Review

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A Review of the Ethno-dentistry Activities of *Calotropis gigantea*

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Abstract

Calotropis gigantea is a medicinal herb that thrives in arid climates. All parts of this plant are rich in secondary metabolites, which are very beneficial for health. Phytochemicals of this plant include flavonoid, alkaloids, steroids, cardiac glycosides, and terpenoids, which have a wide range of pharmacological effects. The potential of metabolit compound from *C. gigantea* can be used in dental treatment. This review describes the potential use of *C. gigantea* in ethno-dentistry, specifically as anti-caries, soft tissue inflammation (periodontitis and gingivitis), degenerative diseases (tumor/cancer), and wound healing. This review provides general perspectives and basic literature on the use of *C. gigantea* in the field of etno-dentistry. Based on this paper, it can be seen that *C. gigantea* has potential as a therapy in the field of ethnodentistry.

1. Introduction

Herbal medicine is the use of natural, non-synthetic substances as medicine in the field of ethnodentistry. The majority of herbal medicine used in dentistry is derived from medicinal plants and microbial endophytes [1–3]. Both medicinal plants and microbial endophytes produce metabolites, which are metabolic products that are converted in the body to active drug compounds. Traditional societies have relied on herbal medicine for centuries to treat a wide range of diseases, including those related to oral and dental health [4, 5]. This is because the efficacy of this traditional medicine has been scientifically proven to have medicinal properties such as antimicrobial [6], antibacterial [7, 8] antibiofilm [9] and even effective against skin disease [10, 11].

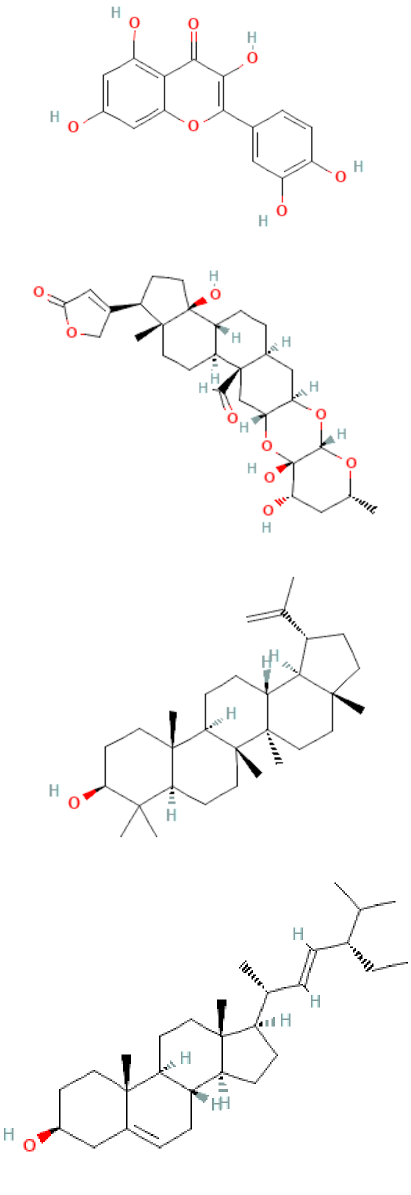
One of the most popular medicinal plants is *Calotropis gigantean* (L.) W.T.Aiton [1]. This plant, a part of family Apocynaceae also known as *Biduri*, is easily found in Indonesia and other parts of Asia (Figure 1). Recent studies reported that *C. gigantea* can be found in many geothermal area in Aceh Province, Indonesia such as in Ie Jue [12, 13] Ie Broek [14, 15] and Ie Seu'um [12, 16]. *Calotropis gigantea* contains numerous secondary metabolites that have medicinal properties and

Figure 1. *Calotropis gigantea* plants (Source: Personal collection).

beneficial in etno-dentistry [17]. This review provides general perspectives and basic literature on the use of *C. gigantea* in ethno-dentistry. The potential of antimicrobial (antibacterial, antiviral, and antifungal) and analgesic properties of secondary metabolites, as well as their use to treat painful teeth (analgesic), soft tissue inflammation (periodontitis and gingivitis), degenerative diseases (tumor/cancer), and wound healing are discussed.

