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REVIEW ARTICLE

Harnessing the medicinal properties of *Cussonia barteri* Seem. (*Araliaceae*) in drug development. A review

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Summary

Cussonia barteri Seem (*Araliaceae*) is a deciduous tree growing in savannah of Africa. Ethnomedicinally, it is used in Africa as an analgesic, anti-malarial, anti-inflammatory, anti-anaemic, anti-diarhoea, anti-poison, ani-pyschotic and anti-epileptic agent. This review provides a brief summary on the phytochemical screenings, ethnomedicinal and pharmacological applications of various parts of *C. barteri.* Leaves, stem bark and seed of *C. barteri* have been shown to be rich in saponins, flavonoids, phenols, sugars and alkaloids. Some of these constituents have been isolated and elucidated from *C. barteri*. Several compounds isolated from plant include triterpenes, saponins, polyenyne and quinic esters. Phytochemical constituents are also partly responsible for biological activities of *C. barteri*. Extracts and components isolated from the plant have demonstrated neuropharmacological, anti-larvicidal, anti-microbial, anti-inflammatory and antioxidant activities. Overall, the insights provided by this review reinforce the potential of *C. barteri* for drug development and create the need for further scientific probe of constituents of the plant with the aim of developing novel drug candidates.

Key words: ***Cussonia barteri, isolated compounds, phytochemical constituents, ethnomedicine***

Słowa kluczowe: ***Cussonia barteri, wyizolowane związki, składniki fitochemiczne, medycyna ludowa***

INTRODUCTION

Medicinal plants are sources of alternative therapies for many diseases both in developing and developed nations [1-3]. This increasing use of medicinal plants can be due to the availability, affordability, and traditional application of medicinal plants [4, 5]. As a consequence of this widespread usage, medicinal plants have gained relevant recognition from researchers, regulatory authorities and governments, leading to continuous, dynamic and broad-based research in order to evaluate them for efficacy,

appropriate dosage, safety and scientific approval of their ethnomedicinal usefulness [6-10]. There is a widespread scientific evidence concerning biological activity of medicinal plants and compounds isolated from these plants and this immensely contributed both to use of medicinal plants formulations in therapy and in search for new drug leading the process of drug development [11-13].

The genus *Cussonia* has been traditionally used to manage different conditions and in production of farm tools in Africa [14]. In African traditional medicine, the uses of *Cussonia* and related species have been documented and reported to possess analgesic [15], anti-malarial [16], anti-inflammatory [17], anti-anaemic [18], anti-diarrhoea [19], wound healing [20], anti-poison [21], effects against mastitis, mental disorders, sexually transmitted diseases [22] and as an anti-epileptic [16]. There are about 21–40 *Cussonia* species around African countries including Madagascar, Ghana, Senegal, Ivory Coast, Mali, Nigeria, Guinea, Liberia and Cameroon [23-25]. These species have been documented for their ethnomedicinal uses and investigations have been carried out on these plants and its isolated compounds [16, 24, 26]. Prominent among these species for distribution and ethnomedicinal uses is *C. barteri*.

CUSSONIA BARTERI

C. barteri Seem (*Araliaceae*) is a dicotyledonous, medium-sized deciduous tree, which grows up to 10-13 m in height. (fig. 1). It can be found growing in tropical and subtropical regions of Sub-Saharan Africa, Yemen and has a convoluted trunk and very compact, hard bark [26]. The plant has digitate leaves (5–8 ovate-elliptic leaflets); with small greenish-white flowers contained in clusters of narrow spikes up to 50 cm long [27]. Fruits are fleshy and turn purple to white on maturation [28]. Seasonal variations affect the shape of the plant especially in dry season where it undergoes complete defoliation. The defoliated tree resembles a 'cut off limb', earning it the name 'stump of an amputated limb' in Mali and Volta, 'leper's hand' in Hausa, Northern Nigeria [29]. The plant is also known as 'Ako-sigo' in Yoruba, 'Tuwongiwa' in Hausa, 'Bolo Koro' in Senegal and 'Kokobidua' in Ghana [30]. The seeds are also called 'jansa' seeds (Cameroun), 'Ugbaokwe' (Igbo), 'Takandagiwa' (Hausa), 'Bumarlahi' (Fulani) and 'Shigo' (Yoruba) in Nigeria [31]. The leaves, stem and root of *C. barteri* have been used in different African cultures in a variety of ailments.

