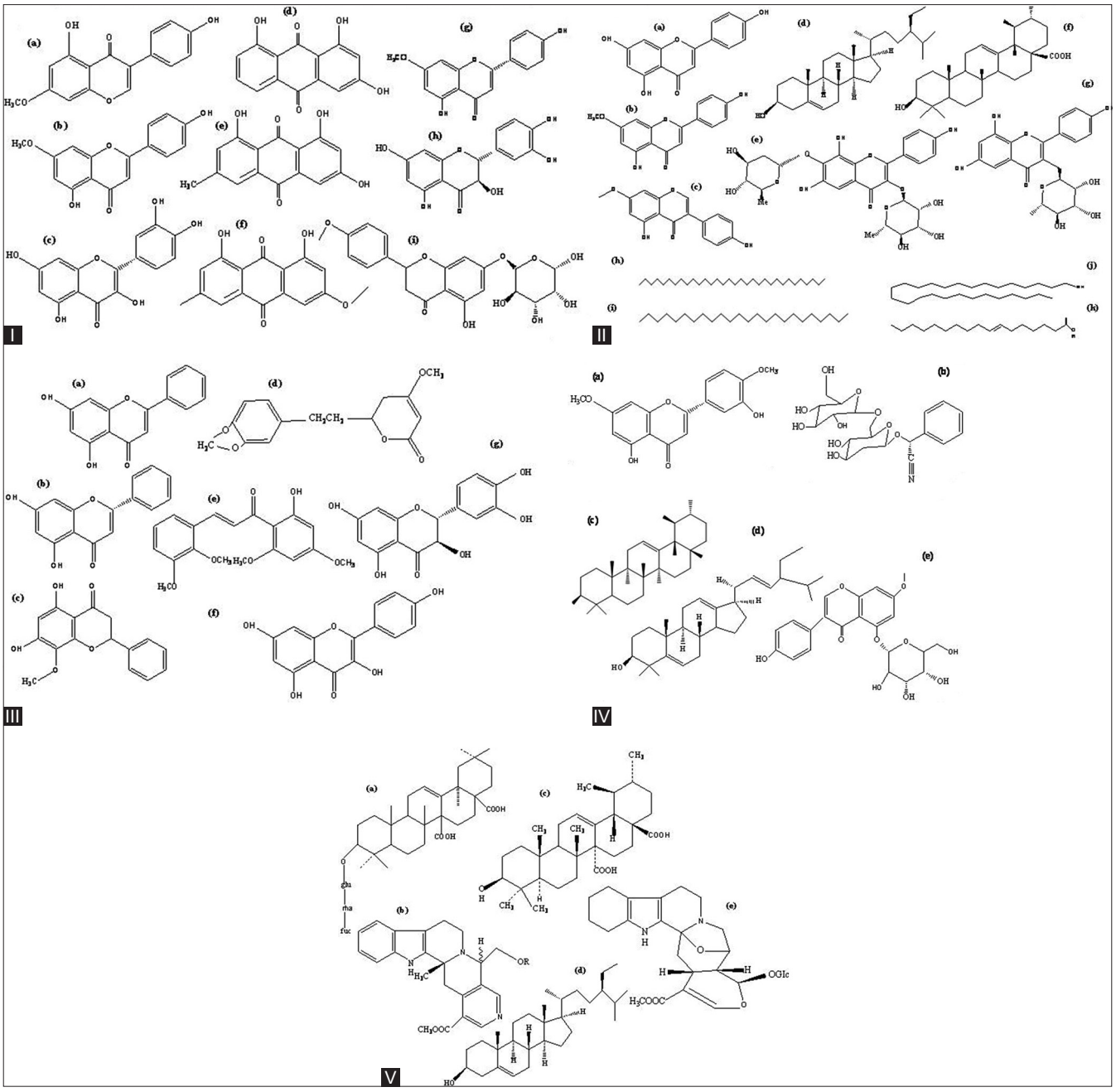

Figure 3: I. Phytochemicals from stem bark of *Cadamba*; (a) Padmakastein (b) Tectochrysin (c) Leucocyanidin (d) Chrysophenol (e) Emodin (f) Physcion (g) Sakuranetin (h) Puddumin B (i) Taxifolin. II. Phytochemicals from the stem of *Cadamba*; (a) Apigenin (b) Sakuranetin (c) Prunetin (d) β-sitosterol (e) Kaempteritrin (f) Ursolic acid (g) Afzelin (h) n-octacosanol (i) Triacontane (j) n-octacosanol (k) Oleic acid. III. Phytochemicals from heartwood of *Cadamba*; (a) Chrysin (b) Naringenin (c) Dihydrowogonin (d) Dihydromethycitin (e) 2´-hydroxy 2, 4, 4´, 6'-tetramethoxychalcone (f) Kaempferol (g) Quercetin. IV. Phytochemicals from leaves, branches, and root bark of *Cadamba*; (a) Quercetin-3-rhamnoglucoside (b) Amygdalin (c) Ursolic acid (d) Stigmasterol (e) Prunetinoside. V. Commercially significant phytochemicals from *Cadamba*; (a) Cadambagenic acid (b) Cadamine (c) Quinovic (d) β-sitosterol (e) Cadambine (structures are drawn using Chemdraw)

whether plants, animals, or microorganisms, are under the influence of the forces of the planets. It is believed that each and every person born on Earth belongs to any one of the 27 *nakshatras* (stars) present in the universe. There are 27 stars, which are correspondingly correlated to 27 trees present on Earth as given in Table 1. This correlation signifies that humans are directly related to plants. These 27 celestial plants have the power to fight against the harmful effects of the planets on human lives. Plants and herbs have been found to be extremely effective in neutralizing the detrimental influences of the astral positions of stars. The *Cadamba* is one of the trees enlisted in Table 1, which resembles *Satabhisha nakshatra*. It has been indicated in astrology that humans having *Satabhisha* as their birth star should plant the *Cadamba* near their habitats, which would help in curbing mental depression, heart attack, mood swings, laziness, rudeness, etc.[20]