2. The Secondary Metabolites of *C. gigantea*

C. gigantea is a bushy plant that thrives in dry climates. This plant is rich with secondary metabolites such as alkaloids, steroids, cardiac glycosides, and terpenoids [17] [18], which can be found in all parts of the plant [19]. Previous studies reported that the plant contains almost 81 compounds, 24 of which are bioactive compounds found in the leaves, 22 in the latex, 14 in the flowers, and 21 in the fruits [17, 19]. Gas chromatography - mass spectrometry (GC-MS) analysis showed that *C. gigantea* contains 2-methoxy-4-vinylphenol, phenol-4- methoxy-3-(methoxy methyl), 8-octadecenoic acid, methyl esters, and ethyl acetates such as Benzhydrazide, 4-methoxy-N_2-(5-bromo-2-methoxy benzylidene) [20]. Wang et al [21] showed that *C. gigantea* bark contains antiarol (3S, 5R, 6S, 9R) -3,6-dihydroxy-5,6-dihydro-E-ionol, blumenol A, coniferyl aldehyde, stigmast-5-ene-3E, 7E-diol, 3-epi-betulinic acid, lupeol, and D-amyrin. Previous research established that all parts of *C. gigantea* (flower, root, latex, and leaf) possess antibacterial activity [22, 23]. It can also be used as an analgesic [24], anti-asthmatic, sedative, anti-inflammatory, antidiarrheal, hepatoprotective, anticancer/tumor, antioxidant, and a composite, or reinforcing material [25].



(a)

(b)

(c)

(d)

Figure 2. Several metabolite structures in *C. gigantea* plants, (a) Quercetin; (b) Calotropin; (c) Lupeol; (d) Stigmasterol.

3. Ethno-dentistry activities of *C. gigantea*

3.1. Dental Caries

Dental caries, commonly referred to as cavities, is a multifactorial and chronic disease that manifests as tooth decay and demineralization caused by acids produced by bacteria that infect teeth. Dental caries is one of the most prevalent chronic infectious diseases worldwide, and it is caused by dental plaque [26, 27]. Some bacteria that have been studied can be found in the oral cavity, such as *Streptocossus mutans, Enterocossus faecium, Aerococcus viridans, Actinomyces meyeri, Lactobacillus acidophilus*, and *Eubacterium limosum*. These bacteria are known to cause dental caries [26]. Numerous studies on the antibacterial activity of *C. gigantea* leaves have been conducted.

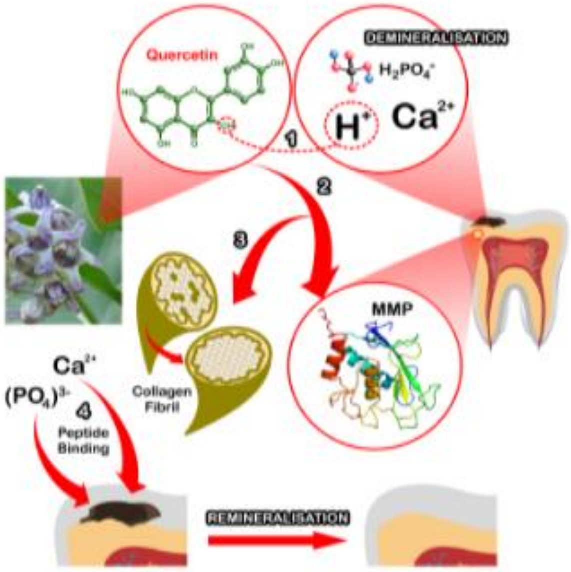


Figure 3. The role of flavonoids in caries inhibition (modified from Epasinghe [28]).

However, research on the plant's bioactivities in the field of dentistry is still limited. The use of plants high in secondary metabolites, such as *C. gigantea*, is one strategy for inhibiting this aggressive bacterial growth. Quercetin, for example, has been shown to inhibit the growth of caries-causing bacteria [29]. The concentration of quercetin of 5.10 ± 0.60 mg/mg in *C. gigantea* is capable of inhibiting caries-inducing bacteria such as *Streptococcus* and *Lactobacillus,* with an inhibition zone of 16 mm [30]. Quercetin is a flavonoid with the chemical formula $C_{15}H_{10}O_7$ (Figure 2). Kumar et al. [30] stated that *C. gigantea* has as much as 19.86 ± 0:02 mg/gr flavonoids.

The ability of flavonoids to prevent carries is consistent with the findings of Kim et al. [31], who reported that flavonoids only inhibited or disrupted the cariogenic properties of biofilms, not the cariogenic bacteria in the oral cavity. Epasinghe et al. [28] reported that flavonoids such as proanthocyanidin, naringin, and quercetin could remineralise dental hard tissues that eventually lead to caries inhibition. The ability of flavonoids to remineralise dentin is due to their hydroxyl groups, which form a hydrogen bridge. Thus, ionic or covalent bonds form between flavonoids and collagen fibrils. Flavonoids substitute a water molecule bond with the collagen inside the extra fibrillary compartment (Figure 3). This can be demonstrated by the reduction in the depth of dental cavities, despite the fact that fluoride remineralisation has a greater effect. These compounds also can inhibit caries by strengthening the collagen matrix, increasing resin-dentin, inactivating collagen-bound protease, and remineralising root caries [28].

