A REVIEW OF BOTANY, THERAPEUTICAL VALUE, PHYTOCHEMISTRY, AND PHARMACOLOGY OF CUSSONIA PANICULATA

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INTRODUCTION
Cussonia paniculata is a small tree widely used as herbal medicine throughout its distributional range in southern Africa. This study is aimed at providing a critical review of the botany, biological activities, phytochemistry, and medicinal uses of C. paniculata. Documented information on the botany, biological activities, medicinal uses, and phytochemistry of C. paniculata was collected from several online sources which included BMC, Scopus, SciFinder, Google Scholar, Science Direct, Elsevier, PubMed, and Web of Science. Additional information on the botany, biological activities, phytochemistry, and medicinal uses of C. paniculata was gathered from pre-electronic sources such as book chapters, journals, articles, and scientific publications sourced from the University Library. This study showed that the bark, fruits, leaves, roots, and stems of C. paniculata are used as a tonic, for sore throat, colds, domestic catarrh, coughs, colds, bruises, bruises, sprains, and wounds. Phytochemical compounds identified from the leaves of C. paniculata include acetylated triterpene glycosides, unacetylated triterpene glycosides, flavonoids, steroidal saponins, and triterpenoid saponins. Pharmacological research revealed that C. paniculata extracts have analgesic, antibacterial, antitumor activities [29,33-39]. The genus Cussonia comprises about 22 species which are mainly trees or shrubs or occasionally subshrubs recorded in grasslands, woodlands, and forests of sub-Saharan Africa, the Arabian Peninsula (Yemen), and the Comoro Islands [40-46]. C. paniculata is widely used as a decorative and ornamental plant, as the species is frost-resistant and therefore recommended for mceries, bonsai, and other gardens [42,47-55]. C. paniculata is domesticated in home gardens in South Africa [56], and the thick tuberous roots are peeled and eaten raw as an emergency food, as a source of water or snack in South Africa and Swaziland [57-59]. In South Africa, research by Makunga et al. [60] showed that the flowers, leaves, and roots of C. paniculata are used in the production of essence and tinctures. Local communities in the Eastern Cape province in South Africa described C. paniculata as “rare” in the Eastern Thorn bushveld [61], an observation which has important implications for conservation and sustainable use of the species. It is against this background that this study was undertaken aimed at appraising the botany, medicinal uses, phytochemistry, and biological activities of C. paniculata.

TAXONOMY AND BOTANICAL DESCRIPTION OF C. PANICULATA
The genus name Cussonia is in honor of Pierre Cusson (1727–1783), a French botany professor at the University of Montpellier who specialized in the plant group Umbrelliferae [50,62,63]. The specific name “paniculata” refers to the paniculate or branched inflorescence which terminates the growth of the species’ branches. The English common name of C. paniculata is “mountain cabbage tree,” mainly because the species is associated with dry stony hills and the thick, often blue-green leaves resemble those of a cabbage (Brassica oleracea) [49]. The leaves of C. paniculata are gray-green or blue-green in color which is probably due to the thick waxy layers on the leaves. These waxy layers are believed to protect the leaves from severe frost in winter [49]. Two subspecies of C. paniculata are recognized subsp. paniculata and subsp. sinuata (Reynke and Kok) De Winter [64]. The subsp. paniculata is characterized by entire leaflet margins, confined to the northern Karoo, Eastern Cape, KwaZulu-Natal, Northern Cape, and Western Cape provinces of South Africa at an altitude ranging from 300 m to 2000 m above the sea level [41,64]. The subsp. sinuata is characterized by shallowly to deep lobed and waxy (sinuate) leaflet margins and widely distributed and recorded in Botswana, Lesotho, Swaziland, the Free State, Gauteng, KwaZulu-Natal, Limpopo, Mpumalanga, and North West provinces of South Africa at an altitude ranging from 900 m to 1980 m above the sea level [41,64]. However, most ethnobotanical and ethnomedicinal literature do not separate C. paniculata into specific subspecies but rather to C. paniculata sensu lato, which is the approach that has been adopted in this study. Synonyms associated with C. paniculata include C. paniculata Eckl. and Zeyh. var. paniculata and C. paniculata Eckl. and Zeyh. var. sinuata Reynke and Kok. [64]. C. paniculata is an evergreen small tree with a sturdy trunk which is sparsely branched, rarely exceeding 5 m in height [41,63,65-68]. The stem is reddish gray to gray, rough, corky, swollen at the base and roughly 3.5 cm in diameter, the branches marked with prominent leaf scars as the species usually sheds old leaves while new flush of leaves are being produced. The branches have a mop-like crown of leathery, green, frequently blue-green leaves, composed of several leaflets on short stalks springing from the same point at the end of a stout common stalk. The leaves are bi-digitate, oblong in shape, apex and base tapering, margin
sparserly to distinctly toothed. The flowers are a branched panicle of spikes which are greenish yellow in color. The fruits are fleshy, almost globose in shape, pale purplish in color, and closely clustered along the spikes. C. paniculata has been recorded in Botswana, Lesotho, South Africa, and Swaziland [41,63,66-68] in bushveld, wooded grassland, usually in rocky places at an altitude ranging from 300 m to 2000 m above the sea level [64].