Table 1: Correlation of stars with trees

Birth star	Botanical name	Common name
Ashwini	*Strychnos nux vomica*	Poison nut
Bharani	*Embilica officionalis*	Amla
Krittika	*Ficus racemosa*	Fig
Rohini	*Syzygium jambolanum*	Jamoon
Mrugasira	*Acacia catechu*	Kadhira
Arudra	*Aquilaria agallocha*	Agar wood
Punarvasu	*Bambusa*	Bamboo
Pushyami	*Ficus religiosa*	Peepal
Aslesha	*Mesua ferrea*	Naga champa
Magha	*Ficus bengalensis*	Banyan
Pubba	*Butea monosperma*	Flame of the forest
Uttara	*Ficus infectoria*	Juvvi
Hastha	*Spondias mangifera*	Wild mango
Chitra	*Aegle marmelos*	Bilva
Swathi	*Terminalia arjuna*	Arjun
Visakha	*Limonium acidissimum*	Elephant apple
Anuradha	*Mimusops elengi*	Bakul
Jyeshta	*Pinus*	Pine
Moola	*Canarium strictum*	Black dammar
Purvashada	*Saraca indica*	Sita Asoka
Uttarashada	*Artocarpus heterophyllus*	Jack
Sravana	*Calotropis gigantia*	Milk weed
Dhanishta	*Acacia ferruginea*	Shami
Satabhisha	*Anthocephalus cadaba*	Kadamba
Purvabhadra	*Azardirachta indica*	Neem
Uttarabhadra	*Mangifera indica*	Mango
Revathi	*Madhuca indica*	Ippe

Antivenom activity

Snakebite is one of the major causes of the high mortality rate in India and other developing countries. Various antivenom immunotherapies have been developed for specific treatment against snake venom envenomation. There are various side effects of such therapies, *viz*., anaphylactic shock, pyrogen reaction, and serum sickness. Most of these symptoms may be due to the action of higher concentrations of non-immunoglobulin proteins present in commercially available hyperimmune antivenom.

