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A review of botany, therapeutic value, phytochemistry and pharmacology of *Cussonia zimmermannii*

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Abstract

Cussonia zimmermannii is a medium-sized to a large tree widely used as herbal medicine in east Africa. This study is aimed at providing a critical review of the botany, biological activities, phytochemistry and medicinal uses of *C. zimmermannii*. Documented information on the botany, biological activities, medicinal uses and phytochemistry of *C. zimmermannii* 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. zimmermannii* was gathered from pre-electronic sources such as book chapters, books, journal articles and scientific publications sourced from the University library. This study showed that the leaves, rootbark, roots and stembark of *C. zimmermannii* are mainly used as herbal medicines for epilepsy, fever, gonorrhoea, hypertensive encephalopathy, induce labour, malaria, mental illness and postpartum haemorrhage. Pharmacological research revealed that *C. zimmermannii* crude extracts and polyacetylene compounds isolated from the species have antileishmanial, antiplasmodial, antitrypanosomal, cytotoxicity and GABAA receptor stimulation activities. Future research should focus on evaluating the toxicological properties of *C. zimmermannii* crude extracts as well as compounds isolated from the species.

Keywords: Araliaceae, *Cussonia* zimmermannii, ethnopharmacology, herbal medicine, indigenous pharmacopeia

INTRODUCTION

Cussonia zimmermannii Harms is a member of the Araliaceae or ginseng or ivy family. Ginseng is a common name for several herbaceous plants used in traditional medicine such as *Panax bipinnatifidus* Seem., *P. ginseng* C.A. Meyer, *P. japonicus* (T.Nees) C.A. Meyer, *P. notoginseng* (Burkill) F. H. Chen, *P. pseudoginseng* Wall., *P. quinquefolius* L., *P. stiphuleanatus* H.T. Tsai & K.M. Feng and *P. vietnamensis* Ha & Grushv. that are widely used as herbal medicines throughout the world.[1-4] Ivy is a common name for *Hedera* L. species grown as ornamental and house plants throughout the world.[5] Several *Hedera* species are used as herbal medicines for respiratory, skin problems and other health-related conditions.[6-10] The genus *Cussonia* Thunb. 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.[11-14] *Cussonia zimmermannii* is an important timber tree in tropical Africa,[15] with its wood used for coffins, drums, boats, carvings, furniture and light interior construction. But over the last 50 years, the ethnomedicinal applications, phytochemistry, pharmacological activities of *C. zimmermannii* and the two patents awarded to the University of Basel[16] and University of Montana[17] generated a lot of interest on the ethnopharmacology of the species. The invention filed by Simmen et al.[16] relates to the polyacetylene compounds isolated from *C. zimmermannii* that exhibited positive allosteric modulating activity of the γ-aminobutyric acid type-A ($GABA_A$) receptor which could be used as an agent for the treatment of the diseases of the central nervous system (CNS) in humans and other ailments such as anxiety and epilepsy. The invention filed by Hoody and Bolstad[17] is based on the discovery of polyacetylenes compounds identified from *C. zimmermannii* that exhibited antileishmanial, antiplasmodial and antitrypanosomal activities and these compounds could be used clinically to treat or prevent infirmary in a patient caused by protozoal such as leishmaniasis, malaria or Chagas disease. It is against this background that this study was undertaken aimed at appraising the botany, medicinal uses, phytochemistry and biological activities of *C. zimmermannii*.