MEDICINAL USES OF C. PANICULATA

The bark, fruits, leaves, roots, and stems of C. paniculata are used as herbal medicines against 32 human diseases in southern Africa (Table 1). C. paniculata is mainly used as emetic, immune booster, and herbal medicine for dysmenorrhea, intestinal parasites and worms, mental problems, boils, shingles and skin diseases, indigestion and stomach complaints, sores, and wounds (Fig. 1). In Lesotho, the leaves of C. paniculata are mixed with those of Searsia divaricata (Eckl. and Zeyh.) Moffett and Scabiosa columbaria L. as herbal medicine for menstrual problems [69].

PHYTOCHEMISTRY OF C. PANICULATA

Several researchers such as Dogoví et al. [93], Grishkovets et al. [94], Adedapo et al. [95], and Thakur et al. [76] identified acetylated triterpene glycosides, unacylated triterpene glycosides, flavonoid, steroidal saponin, and triterpenoid saponins from the leaves of C. paniculata (Table 2). Some of these phytochemical compounds may be responsible for the pharmacological properties associated with C. paniculata. For example, research by Panche et al. [96] revealed that flavonoids are associated by acetylicholinesesterase, antioxidant, steroid-genesis modulating, xanthine oxidase modulating, countering antibiotic resistance, and disease-combating activities. Research by Careaga et al. [97] and Bahrami and Franco [98] showed that acetylated triterpene glycosides have induction of caspase, antiproliferative, apoptosis, hemolytic, cytotoxicity, antitumor, antifungal, and antibacterial properties. While saponins have demonstrated anti-apoptosis, hemolytic, cytotoxicity, anticancer, antifungal, and antibacterial properties. While saponins have demonstrated anti-apoptosis, hemolytic, cytotoxicity, anticancer, antifungal, and antibacterial properties. While saponins have demonstrated anti-apoptosis, hemolytic, cytotoxicity, anticancer, antifungal, and antibacterial properties. While saponins have demonstrated anti-apoptosis, hemolytic, cytotoxicity, anticancer, antifungal, and antibacterial properties. While saponins have demonstrated anti-apoptosis, hemolytic, cytotoxicity, anticancer, antifungal, and antibacterial properties.

BIOLOGICAL ACTIVITIES OF C. PANICULATA EXTRACTS

Biological activities of C. paniculata extracts include analgesic [95], antibacterial [104], antitumor [105,106], anti-inflammatory [52,75,95], antiparasitic [52,75,104], antiviral [104], anti-inflammatory [95], and cytotoxic [104] activities.

Analgesic activities

Adedapo et al. [95] evaluated the analgesic activities of aqueous extract of the stem bark of C. paniculata using the formalin test by treating male Wistar rats with 50 mg/kg, 100 mg/kg, and 200 mg/kg of extract; 10 mg/kg of indomethacin; and 2 ml/kg of normal saline, and the licking time and frequency of the injected paw were recorded for 30 min. In the acetic acid-induced writhing model, the extract showed a good analgesic effect characterized by reduction in the number of writhes when compared to the control. The extract caused dose-dependent decrease of licking time and licking frequency in rats injected with 2.5% formalin, signifying its analgesic effect [95].