In addition, fatty acid esters such as methyl nonanoate can also act as anticaries or anticariogenic. Ishnava et al. [25] suggested that fatty acid esters from *C. gigantea*, such as methyl nonanoate ($C_{10}H_{20}O_2$), are responsible for anticariogenic activity. These esters can disturb the pathogenesis pathway of bacteria by inhibiting bacterial food production [25, 32, 33]. Another study examined the antibacterial activity of *C. gigantea* as a whole plant part, demonstrating that a chloroform extract of the flower extract (20 mg) exhibited the greatest inhibitory activity against *S. aureus* (34 ± 0.43 mm). The methanolic extract of root (20 mg) demonstrated the highest antibacterial activity against *S. aureus* (28 ± 0.30 mm), whereas the chloroform extract demonstrated significantly less activity against *K. pneumonia* (9 ± 0.01 mm). Methanolic leaf extract (20 mg) demonstrated greater activity against *K. pneumonia* (12 ± 0.44 mm), whereas chloroform extract demonstrated less activity against *E. coli* [22]. However, another study using the leaf extract demonstrated a different result, with the maximum zone of inhibition being 17.6±1.15 mm against *E. coli*, and the lowest being 12.6±1.52 mm against *K. pneumonia*. Crude extract showed the maximum relative percentage (188.52 %) inhibition against *B. cereus*, and the lowest relative percentage inhibition (24.92 %) against *M. luteus* [34]. *C. gigantea* latex has also been shown to have antibacterial activity. The aqueous and ethanolic extracts of latex inhibited *E. coli*, *P. aeruginosa*, and *S. aureus*, ranging from 10 mm to 18 mm in the inhibitory zone. In this study, bacterial extracts inhibited the growth of tested organisms in a different zone than n-hexane, benzene, ethanol, and aqueous [18].

3.2. Soft Tissue Inflammation (Periodontitis and Gingivitis)

Periodontitis and gingivitis are two soft tissue inflammatory diseases that are frequently found in the oral cavity [35]. These are periodontal (tooth-supporting) tissue inflammations caused by specific microorganisms. However, gingival pockets and bone loss are frequently discovered in periodontitis cases. Generally, the pathogenesis of periodontitis is initiated by bacterial byproducts in the form of bacterial plaque [35, 36]. The most important bacteria that cause inflammation in periodontal problems are *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia*, and *Tannerella forsythensis*. These bacteria will produce plaque that can damage periodontal tissue caused by inflammation [36]. Inflammatory cells have been shown to promote bone resorption and contribute to periodontal disease, inducing prostaglandins and their precursors, interleukin 1-α (IL-α) and 1-β (IL-1β), and tumor necrosis factor alpha (TNFα) [35–37]. Natural anti-inflammatory agents can be used in dentistry to treat inflammation because the inflammatory process in teeth is similar to that in other tissues. Plants that produce these anti-inflammatory agents include *Cinnamomum camphora*, *Emblica officinalis* Gaertn (Amla), *Terminalia chebula* Retz. (Haritaki), and *Terminalia belerica* Roxb (Bibhitaki), *Acacia arabica, Curcuma longa*, and *Ocimum sanctum* [38–41]. The anti-inflammatory activities are contributed by linoleic acid, lupeol, vitamin C, polyphenols, and flavonoids produced by these plants. In *C. gigantea*, similar compounds are also found, such as linoleic acid, lupeol, 2-methoxy-4-vinyl phenol, neophytadiene, 3S,5R,6S9R-3,6-dihydroxy-5,6-dihydro-ionol etc. Numerous studies have demonstrated that these compounds are anti-inflammatory. Nonetheless, research on this plant's anti-inflammatory properties in the oral cavity is limited.