Botanical description of *Cussonia zimmermannii*

The genus name *Cussonia* is in honour of Pierre Cusson (1727-1783), a French botany professor at the University Montpellier who specialized in the plant group Umbrelliferae.[18,19] The specific name "*zimmermannii*" is in honour of Philipp Wilhelm Albrecht Zimmermann (1860-1931), a German botanist who was stationed at the Coffee Culture Experiment in Amani, Tanzania.[20] *Cussonia zimmermannii* is a medium-sized to a large tree, growing up to 45 metres in height.[21] The bole is straight with a rounded crown, dense and glabrous twigs. The bark surface is grey to greenish grey in colour, fissured and scaly. The leaves are arranged spirally, clustered at ends of the branches and are digitately compound. The leaflets are sessile, elliptical to obovate in shape, cuneate at the base, acute to acuminate at the apex. The leaflet margins are toothed to entire, papery to leathery, glabrous and pinnately veined. The inflorescence is a spike-like raceme with bisexual flowers which are greenish white in colour. The fruit is an obconical to globose drupe-like berry which is greenish white in colour and seeds are ovoid-globose in shape. *Cussonia zimmermannii* has been recorded in eastern Kenya, eastern Tanzania and northern Mozambique in lowland rain-forest, lowland dry evergreen forest and woodland at an altitude ranging from sea level to 400 m above sea level.[21]

Medicinal uses of *Cussonia zimmermannii*

The leaves, rootbark, roots and stembark of *C. zimmermannii* are used as herbal medicines against 12

human diseases in Kenya and Tanzania (Table 1). *Cussonia zimmermannii* is mainly used as herbal medicine for epilepsy, fever, gonorrhoea, hypertensive encephalopathy, induce labour, malaria, mental illness and postpartum haemorrhage (Figure 1). In Tanzania, the roots of *C. zimmermannii* are mixed with those of *Deinbollia borbonica* Scheff. (family Sapindaceae) as herbal medicine for hypertensive encephalopathy, mental illness and postpartum haemorrhage.[15,16,22-24]

Table 1: Medicinal uses of *Cussonia zimmermannii*

Medicinal use	Parts used	Country	References
Dysentery	Roots	Tanzania	Choi et al.[25]
Epilepsy	Roots and stembark	Tanzania	Lemmens[15]; Simmen et al.[16]; Chhabra et al.[22]; Senn[23]; Umberto Quattrocchi[24]; Baur et al.[26]; Moshi et al.[27]; Johnson et al.[28]; Magadula and Erasto[29]; Ntie-Kang et al.[30]
Fever	Leaves	Tanzania	Lemmens[15]; Simmen et al.[16]; Senn[23]; Umberto Quattrocchi[24]; Baur et al.[26]; Magadula and Erasto[29]; Ntie-Kang et al.[30]; Kokwaro[31]; Lovett et al.[32]
Gonorrhoea	Leaves and roots	Tanzania	Lemmens[15]; Simmen et al.[16]; Senn[23]; Umberto Quattrocchi[24]; Baur et al.[26]; Kokwaro[31]; Lovett et al.[32]
Hypertensive encephalopathy	Roots mixed with those of *Deinbollia borbonica* Scheff.	Tanzania	Simmen et al.[16]; Chhabra et al.[22]; Senn[23]
Induce labour	Stembark	Tanzania	Lemmens[15]; Simmen et al.[16]; Chhabra et al.[22]; Senn[23]; Umberto Quattrocchi[24]; Baur et al.[26]; Johnson et al.[28]
Kwashiorkor	Roots	Kenya	Pakia and Cooke[33]
Magical purposes	Roots	Kenya and Tanzania	Chhabra et al.[22]; Pakia and Cooke[33]
Malaria	Leaves and roots	Tanzania	Lemmens[15]; Simmen et al.[16]; Chhabra et al.[22]; Senn[23]; Umberto Quattrocchi[24]; Magadula and Erasto[29]; Ntie-Kang et al.[30] Chhabra et al., 1987; Lovett et al.[32]
Mental illness	Roots mixed with those of *D. borbonica*	Tanzania	Lemmens[15]; Simmen et al.[16]; Chhabra et al.[22]; Senn[23]; Umberto Quattrocchi[24]
Mouthwash and to stop gum bleeding	Roots	Tanzania	Lovett et al.[32]; Gessler et al.[34]
Postpartum hemorrhage	Roots mixed with those of *D. borbonica*	Tanzania	Lemmens[15]; Simmen et al.[16]; Chhabra et al.[22]; Senn[23]; Umberto Quattrocchi[24]