Antibacterial activities

De Villiers et al. [104] evaluated antibacterial activities of aqueous and methanol leaf extracts of C. paniculata subsp. paniculata and C. paniculata subsp. sinuata against Enterococcus faecalis, Escherichia coli, Neisseria gonorrhoeae, Staphylococcus aureus, and Pseudomonas aeruginosa using the microplate bioassay with ciprofloxacin (0.01 mg/mL) as a positive control. The extract exhibited activities with minimum inhibitory concentration values ranging from 0.3 mg/mL to 16.0 mg/mL [104].

Anticancer activities

Fouché et al. [105] evaluated anticancer activities of dichloromethane leaf extracts of C. paniculata against sixty human cancer cell lines organized into subpanels representing leukemia, melanoma and cancer of the lung, colon, kidney, ovary, and central nervous system. The extracts exhibited a moderate growth inhibition of above 50% for two or more of the cell lines (GI50) with values ranging from >0 µg/mL to 1.1 µg/mL [105]. Similarly, Fouché et al. [106] evaluated anticancer

| Medicinal use          | Plant part used        | Country             | References |
|------------------------|------------------------|---------------------|------------|
| Anemia                 | Bark                   | Lesotho             | [70]       |
| Bladder problems       | Bark                   | Lesotho             | [71-74]    |
| Breast and cervical cancer | Leaves                | Lesotho             | [69,74]    |
| Cardiovascular problems | Bark                   | Lesotho             | [70]       |
| Cleanses blood         | Bark                   | Lesotho             | [70]       |
| Colic                  | Bark                   | South Africa        | [52,75,76] |
| Dysmenorrhea           | Bark                   | South Africa        | [52,75,76] |
| Menstrual problems     | Leaves mixed with those of Searsia divaricata (Eckl. and Zeyh.) Moffett and Scabiosa columbaria L. | Lesotho | [69] |
| Emetic                 | Bark and leaves        | Lesotho and Swaziland | [57,71-74] |
| Heartburn              | Bark                   | Lesotho and Swaziland | [57,71-74] |
| Human immunodeficiency virus | Bark and leaves         | South Africa        | [78-80]    |
| Opportunistic infections | Bark and leaves       | Lesotho and Swaziland | [77-81]    |
| Immune booster         | Bark, leaves, and roots| Lesotho and South Africa | [71-74,77] |
| Intestinal ulcers      | Leaves                 | Lesotho and South Africa | [70,82,83] |
| Intestinal parasites and worms | Bark, fruits, roots, and stems | Lesotho and South Africa | [71-74] |
| Kidney problems        | Leaves                 | Lesotho             | [77]       |
| Loss of appetite       | Roots                  | South Africa        | [78,79,84-86] |
| Malaria                | Roots                  | South Africa and Swaziland | [52,57,58,75,82,87,88] |
| Mental problems        | Leaves                 | South Africa        | [52,75,76,82,87,89] |
| Nervous problems       | Leaves                 | Lesotho             | [70]       |
| Phlegm                 | Bark                   | Lesotho             | [70]       |
| Pelliagra              | Bark                   | South Africa        | [78,79]    |
| Purgative              | Leaves                 | South Africa        | [75,76,90] |
| Rheumatism and swollen limbs | Leaves               | Lesotho and South Africa | [71-74,78-81] |
| Boils, shingles, and skin diseases | Bark and leaves | Lesotho and South Africa | [71-74,77-79,84,91] |
| Indigestion and stomach complaints | Leaves and roots | South Africa | [78-80] |
| Tonic                  | Bark and leaves        | Lesotho and South Africa | [70-74,82,90,92] |
| Sores and wounds       | Bark and leaves        | Lesotho and South Africa | [70-74,82,90,92] |

Table 1: Medicinal uses of Cussonia paniculata
activities of dichloromethane: methanol (1:1) leaf extracts of *C. paniculata* against sixty human cancer cell lines organized into subpanels representing leukemia, melanoma and cancer of the lung, colon, kidney, ovary, and central nervous system. The extracts exhibited activities against leukemia RPMI-8226, colon HCT-116, and colon KM12 with total growth inhibition (TGI) values of 1.0 µg/ml, 1.5 µg/ml, and 2.7 µg/ml, respectively [106].