According to Jagtap et al. [42], the ethanolic extract of *C. gigantea* leaves was more anti-inflammatory than other solvent extracts. Furthermore, Gupta et al. [29] and Fritsche [32] stated that such anti-inflammatory activity was shown by linoleic acid, which blocked cyclooxygenase and lipoxygenase pathways in arachidonate metabolism. According to reports, fatty acids such as linoleic acid can help to inhibit inflammatory processes [32]. The saturated fatty acid content of *C. gigantea* can affect inflammation biomarkers such as TNF-α, IL-1, and IL-6. Lupeol ($C_{30}H_{50}O$) is a terpenoid that can inhibit inflammation and cancer formation. Lupeol has the ability to inhibit or cease inflammation and modify certain molecules, thereby contributing to inflammation either directly or indirectly [43]. Moreover, in *C. gigantea* flower extract, 4-methoxy-3-(methoxymethyl) phenol and (*E*)-N'-(5-bromo-2-methoxybenzylidene)-4-methoxy benzohydrazide also anti- inflammatory activity via edema inhibition in albino rat's feet [44]. Additionally, research indicates that decreased inflammation is comparable to the effects of diclofenac sodium (2.65 ± 0.04 cm). At 100 mg/kg and 200 mg/kg concentrations, 4-methoxy-3-(methoxy-methyl) phenol can inhibit inflammation as much as 3.45 ± 0.03 cm and 2.98 ± 0.05 cm, respectively. Meanwhile, the same concentrations of (*E*)-N'-(5-bromo-2-methoxybenzylidene)-4-methoxy benzohydrazide can inhibit inflammation up to 3.30 ± 0.02 cm and 2.73 ± 0.04 cm.

3.3. Degenerative Diseases (Tumor/Cancer)

Degenerative diseases are the result of cellular degeneration and manifest themselves as benign or malignant tumors or cancer. Tumors in the oral cavity are common (27.4%), while vascular and salivary gland tumors account for up to 23.3 % and 16.5 % of total cases, respectively. Cancer in the oral cavity comprises 30% of overall malignant head and neck tumors. Around 90% cases are squamous cell carcinoma, while 10% are rare malignancies (irregular forms of squamous cell carcinoma, minor salivary gland tumors, melanoma, lymphoma, and sarcoma) along with various odontogenic malignant tumors [45, 46]. This condition is exacerbated by poor oral hygiene, which contributes to tumors transforming into cancer [45].

Systemic treatment and targeted radiotherapy can be used to treat tumors and cancer. However, these treatments have a number of adverse effects, including cardiomyopathy, coronary artery disease, pericardial disease, valvular disease, arrhythmias, pericarditis, and secondary cancer [47]. For that reason, herbs such as *C. gigantea* can provide alternative therapies. This plant has never been studied as a possible treatment for tumor/cancer or oral degenerative disease. In fact, on the other hand, it has the potential to inhibit the tumor/cancer process. As reported by Habib [48], tumor cells were strongly inhibited/terminated by methanolic and chloroform extracts of *C. gigantea* roots. Methanolic extract showed high cytotoxic activity against HepG2 and MCF-7 cells, with average IC_{50} of 85.05 μg/ml and 92.4 μg/ml, respectively [49]. Furthermore, cardiac glycosides isolated from *C. gigantea* can also inhibit tumor/cancer cell growth. Cardiac glycosides such as calactin, calotropin, asceplin, and cymarin can affect the expression of p53 and Bcl-2 genes in breast cancer CF-7 in vitro. Tumor suppression activities on the mediated test sample more likely occurred through Bcl-2 regulation (disrupting antiapoptotic activity) than through p53 (facilitating apoptosis) [50].

Cardenolides such as 3'-epi-12β-hydroxyfroside (HyFS), 19-Nor- and 18,20-Epoxy-cardenolides from *C. gigantea* roots can inhibit cancer cell growth [51]. These terpenoids inhibit cell proliferation and autophagy in cancer patients. They can also prevent tumor and cancer cell proliferation by inducing apoptosis in tumor cells and regulating cancer cells through several signaling pathways [30]. Steroids in this plant also had inhibitory effects on cancer and tumor cell growth. Terpenoids have been suggested to stimulate signaling cells in the NF-κB pathway through different mechanisms, primarily through IκB phosphorylation, DNA binding, and p65 translocation, among others [52].

Calotropis gigantea extract induced apoptosis through the stimulation of intrinsic and extrinsic signaling pathways in A549 and NCI-H1299 lung cancer cells. In both cell lines, the *C. gigantea* extract caused cell cycle arrest. In the *C. gigantea*-treated A549 and NCI-H1299 cells, reactive oxygen species (ROS) were also produced, which can cause cell death. Cell cycle arrest was induced in p53-

dependent and independent manners in A549 (p53+/+) and NCI-H1299 (p53−/−) cells, respectively. Inactivation of cyclin D1 and cyclin A during the cell cycle boosted the sub-G1 population in A549 and NCI-H1299 cells. *C. gigantea* induced both the extrinsic and intrinsic apoptotic signaling pathways, which were mediated via death receptors, cytochrome c, and caspases, and in A549 and NCI-H1299 cells, this was followed by a decrease in PARP, a DNA damage repair protein. *C. gigantea* also caused ROS stress in A549 and NCI-H1299 cells, which resulted in cell death [53].