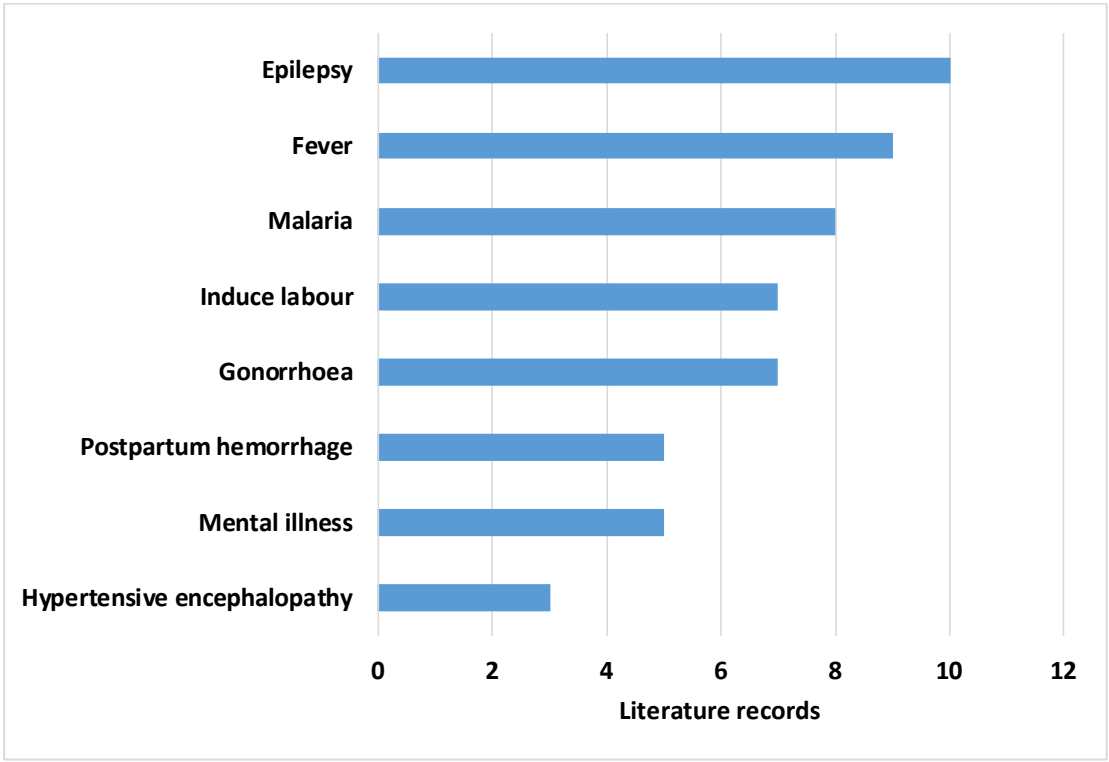
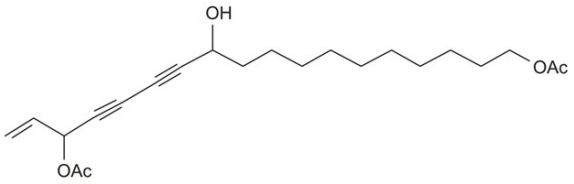


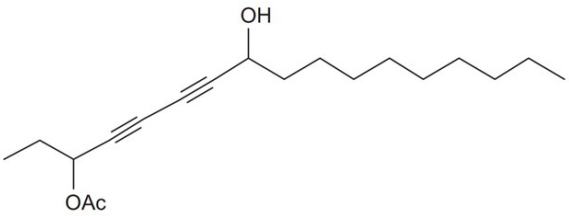
Figure 1. Medicinal applications of *Cussonia* zimmermannii derived from literature records