Over the years, many attempts have been made for the development of snake venom antagonists, especially those with plant origin. Many ethnobotanical survey reports and books were published highlighting the use of plant drugs for the management of snakebites.[21] Many Indian medicinal plants are recommended for the treatment of snakebite. It has been found that methanolic extract of the root bark of the *Cadamba* can be used as an antidote against snakebite. It is used in neutralizing *Vipera russellii* and *Naja kaouthia* venom, which can induce hemorrhage, cardiotoxicity, neurotoxicity, defibrinogenation, and inflammation. The pentacyclic triterpenes (free or as glycosides) have a crucial significance in providing ~20% protection against snake venom.[21]

Antioxidant activity

Studies on antioxidants are crucial, particularly in the food industry and in therapeutic research. The reactive oxygen species (ROS) and free radicals are byproducts of biological metabolism, which is responsible for cell membrane breakdown, membrane protein damage, and DNA mutation. These can further initiate the development of many diseases such as cancer, liver injury, cardiovascular diseases, cellular damage, and the aging process.[22-27] The indigenous enzymatic systems (superoxide dismutase, glutathione peroxidase, catalase), chemical scavengers and dietary antioxidants (α-tocopherol, β-carotene, ascorbic acid, glutathione, uric acid), and hormones (estrogen, angiotensin) are able to remove free radicals formed in cells and thus protect against oxidative damage.[22,23] Further, antioxidant phytochemicals found in several medicinal plants, fruits, and vegetables also protect the human body from disease by scavenging ROS and free radicals.[24-28] The *Cadamba* is a medicinal plant known to have antioxidant properties that are found particularly in its leaves.[29] Antioxidant properties in the ethanolic extract of the *Cadamba* leaves were assayed by estimating liver and kidney tissue enzymes using the 2'-diphenyl-1-picrylhydazyl (DPPH) assay, the superoxide anion radical scavenging assay, and DNA damage. It was found that the *Cadamba* possesses potent antioxidant properties. Further, UPLC-ESI-QTOF/MS has also confirmed the presence of various bioactive compounds from the *Cadamba* leaves having antioxidant properties.[30]

Biological significance

- *Antihelminthic activity*

Recently, the antihelminthic activity of the *Cadamba* has been elucidated.[31] It was examined on adult Indian earthworms, *Pheritima posthuma,* due to its anatomical and physiological resemblances with the intestinal roundworm parasites of the human beings. Each group was treated with aqueous and ethanolic extracts of the mature bark of the *Cadamba* with varied concentrations ranging from 10 mg/ml to 25 mg/ml along with vehicle (piperazine citrate, 15 mg/ml, prepared in 1% tween-80).[32,33] It was observed that paralysis and subsequently death of an individual worm have taken almost 4 h. Here paralysis was said to occur when the normal worm did not revive in saline, while death was concluded to have occurred when the worms lost their motility followed by the fading of their body color.

- *Antifungal activity*

Patel *et al*.[34] have demonstrated the antifungal property of the *Cadamba*. They have reported that the extract of the bark and leaf of the *Cadamba* showed antifungal activity against *Aspergillus fumigatus* and *Candida albicans*. They have also found that the *Cadamba* leaf extract shows higher antifungal activity than the bark extract.

- *Antifilarial and antimalarial activities*

Mosquito-borne diseases like malaria, dengue, chikungunya, filariasis, and Japanese encephalitis cause thousands of deaths per year in India as well as in other developing countries. Therefore, mosquito control is a serious concern and necessary to enhance the health and quality of life of the country's residents and visitors. The management of vector-borne diseases has failed due to their increased resistance and revitalization against synthetic chemicals. There is a number of reports on the use of plant extracts for killing mosquito larvae. Recently, it was reported

that *Cadamba* leaf extract has excellent larvicidal and pupicidal activities against the filarial vector, *Culex quinquefasciatus*, even at low concentrations.[35] It was found that the methanolic extract of *Cadamba* leaves was most effective against stage I, i.e. the larval stage, where 46% mortality was observed at 5 ppm and increased to 100% at 80 ppm. The observed LC_{50} and LC_{90} values were 12.15 ppm and 56.62 ppm, 15.15 ppm and 64.72 ppm, 21.82 ppm and 79.52 ppm, and 31.29 ppm and 102.13 ppm against stages I, II, III, and IV of larval pupae, respectively. Moreover, the addition of gold nanoparticles to the extract has proved to be more lethal, leading to 100% mortality at the larval stage at a very low concentration with LC_{50} at 0.61 ppm. There is another study, which found that the dimethyl sulfoxide extract of the *Cadamba* shows antimalarial activity with LC_{50} of 3.7 μg/ml against *Plasmodium falciparum*, K1 strain.[36]