Bearing in mind the promise *C. barteri* holds for drug development, the need to provide a literature update guide that will incite and guide further research on the plant, with the aim of developing novel medicines, has become imperative. Thus, this review focuses on the ethnomedicinal, phytochemical and pharmacological properties of *C. barteri.*

ETHNOMEDICINAL USES

C. barteri has found different applications in ethnomedicine. The plant and its macerated stem bark are used as a purgative, an aphrodisiac and as external lotion in Mali [32]. The seeds are used as additive in soup because of its pleasant aroma and sweet taste [31]. In Nigeria and Ghana, decoctions of the root and stem bark are used for menorrhagia, rheumatism, as an emetic, as a purgative agent, poison antidote and occasionally in cases of epilepsy [33, 34]. Decoction of the root bark is used for gonococci infections in Cameroun and Tanganyika [35, 36]. The powdered stem bark is applied to leprous sores, boiled leaves are used for conjunctivitis, while the young plants are used for diarrhea in Ivory Coast and Volta [36, 37]. The fresh twigs are used to perform magical rites for oedema, paralysis and sleeping disorders [20].

Figure 1.
Cussonia barteri in its natural habitat

PHYTOCHEMISTRY

Phytochemical constituents of various parts of the plant have been clarified by various studies (tab. 1). Early reports on the phytochemistry showed that the plant possessed constituents like oleanolic acid, sugars

Table 1.

Isolated compounds from *Cussonia barteri*

Compound	Type	Plant part	References
1-O-Chlorogenoylchlorgenic acid	Quinic ester	Leaves	[22]
1-O- Chlorogenoylneochlorogenic acid	Quinic ester	Leaves	[22]
C18-Polyacetylene, (+)-9(Z),17-octadecadiene-12,14-diyne-1,11,16-triol	Polyenyne	Leaves	[43]
Cussonosides A and Cussonosides B	Triterpenes saponins	Stem bark	[23]

(glucose, L-rhamnose, L-arabinose and o-xylose) and hederagenin as aglucones [38]. The ethanol extract of leaves contains flavonoids, saponins, steroids, tannins, glycosides and carbohydrates [39]. Preliminary screening of n-hexane extract of seeds and seed marc reported the presence of flavonoids, tannins, and glycosides and alkaloids. Quantitative phytochemical screening using the method of Harbone (1992) [40] was carried out on the powdered seed, the results revealed the amount of tannins (720 mg/ml), glycosides (121.4 mg/ml), saponins (4.4%), alkaloids (2.4 %) and flavonoids (2.6%). The seed was reported to contain oil (27.8% yield) with a composition of stearic acid (1.3%), linolenic acid and myristic acid (1%) [31]. Nwokonkwo' (2013) study [31] demonstrated that seed oil contains high iodine (119.5%) content and low acid values (1.4%) and stated the seed oil's comparative advantage over commercially available oils. Low amounts of glycosides, phenols, triterpenes, sterols, saponins, alkaloids, flavonoids, tannins have been reported to be present in the methanol, hydromethanol, aqueous and hydrolysed (1.2 N HCl/methanol) extracts of stem bark [41]. The hydrolysed extract was found to contain high amounts of glycosides, phenols, triterpenes, sterols, saponins, alkaloids, flavonoids and tannins constituents [41]. *C. barteri* contains constituents called polyacetylenes that have been documented to be highly toxic towards fungi, bacteria, and mammalian cells, and to display neurotoxic, anti-inflammatory and anti-platelet-aggregatory effects as well as for allergic skin reactions [42]. Methanol extract of leaves have been shown to possess rutin, different categories of quinic esters and saponins. Some of quinic esters and saponins have been isolated and elucidated. The isolated quinic esters include 1'-O-chlorogenoylchlorogenic acid and 1'-O-chlorogenoylneochlorogenic acid (fig. 2) while the isolated triterpene saponins from the methanol stem bark extract include cussonosides A and B (fig. 3) [22, 23]. The compound, C18-polyacetylene, (+)-9(Z),17-octadecadiene-12,14-diyne-1,11,16-triol (fig. 4), has been isolated from ethyl acetate extract of *C. barteri* leaves [43].