Phytochemistry of *Cussonia zimmermannii*

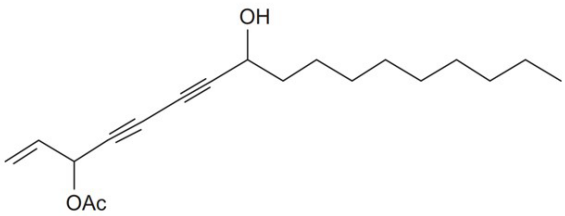
Four polyacetylene compounds and stigmasterol (Figure 2) have been identified from the rootbark of *C. zimmermannii*.[16,17,23,26,35] These polyacetylene compounds exhibited antileishmanial, antiplasmodial, antitrypanosomal, cytotoxicity and $GABA_A$ receptor stimulation activities.[23,35] These phytochemical and pharmacological reports support the traditional use of *C. zimmermannii* as herbal medicine for the diseases of the central nervous system (CNS) such epilepsy, hypertensive encephalopathy malaria and mental illness.



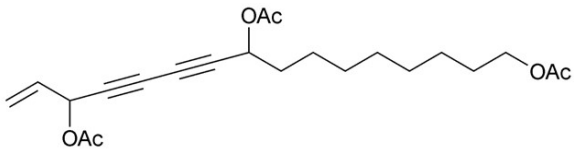
16-acetoxy-11-hydroxy octadeca-17-ene-12,14-diynyl acetate



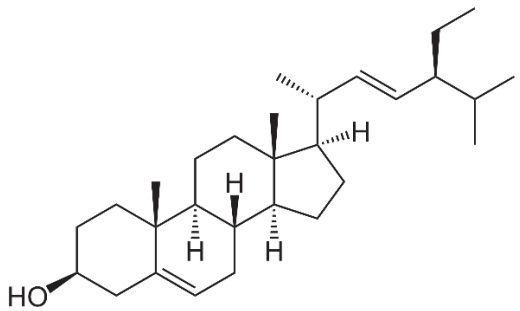
8-hydroxyheptadeca-4,6-diyn-3-yl acetate



8-hydroxyheptadeca-1-ene-4,6-diyn-3-yl acetate



11,16-diacetoxyoctadeca-17-ene-12,14-diynyl acetate



Stigmasterol

Figure 2: Chemical compounds that have been identified from the rootbark of *Cussonia zimmermannii*

Biological activities of *Cussonia zimmermannii* extracts and compounds isolated from the species

Biological activities of *C. zimmermannii* rootbark extracts and compounds isolated from the species include: antileishmanial,[23,35] antimalarial,[34] antiplasmodial,[23,35] antitrypanosomal,[23,35] cytotoxicity[23,36] and $GABA_A$ receptor stimulation[23,26] activities.

Antileishmanial activities

Senn[23] and Senn et al.[35] evaluated the antileishmanial activities of the polyacetylene compounds 8-hydroxyheptadeca-4,6-diyn-3-yl acetate, 8-hydroxyheptadeca-1-ene-4,6-diyn-3-yl acetate and 16-acetoxy-11-hydroxyoctadeca-17-ene 12,14-diynyl acetate isolated from *C. zimmermannii* using the *in vitro* sensitivity of *Leishmania donovani* amastigotes in a mouse peritoneal macrophage model with miltefosine as a positive control. All the three compounds exhibited activities with half maximal inhibitory concentration (IC_{50}) values ranging from 0.4 µg/ml to 3.0 µg/ml while the positive control exhibited IC_{50} value of 0.2 µg/ml to 0.3 µg/ml.[23,35]