- *Antibacterial activity*

The alcoholic and aqueous extracts of *Cadamba* fruits have shown significantly higher antibacterial activity against microorganisms (*Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Micrococcus luteus, Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa, Salmonella typhi, Klebsiella pneumonia, Proteus mirabilis, Candida albicans, Trichophytonrubrum, Asperagillus niger, Asperagillus flavus*, and *Asperagillus nidulans*). An experiment demonstrated by Mishra *et al*.[37] concluded that the antibacterial properties of *Cadamba* have zones of inhibition as 22.0 cm and 24.0 cm against *E. coli* and *P. aeruginosa*, respectively, at minimum inhibitory concentration (MIC) of 1.00 mg/ml. The extract of *Cadamba* was also effective against the foot and mouth disease of animals.[38] Further, the aqueous extract of *Cadamba* was effective against *Rathyibacter tritici*, a causal organism of tundu disease of wheat.[39]

Pharmacological significance of phytochemicals of Cadamba

- *Antidiabetic activity*

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia and alterations in carbohydrate, fat, and protein metabolism.[40] Different types of oral hypoglycemic agents are available in the market for the treatment of *diabetes mellitus*. There is a growing interest in herbal remedies due to the various side effects associated with these therapeutic agents. Herbal drugs have higher efficacy, minimal side effects, and have a relatively low cost. Bussa *et al*.[41] demonstrated an experiment to determine the antidiabetic study of *Cadamba* in which they have used the *Cadamba* stem bark which contains flavonoids (7.83 mg) and phenolic acids (12.26 mg) per 100 g of dry weight of the stem bark powder. The effect of the different doses of ethanolic extract of *Cadamba* stem bark on the fasting blood glucose levels of both normal and diabetic mice was studied. It was found that the fasting blood glucose levels of diabetic untreated mice were significantly higher than those of normal untreated rats. The ethanolic extracts of *Cadamba* bark powder extract at a dosage of 0.5 g/kg produced a fall of 23.8% in the blood glucose levels of diabetic rats after 5 h of treatment [Figures 3 and 4].

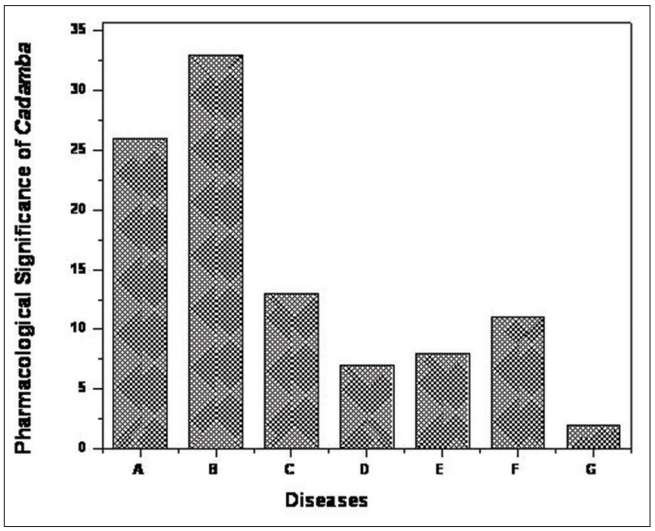

Figure 4: Literature reporting pharmacological significance of Cadamba in various human diseases (%); (a) Diabetes (b) Cancer (c) Inflammation (d) Diarrhea (e) High-cholesterol diseases (f) Liver diseases (g) Kidney diseases (here number in Y-axis indicates % of total data available on pharmacological significance of phytochemicals found in Cadamba in treatment of specific disease)