SOME ISOLATED COMPOUNDS AND THEIR BIOLOGICAL ACTIVITIES

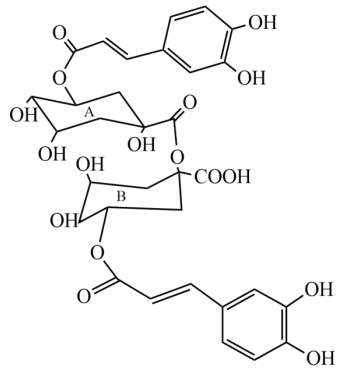
The methanol leaf extract of *C. barteri* accounts for some of its isolated compounds. The isolated quinic esters includes 1-O-chlorogenoylchlorgenic acid, 1-O- chlorogenoylneochlorogenic acid and rutin (fig. 2). The structures of these isolates were determined using 1H- and 13C-NMR spectra [22]. Papajewski *et al.* [22] evaluated the isolated quinic esters, saponins and rutin for anti-inflammatory activity by testing against 5-lipoxygenase and cyclooxygenase-1 inhibition and for antibacterial, antifungal and haemolytic effects; the compounds produced no effect at the studied test doses. Activity guided isolation from the ethyl acetate leaf extract has also led to the elucidation of a polyenyne; C18-polyacetylene, (+)-9(Z),17-octadecadiene-12,14-diyne-1,11,16-triol [43]. The polyenyne isolate, C18-polyacetylene (+)-9(Z), 17-octadecadiene-12,14-diyne-1,11,16-triol (fig. 4), possesses antibacterial activity against *B. subtilis* and *Pseudomonas flourescens* at 0.01 μg and 2.56 μg, respectively, antifungal activity against *Cladosporium cucumerinium* at 0.16 μg, molluscicidal effect on *Biomphalaria glabrata* and haemolytic activitiy at 0.32 μg against pig's blood [43]. Papajewski and his colleagues [43] also elucidated the compounds using nuclear magnetic resonance (NMR), mass spectrophotometry, infrared (IR), and ultraviolet (UV) spectroscopy. Triterpenes saponins (cussonosides A and cussonosides B) (fig. 3) have been isolated from stem bark. In this study [23], oral administration of 10 mg/kg crude extract and 1 mg/kg cussonoside A to male Swiss albino mice (25–30 g) was performed. Thirty minutes after the administration, the mice were monitored in an activity cage at graded time intervals. The crude extract was active at 10 mg/kg while cussonoside alone demonstrated sedative activity at a low dose of 1 mg/kg by decreasing motility in mice [44]. These effects were time-dependent and increased with time [23]. There was lack of activity against *Biomphalaria glabrata* for the crude extract and cussonoside A at 200 ppm and 50 ppm, respectively[45].

PHARMACOLOGY

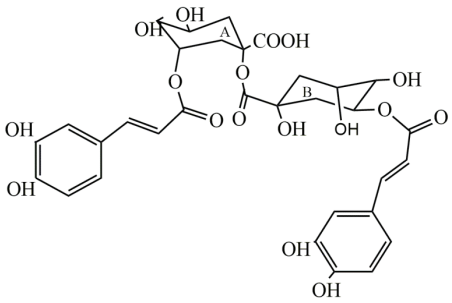
Anti-convulsant, toxicological evaluation, behavioural effects, antibacterial, molluscidal, antifungal, sedative, hemolytic effects are some of the pharmacological activities that have been investigated (tab. 2).

Toxicological evaluations

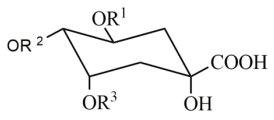
Yakubu [39] demonstrated the acute and subacute toxicities of ethanol leaf extract in Swiss albino mice and Wistar rats. Using the method of Lorke [46], Yakubu reported the LD_{50} after i.p. administration of ethanol extract to be 2154.1 mg/kg in mice; however, the extract had LD_{50} higher than 5000 mg/kg when administered orally. The extract was thus safe at oral doses but mortalities higher than 2154.1 mg/kg on intra-peritoneal administration were recorded. The repeated 28-day administration at doses of 100, 200 and 400 mg/kg of ethanol leaf extract had no significant effect (p<0.05) on the animal body weights, however, there was a significant increase in the organ weight index of the brain, liver and heart at 200 and 400 mg/kg. Haematological, biochemical, lipid parameters were not significantly different (p>0.05) from the control group after 28 days. Photomicrographs of heart showed no gross architectural abnormalities at all doses of extract. The extract had a dose-dependent effect on the histopathology of the kidney, liver and lungs, while 100 mg/kg caused no abnormalities, 200 and 400 mg/kg produced hyperplasia and congestion with hepatic and tubular necrosis [39]. USA).