Antimalarial activities

Gessler et al.[34] evaluated the antimalarial activities of crude ethanol, petroleum ether, ethyl acetate and water root bark extracts of *C. zimmermannii* using the [^{3}H] hypoxanthine incorporation assay against multidrug resistant *Plasmodium falciparum* strain K1 and the chloroquine sensitive strain NF54. The petroleum ether extract exhibited the best activity against *Plasmodium falciparum* strain K1 with IC_{50} value of 3.3 µg/ml whilst ethyl acetate and ethanol extracts exhibited IC_{50} values of 20.0 µg/ml and 90.0 µg/ml, respectively while water extracts were inactive.[34]

Antiplasmodial activities

Senn[23] evaluated the antiplasmodial activities of petroleum ether, dichloromethane, methanol and water rootbark and stembark extracts of *C. zimmermannii* using the [^{3}H] hypoxanthine incorporation assay against K1 strain of *Plasmodium falciparum* with chloroquine and artemisinin as positive controls. The petroleum ether extract of the rootbark exhibited moderate activities with IC_{50} value of 3.3 µg/ml while chloroquine and artemisinin exhibited an IC_{50} values of 0.036 µg/ml and 0.0023 µg/ml, respectively. Senn[23] and Senn et al.[35] also evaluated the antiplasmodial activities of the polyacetylene compounds 8-hydroxyheptadeca-4,6-diyn-3-yl acetate, 8-hydroxyheptadeca-1-ene-4,6-diyn-3-yl acetate and 16-acetoxy-11-hydroxyoctadeca-17-ene 12,14-diynyl acetate isolated from the species. All the three compounds exhibited activities against *Plasmodium falciparum* with IC_{50} values of 5.9 µg/ml, 0.4 µg/ml and 0.8 µg/ml for 8-hydroxyheptadeca-4,6-diyn-3-yl acetate, 8-hydroxyheptadeca-1-ene-4,6-diyn-3-yl acetate and 16-acetoxy-11-hydroxyoctadeca-17-ene 12,14-diynyl acetate.[23,35]

Antitrypanosomal activities

Senn[23] evaluated the antitrypanosomal activities of petroleum ether, dichloromethane, methanol and water

rootbark and stembark extracts of *C. zimmermannii* using the assays for *Trypanosoma brucei rhodesiense* and *Trypanosoma cruzi* which were based on the long incubation low inoculation test (LILIT) with minor modifications with melarsoprol as a positive control. The petroleum ether extract of the rootbark and stembark on *Trypanosoma brucei rhodesiense* exhibited moderate activities with IC_{50} values of 4.8 µg/ml and 8.8 µg/ml, respectively, while melarsoprol exhibited an IC_{50} value of 0.0042 µg/ml. Senn[23] and Senn et al.[35] also evaluated the antitrypanosomal activities of the polyacetylene compounds 8-hydroxyheptadeca-4,6-diyn-3-yl acetate, 8-hydroxyheptadeca-1-ene-4,6-diyn-3-yl acetate and 16-acetoxy-11-hydroxyoctadeca-17-ene 12,14-diynyl acetate isolated from the species. All the three compounds exhibited activities against *Trypanosoma brucei rhodesiense* with IC_{50} values of 5.4 µg/ml, 0.1 µg/ml and 0.4 µg/ml for 8-hydroxyheptadeca-4,6-diyn-3-yl acetate, 8-hydroxyheptadeca-1-ene-4,6-diyn-3-yl acetate and 16-acetoxy-11-hydroxyoctadeca-17-ene 12,14-diynyl acetate. All the three compounds also exhibited activities against *Trypanosoma cruzi* with IC_{50} values of 7.9 µg/ml, 0.2 µg/ml and 0.2 µg/ml for 8-hydroxyheptadeca-4,6-diyn-3-yl acetate, 8-hydroxyheptadeca-1-ene-4,6-diyn-3-yl acetate and 16-acetoxy-11-hydroxyoctadeca-17-ene 12,14-diynyl acetate while the positive control, benznidazole exhibited IC_{50} value of 0.6 µg/ml.[23,35]