**Anti-inflammatory activities**

Tetyana [52] and Tetyana et al. [75] evaluated anti-inflammatory activities of bark, leaves, roots, and stems ethanolic, ethyl acetate and water extracts of *C. paniculata* using the cyclooxygenase-1 (COX-1) assay. The extracts inhibited COX in the COX-1 assay with 85.0% being the highest inhibition [52,75]. Adedapo et al. [95] evaluated the anti-inflammatory activities of aqueous extract of the stem bark of *C. paniculata* using the carrageenan-induced rat paw edema and histamine-induced rat paw edema assays with indomethacin and cyproheptadine as positive controls. The extract at 50 mg/kg, 100 mg/kg, and 200 mg/kg body weight reduced significantly, the formation of edema induced by carrageenan and histamine [95].

**Antiplasmodial activities**

Tetyana [52] and Tetyana et al. [75] evaluated antiplasmodial activities of the bark ethanolic, ethyl acetate and water extracts of *C. paniculata* against *Plasmodium falciparum* in an *in vitro* assay, a slightly modified version of the parasite lactate dehydrogenase assay with chloroquine as a positive control. The extracts exhibited weak inhibitory activities ranging from 10% to 35% at a concentration of 200 mg/ml [52,75]. De Villiers et al. [104] evaluated antiplasmodial activities of aqueous and methanol leaf extracts of *C. paniculata* subsp. paniculata and *C. paniculata* subsp. sinuata against protozoan pathogen associated with urogenital or sexually transmitted infections, *Trichomonas vaginalis* using the microplate bioassay with ciprofloxacin.

**Antiprotozoan activities**

De Villiers et al. [104] evaluated antiprotozoan activities of aqueous and methanol leaf extracts of *C. paniculata* subsp. paniculata and *C. paniculata* subsp. sinuata using the microplate bioassay with ciprofloxacin in an adapted version of the parasite lactate dehydrogenase assay with chloroquine as the test organism. The extracts exhibited moderate antiprotozoal activities with half maximal inhibitory concentration (IC$_{50}$) value of >50.0 mg/ml [104].

**Phytochemical composition**

| Phytochemical composition | References |
|---------------------------|------------|
| Acetylated triterpene glycosides | [94] |
| 3-O-acetyl-α-L-rhamnopyranosyl-(1→4)-O-β-D-glucopyranosyl-(1→6)-O-β-D-glucopyranosides of 23-hydroxybetulinic acid | [94] |
| 28-O-(α-L-arabinopyranosyl-(1→4)-O-β-D-glucopyranosyl-(1→6)-O-β-D-glucopyranosides of hederagenin | [94] |
| 3-O-acetyl-α-L-rhamnopyranosyl-(1→4)-O-β-D-glucopyranosyl-(1→6)-O-β-D-glucopyranosides of hederagenin | [94] |
| 3-O-α-L-arabinopyranosyl-28-O-(α-L-arabinopyranosyl-(1→4)-O-β-D-glucopyranosyl-(1→6)-O-β-D-glucopyranosides of oleic acid | [94] |
| 3-O-acetyl-α-L-rhamnopyranosyl-(1→4)-O-β-D-glucopyranosyl-(1→6)-O-β-D-glucopyranosides of oleic acid | [94] |
| 3-O-α-L-arabinopyranosyl-28-O-(α-L-arabinopyranosyl-(1→4)-O-β-D-glucopyranosyl-(1→6)-O-β-D-glucopyranosides of ursolic acid | [94] |
| 3-O-acetyl-α-L-rhamnopyranosyl-(1→4)-O-β-D-glucopyranosyl-(1→6)-O-β-D-glucopyranosides of ursolic acid | [94] |
| 3-O-α-L-arabinopyranosyl-28-O-(α-L-arabinopyranosyl-(1→4)-O-β-D-glucopyranosyl-(1→6)-O-β-D-glucopyranosides of hederagenin | [94] |
| 2-O-acetyl-α-L-rhamnopyranosyl-(1→4)-O-β-D-glucopyranosyl-(1→6)-O-β-D-glucopyranosides of hederagenin | [94] |
| 3-O-α-L-arabinopyranosyl-28-O-(α-L-arabinopyranosyl-(1→4)-O-β-D-glucopyranosyl-(1→6)-O-β-D-glucopyranosides of ursolic acid | [94] |
| 3-O-acetyl-α-L-rhamnopyranosyl-(1→4)-O-β-D-glucopyranosyl-(1→6)-O-β-D-glucopyranosides of oleic acid | [94] |
| Acetylated triterpene glycosides | [93] |
| 28-O-α-L-rhamnopyranosyl-(1→4)-O-β-D-glucopyranosyl-(1→6)-O-β-D-glucopyranosides of 23-hydroxyursolic acid | [94] |
| 3-O-β-D-glucopyranosides of β-sitosterol | [93] |
| 3-O-α-L-arabinopyranosides of oleic acid | [93] |
| 3-O-α-L-arabinopyranosides of ursolic acid | [93] |
| 3-O-α-L-arabinopyranosides of hederagenin | [93] |
| 3-O-β-D-glucopyranosyl-(1→2)-α-L-arabinopyranoside of oleic acid | [93] |
| 3-O-α-L-arabinopyranosyl-28-O-α-L-rhamnopyranosyl-(1→4)-O-β-D-glucopyranosyl-(1→6)-O-β-D-glucopyranosides of oleic acid | [93] |
| Flavonoid | [76] |
| Rutin | [76] |
| Steroidal saponin | [76] |
| Pseudoprostodioscin | [76] |
| Triterpenoid saponin | [76] |
| Glaucinoid B | [76] |
| Spinasaponin A | [76] |
(0.01 mg/mL) as a positive control. Only methanol extract exhibited activities with MIC value of 1.0 mg/mL and 1.3 mg/mL against C. paniculata subsp. paniculata and C. paniculata subsp. sinuata extracts, respectively, and these values were higher than 0.001 mg/mL exhibited by the control [104].