3.4 Candidiasis and Viral Diseases in Oral Cavity

The human oral cavity is home to a rich microbial flora including fungi and viruses. Fungi are eukaryotic microorganisms, with the Candida genus being the most important in dentistry [54]. In the oral cavity of candida that is often encountered is *C. albicans, C. glabrata*, *C. guillermondii*, *C. krusei*, *C. parapsilosis*, *C. pseudoropicalis, C. stellatoidea*, *C. tropicalis* [48, 55]. Among these, *C. albican* is the most common that can be found in the oral cavity. *C. albicans* is the fungus that causes oral candidiasis, the most common fungal infection in humans, especially in children and the elderly [56]. Oral candida can manifest in several diseases such as denture stomatitis, pseudomembranous, erythematous, angular cheilitis, median rhomboid glossitis, leukoplakia, and lichen planus [54]. In general, candidiasis can be treated with nystatin or fluconazole [54, 57]. These antifungal agents will work in a variety of ways, including by targeting specific components of the fungal plasma membrane or their biosynthetic pathways, as well as by targeting components of the fungal cell wall [58]. This ability was also observed in *C. gigantea's* antifungal activity. Parts of *C. gigantea* that are often tested as antifungal are leaves [59], flowers and endophytic fungi [60]. The mechanism of action of *C. gigantea* is by destroying the membrane [60].

In comparison to other pathogenic microbes, viruses are more difficult to detect. Viruses in the oral cavity are generally human herpes (HVH), which consists of HSV-1, HSV-2, EBV, and KSHV; others are varicella-zoster virus (VZV), human cytomegalovirus (HCMV), HHV-6, and HHV-7 [61]. Squamous cell carcinoma of the oral cavity is one of the malignant manifestations of this virus [26]. In the dental practice, viruses in the oral cavity can be treated with the use of asyclovir, atazanavir, valganciclovir and valaciclovir, etc [62, 63]. This antiviral medicine is known to act by enhancing cell resistance to viruses (interferon), decreasing virus adsorption in cells or diffusion into cells (amantadine), and inhibiting nucleic acid synthesis (antimetabolites) [63]. *C. gigantea* extract is known to work by inhibiting the NF-B pathway, thereby impairing the viral immune response, as well as by inhibiting nucleic acids replication [64].

3.5 Wound Healing

Wound healing in dentistry is a critical point of study, because it is crucial in repairing damaged periodontal tissues and oral soft tissue, as well as dental extraction wounds. Wound healing properties of *C. gigantea* are found in the latex, as reported by Saratha [65]. This observed by the formation of granulation tissue and multilayered epithelium after 7-14 days of treatment. Ointment from the latex of *C. gigantea* heals wounds more effectively than standard ointment [65, 66]. These effects are associated with the presence of hydroxyproline, affecting the growth of collagen and accelerating the wound healing [65]. The high wound-healing capacity of *C. gigantea* is a result of its high antioxidant content, which stimulated the formation of fibroblast cells, improved regulation, produced collagen, and induced keratocyte migration from epithelial tissues [67]. Researchers found that the DPPH of radical scavenging activity in *C. gigantea* was as high as 37-85.17% in the leaves, and 23-33% in the roots. Flavonoids and triterpenoids also increase the rate of wound contraction and epithelial formation [66].

Rahman et al. [68] stated that flavonoids from *C. gigantea* stimulated red blood cells (erythrocytes), causing proliferation and differentiation of cysteine protease which acts as a procoagulant in blood clotting [69]. Furthermore, the crude extract of *C. gigantea* has a proteolytic effect, enabling the hydrolysis of casein and fibrinogen and contributing to blood clotting (fibrin clot) [69]. The presence of lupeol as a triterpenoid affects wound healing by reducing monocyte levels [70]. Beserra [71] described the effects of lupeol in reducing inflammation, as well as accelerating neo vasculogenic and fibroblast proliferation, compared with a control group. Lupeol is also a radical oxygen scavenger and a strong antioxidant, contributing to wound healing [71].

4. Conclusions

Calotropis gigantea contains compounds that have many therapeutic effects such as dental caries, *soft tissue inflammation (periodontitis and gingivitis), degenerative diseases (tumor/cancer), oral candidiasis and viral infection, wound healing*. With a thorough understanding of the role of the plant's properties in various aspects, it has the potential to be a high-quality medicinal herb used in the formulation of drugs used in dentistry (ethnodentistry). The high potential of this plant justifies further investigation of its ethnodentistry applications. Further research should be conducted to determine whether *C. gigantea* can be used for manufacturing drugs that are inexpensive to produce, high quality, and have few side effects.

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