Cytotoxicity activities

Gessler et al.[36] evaluated the cytotoxicity activities of petroleum ether rootbark extract of *C. zimmermannii* by determining the minimum inhibitory concentration (MIC) by comparing microscopically the cells of the extract with the cells of the control and also by using the colorimetric cytotoxicity assay using the human cell lines KB and HT 29. The MIC value was 37.0 µg/mL for both the cell lines while the MIC value for the control, chloroquine was 111 µg/mL for KB. The IC_{50} values for HT29 and KB were 6.3 µg/mL and 16.0 µg/mL, respectively, while the IC_{50} value for the control, chloroquine was 58.0 µg/mL for KB.[36] Senn[23] evaluated the cytotoxicity activities of petroleum ether, dichloromethane, methanol and water rootbark and stembark extracts of *C. zimmermannii* using an Alamar Blue assay with mefloquine as a positive control. The rootbark extract exhibited IC_{50} value of 6.9 µg/ml and selective index of 1.4 to 2.1, while the positive control exhibited IC_{50} value of 1.7 µg/ml. Senn[23] also evaluated the cytotoxicity activities of the polyacetylene compounds 8-hydroxyheptadeca-4,6-diyn-3-yl acetate, 8-hydroxyheptadeca-1-ene-4,6-diyn-3-yl acetate and 16-acetoxy-11-hydroxyoctadeca-17-ene 12,14-diynyl acetate isolated from the species. All the three compounds exhibited activities with IC_{50} values of 16.5 µg/ml, 3.6 µg/ml and 21.8 µg/ml for 8-hydroxyheptadeca-4,6-diyn-3-yl acetate, 8-hydroxyheptadeca-1-ene-4,6-diyn-3-yl acetate and 16-acetoxy-11-hydroxyoctadeca-17-ene 12,14-diynyl acetate.[23]

$GABA_A$ receptor stimulation activities

Senn[23] evaluated the $GABA_A$ receptor stimulation activities of petroleum ether, dichloromethane, methanol and water rootbark and stembark extracts of C. zimmermannii using the $GABA_A$ receptor binding assay. The petroleum ether rootbark and stembark extracts in the [^{3}H]flunitrazepam binding assay to rat cortex membranes exhibited an enhanced relative specific binding of 151% and 148%, respectively, while dichloromethane and water rootbark extracts exhibited binding of 143% and 120%, respectively which were comparable to the standard GABA compound which exhibited a relative specific binding of 124 % at a concentration of 10 µM. Senn[23] also evaluated the the $GABA_A$ receptor stimulation activities of the polyacetylene compounds 8-hydroxyheptadeca-4,6-diyn-3-yl acetate, 8-hydroxyheptadeca-1-ene-4,6-diyn-3-yl acetate and 16-acetoxy-11-hydroxyoctadeca-17-ene 12,14-diynyl acetate isolated from the species. All the three compounds exhibited enhanced relative specific binding of 100% to 158% which were comparable to the standard GABA compound which exhibited a relative specific binding of 120% at a concentration of 10 µM.[23] Baur et al.[26] showed that the half maximum stimulation by the polyacetylene compounds 8-hydroxyheptadeca-4,6-diyn-3-yl acetate, 8-hydroxyheptadeca-1-ene-4,6-diyn-3-yl acetate and 16-acetoxy-11-hydroxyoctadeca-17-ene 12,14-diynyl acetate was at 1.0 µM to 2.0 µM, and the maximum enhancement ranged from 110% to 450% depending on the subunit composition of the $GABA_A$ receptors.

CONCLUSION

Cussonia zimmermannii is a well-known medicinal plant in Kenya and Tanzania. In many cases, the different plant parts such as leaves, rootbark and stembark are used to manage and treat several human diseases. Not much data are available on *in vivo* and toxicological properties of crude and compounds isolated from the species. Therefore, there is need for further studies focusing on the toxicological and *in vivo* studies involving the crude extracts and chemical ingredients isolated from the species.

Conflict of interest

The author declares that he has no conflict of interest.

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