**Aβ42 protein reduction activities**

Thakur et al. [76] evaluated the Aβ42 protein reduction activities of dichloromethane: methanol (1:1) leaf and stem extracts of C. paniculata using ELISA – sAPPα, sAPPβ, and Aβ peptide assays. The extract reduced the secreted level of Aβ42 in a dose-dependent manner compared to the control by 57.5%. The extract also decreased the levels of Aβ40, sAPPβ-sw, and sAPPα in a dose-dependent manner [76].

**Cytotoxicity activities**

De Villiers et al. [104] evaluated cytotoxicity activities of aqueous and methanol leaf extracts of C. paniculata subsp. paniculata and C. paniculata subsp. sinuata against the human T-cell leukemia (Jurkat) cell line using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide colorimetric assay with (S)-(+)-camptothecin as a positive control. The extracts exhibited moderate cytotoxicity activities with IC₅₀ values ranging from 26.5 mg/mL to >5.0 mg/mL [104].

**Toxicity activities**

Adeapo et al. [95] evaluated acute toxicity activities of aqueous extract of the stem bark of C. paniculata by oral administration of graded doses of the extract of 200 mg/kg, 400 mg/kg, 800 mg/kg, 1600 mg/kg, and 3200 mg/kg body weight in Wistar male rats. All the rats were allowed free access to food and water and observed over a period of 48 h for signs of acute toxicity and deaths within this period. Acute toxicity test showed that the extract caused 80% mortality in rats, and hence, C. paniculata can be regarded as toxic [95].

**CONCLUSION**

The diverse medicinal uses of C. paniculata documented in southern Africa, and the scientific evidence of its phytochemistry and biological activities indicates its potential as herbal medicine. However, there is a need for detailed phytochemical and pharmacological studies aimed at correlating its documented ethnomedical uses with the phytochemical and pharmacological properties of the species. There is a need for clinical and toxicological evaluations since preliminary acute toxicity studies by Adeapo et al. [95] indicated that aqueous extract of the stem bark of C. paniculata contains potentially toxic compounds. Therefore, future research should focus on the identification of toxic compounds, the possible side effects caused by taking C. paniculata as herbal medicine, and mechanisms of how potential toxic components of the species can be managed when the species is used as herbal medicine.

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**AUTHORS’ CONTRIBUTIONS**

The author declares that this work was done by the author named in this article.

**CONFLICTS OF INTEREST**

The author declares that he has no conflict of interest.

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