- *Antitumor activity*

Cancer is a term used for a disease in which abnormal cells tend to proliferate in an uncontrolled way and in some cases metastasize.[42] Extensive research has been done to find therapeutic treatments for cancer. Plant-based products have been frequently examined as potential anticancer agents. The screening of various medicinal plants has found several bioactive compounds which are effective chemopreventive as well as chemotherapeutic agents. The phytochemical screening of *Cadamba* has revealed the presence of lupeol and betulinic acid-type triterpene which have antineoplastic activity.[43] Antitumor activity of defatted methanol extract of *Cadamba* (MEC) on Ehrlich ascites carcinoma (EAC) has been evaluated.[44] There was extensive *in vitro* cytotoxicity as found by trypan blue and *in vivo* antitumor activity was evaluated by inoculating groups of mice with EAC. The antitumor potential of MEC was assessed by evaluating tumor volume, viable and nonviable tumor cell count, tumor weight, hematological parameters, and biochemical estimations. Finally, MEC exhibited significant decrease in the above mentioned parameters in EAC tumor-bearing mice. Further, the hematological profile, biochemical estimations, and tissue antioxidant assay were reverted to normal level in MEC treated mice [Figures 3 and 4].

- *Analgesic and Anti-inflammatory activities*

Flavonoids in *Cadamba* like quercetin, silymarin apigenin, daidzein, and genistein are known to have analgesic and anti-inflammatory activities.[45,46] Research is being done to identify more and more active constituents in *Cadamba* having anti-inflammatory activity. Anti-inflammatory activities of *Cadamba* are studied using active enzyme expressions of cyclooxygenase and lipoxygenase. Further, intact lysosomal membrane is important as the release of lysosomal constituent of activated neutrophil such as bacterial

enzymes and proteases occurs during tissue inflammation. It has been reported that ethanolic extract of *Cadamba* leaves exhibited significant membrane stability as found from heat induced hemolytic effect on erythrocyte membrane [Figures 3 and 4].[47]

- *Antidiarrheal activity*

The dry hydroethanolic extract of the flowering tops of the *Cadamba* has exhibited a dose-dependent decrease in the frequency of fecal droppings in castor oil-induced diarrhea in mice. The extract also produced a dose-dependent reduction in intestinal fluid accumulation [Figures 3 and 4].[48]

- *Hypolipidemic activity*

It has been found from experimental studies that alloxan has the capacity of reducing lipid levels by 30% as observed in diabetic mice. In comparison to this drug, the oral administration of root extract of the *Cadamba* for 30 days in dyslipidemic animals resulted in a significant decrease by 80% in total cholesterol, phospholipids, triglycerides, and lipid peroxides, with a reduction in lipid levels in diabetic mice [Figures 3 and 4].[49]

- *Antihepatotoxic effects*

The *Cadamba* has been reported to be used for its hepatoprotective activity. The hepatoprotective activity is due to the presence of chlorogenic acid (CGA) isolated from the *Cadamba* plant. It was also found that the intraperitoneal administration of CGA to mice at a dose of 100 mg/kg for 8 days exhibited better liver protective action than silymarin (SM) in CCl_4. The study concluded that, surprisingly, the antioxidative activity of CGA prepared in CCl_4 is responsible for its hepatoprotective nature in mice model with liver injury [Figures 3 and 4].[50]

- *Diuretic and laxative activities*

Mondal *et al*.[51] have studied the extracts of bark of the *Cadamba* in various concentrations in different solvents and demonstrated its diuretic and laxative activities. They have reported that the methanolic extract of *Cadamba* bark showed significant increase in urinary output as compared to aqueous, chloroform, and petroleum ether extracts. Moreover, there was higher laxative activity in case of the chloroform extract than with respect to the methanol, petroleum, and aqueous extracts [Figures 3 and 4].

CONCLUSION

The *Cadamba* is an important plant having tremendous medicinal properties. This review has showcased various biological and pharmacological activities of the *Cadamba*. Particularly, the leaves and bark have great significance. Most surprisingly, despite the *Cadamba* being a miraculous plant, very few studies have been done. There are very few derived products from the *Cadamba* known so far that have been commercialized or been recommended in daily life for people. There is an urgent requirement for intensive studies on this plant to exploit it for the treatment of various incurable diseases prevalent across the world.

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