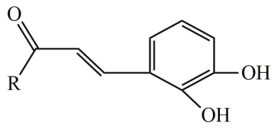
1'-O-Chlorogenoylchlorogenic



1'-O-Chlorogenoylneochlorogenic



quinic acid



5-O-Caffeoylquinic acid, chlorogenic acid

R^1	R^2	R^3
H	H	Caf

3-O-Caffeoylquinic acid, neochlorogenic acid

Caf	H	caf

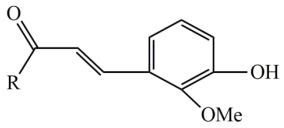
3,5-Dicaffeoylquinic acid

Caf	Caf	H

4,5-Dicaffeoylquinic acid

Caf	H	Fer

3-O-Feruloyl-5-O-caffeoylquinic acid



5-O-Feruloylquinic acid

Figure 2.

Isolated quinic acid esters from the leaves of *C. barteri.*

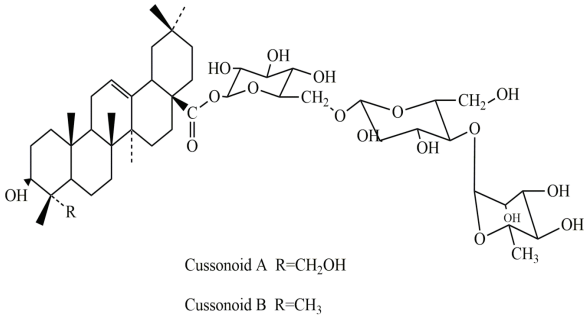


Figure 3.
Isolated triterpene saponins (Cussonoid A and B) from the stem bark of *Cussonia barteri*

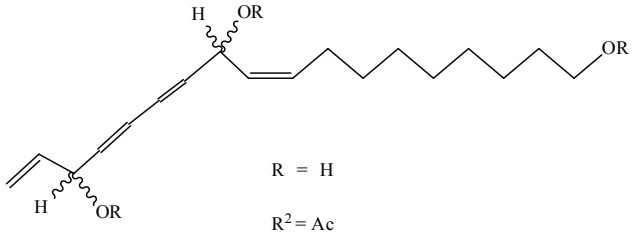


Figure 4.
Isolated polyenyne from the leaves of *Cussonia barteri*

Table 2.
Pharmacological activity of extracts and isolated compounds from *Cussonia barteri*

Type of extract	Pharmacological activity	References
Methanol and ethylacetate extract of leaves	Bacteriostatic against *Bacillus subtilis* and *Pseudomonas fluorescens*	[22, 74]
Ethanol leaf extract	Anti-convulsant activity against PTZ and strychnine induced convulsions	[49, 51]
Ethanol extract of the leaves	Sedative effect	[56, 60]
Dichlomethane, methanol, aqueous and hydromethanol root extract	Larvicidal activity against the larvae of *Aedes aegypti, Anopheles gambiae* and *Culex quinquefascia*	[67]
Dichlomethane, methanol and aqueous root extract, Cussonosides A and B	Molluscidal effect against *Biomphalaria pfeifferi* and *Bulinus truncates* snail	[23, 32]
Dichloromethanol and methanol root extract	Anti-fungal activity against *Cladosporium cucumerinum* and *Candida albicans*	[70, 71]
Methanol leaf extract and butanol stem bark extract	Hemolytic activity	[22, 23]

Antibacterial screening

Bioautographic thin layer chromatography (TLC) assays were used to assess methanol and ethyl acetate extracts for activity against *Bacillus subtilis* and *Pseudomonas fluorescens* at experimental concentrations of 50 μg and 250 μg, respectively. The activity against *Bacillus subtilis* and *Pseudomonas fluorescens* was indicated as inhibition zones or spots at 10 and 30 μg, respectively, on the TLC plates. However, microdilution studies revealed that the results were false positive [22, 47].

Anticonvulsant studies

The ethnomedicinal use of *C. barteri* in mental disorders led to evaluation for anticonvulsant actitvity by Yakubu [39]. Mice and fifty (50) day old white cockerels were used for this study. The extract was evaluated using maximum electroshock (MES) [48], petenelenetratrazol (PTZ) [49], picrotoxin [50], strychnine [51], aminophylline [52], isoniazid induced convulsions [53]. All doses of the extract lengthened the recovery time but did not protect the chicks against MES-induced convulsions. There was 83.3% protection at 400 mg/kg in PTZ induced convulsions, while the 100 and 200 mg/kg gave 33.3% protection. The same precedence was observed in strychnine-induced seizures, where the extract produced 50% protection at highest dose, however, the 200 mg/kg gave 83.3% protection against mortality. The extract had no effect against aminophylline, isoniazid and picrotoxin-induced seizures. The extract was thus suggested to possess anticonvulsant activity in PTZ and strychnine-induced convulsions. The study concluded that the extract may not possess activity against generalized seizures and there may interaction with GABAergic transmission [54]. Flavonoids were suggested to play a role in anti-convulsant effect of the extract [55].

Neurobehavioral evaluations

Behavioral studies on the ethanol leaf extract [39] were performed using the diazepam-induced sleeping time [56], hole board test [57], mouse beam walking assay [58] and open field test [59] in experimental animals. The onset and duration of diazepam-induced sleeping time was significantly (p<0.05) increased by 200 and 400 mg/kg. The extract also significantly (p<0.05) decreased head dips at 200 and 400 mg/kg, suggesting a sedative effect and reduction in exploratory behavior [60]. In the mouse beam walking test, there was significant increase in foot slips at 400 mg/kg, but there was no significant effect on total time taken to complete the test. In the open field study, the number of rearing movements, number of total square and central square crossed and the time spent in enclosed corners were not significantly (p>0.05) affected by all doses of the extract. The study suggested the extract possessed sedative activity but lacked anxiolytic effect [61]. These sedative effects were attributed to flavonoids present in the plant. In another study by Dubois *et al.* [23], sedative effects were reported for 10 mg/kg stem bark extract and 1 mg/kg isolated cussonoids, corroborating claims by Yakubu and his colleagues [39]. Dubois *et al.* [23] posited that the sedative effect may be due to the presence of saponins.

Antioxidant study

The powdered stem bark of four medicinal plants, including *C. barter*i were extracted with water, methanol, hydroethanol and hydrolysed mixture (1.2N HCL/methanol) [41]. The antioxidant potential of each extract was assayed with 1,1-diphenyl-2-picrylhydrazyl (DPPH) [62], reducing property(FRAP) [63] and Folin-Ciocalteu methods [64]. The study revealed that the aqueous and hydroethanol extracts gave the highest antioxidant effect in all assays. All extracts of *C. barteri* showed no significant (p>0.05) DPPH free radical scavenging activity. The hydrolysed extract demonstrated high catechin mg equivalent (> 500 mg/g) in the Folin-Ciocalteu assay and a significant ferric reducing power (> 80mg/g catechin equivalent) in the FRAP assay. The study concluded that the hydrolysed extract had the highest antioxidant effect, although the antioxidant effect of *C. barteri* was not comparable to other studied plants (*H. madagascariensis* and *A. pterocarpoides*).The study predicated the high activity of the aqueous extract to hydrolysis, which resulted in the release of bound anti-oxidant substances such as phenols [65]. In another study by Diallo *et al.* [32], the dichloromethanol, methanol and ethanol root bark extracts were investigated for free radical scavenging activity using thin layer chromatography (TLC). Extracts at 100 μg were applied on silica gel 60 F254 plates. After elution in suitable solvent systems, carotene (0.5 mg/ml in $CHCl_3$) was sprayed on the plates and later exposed to UV light (254 nm). The free radical activity was measured by spraying 2,2-diphenyl-1-picrylhydrazyl (DPPH) (2 mg/ml in MeOH) on the chromatogram [66].

Active compounds were recorded as clear spots in contrast to a purple background. The methanol extract of *C. barteri* showed high antioxidant and negligible DPPH radical scavenging activity.

Antilarvicidal effects

Investigations by Diallo *et al.* [32] on the dichloromethane, methanol, aqueous and hydromethanol extracts of the root of *C. barteri* on *in-vitro* larvicidal activity revealed interesting results. Larvae of *Aedesaegypti, Anopheles gambiae* and *Culex quinquefascia* were placed in 500 mg/ml solution of *C. barteri* extracts, the larvae were monitored for mortality after 24 hours [67]. Activity was measured by 100% kill after 24 hours. All extracts of *C. barteri* were active against all three organisms; after 1 hour of exposure to the dichloromethane, respective percentage killswere 65%, 90% and 40% in *Culex, Anopheles* and *Aedes* larvae. Molluscidal studies were carried out on *Biomphalaria pfeifferi* and *Bulinus truncates* snails (respective hosts of *Schistosoma haematobium* and *Schistosoma mansoni*). The snails were placed in 400 mg/ml concentration of *C. barteri* extracts; the test was repeated five times using 150 ml of distilled water [68]. The snails were subsequently transferred from the test solutions to distilled water and mortality was demonstrated after 24 hours. Dilutions were carried out to determine the minimum concentration of kill. The dichloromethanol, methanol and aqueous extracts of *C. barteri* recorded high molluscidal activity at 100 ppm [69]. Diallo *et al.*[32] attributed the mollusical activity to the presence triterpene saponins (cussonosides A and B), isolated from *C. barteri* [23]. A separate report by Papajewski [22] showed that the methanol extract lacked molluscidal activity against *Biomphalaria glabrata*.

Antifungal studies

Thin-layer chromatography autography study [70] and agar overlay methods [71] were used to evaluate the antifungal effect. In this study by Diallo[32], 100 μg of each *C. barteri* root extract were put on aluminium-backed silica gel plates. The plates were developed with the appropriate solvent system and afterelution; the chromatograms were dried and sprayed with a conidial suspension of *Cladosporium cucumerinum*. Zones of inhibition were recorded after 3 days at normal room temperature. In the agar overlay test, prepared innoculums of *Candida albicans* in yeast in malt agar was spread over the TLC plate. The plates were incubated overnight at 30°C and then sprayed with the indicator: methylthiazolyltetrazolium chloride (MTT), clear spots against a purple-coloured background was positive for activity. Only the dichloromethanol (DCM) and methanol root extract of *C. barteri* showed activity against *Cladosporium cucumerinum* and *Candida albicans*. This contradicts reports from an earlier study by Papajewski [22] which demonstrated a lack of antifungal activity of the 50 μg and 250 μg methanol leaf extract against *Cladosporium cucumerinumin* bioautographic TLC studies [71].

Haemolytic effect

The hemolytic effect of the methanol leaf extract was evaluated using thin layer chromatography (TLC) bioautography [22]. Fresh pig blood buffered with citrate buffer was sprayed on TLC plates embedded with the methanol leaf extract of *C. barteri*; zones of agglutination were observed and recorded [22]. Agglutination zones were observed at 10 μg, signifying hemolytic activity. Hemolytic activity of the butanol stem bark extract was also reported by Dubois *et al.* [23].

RESEARCH ON *C. BARTERI*: OVERVIEW OF PAST AND OUTLOOK ON THE FUTURE

Our research revealed that roots, stem bark, seeds, leaves and young whole plant of *C. barteri* are relevant in ethnomedicinal practice in parts of Africa. Therefore, it is not surprising that the these parts of the plant have been used in pharmacological evaluation and phytochemical screening of *C. barteri*. However, it will also be worthwhile to perform the pharmacological and phytochemical screening of other aerial parts such as the flowers and fruits, especially as studies have shown that bioactive components of plants can be present in all parts [72-74]. Despite rich phytochemical components of seeds, and documented activities of the root bark, data on characterization and isolation are currently unavailable. It is therefore imperative to isolate and characterize pure compounds from extracts of parts of the plant. Similarly, bearing in mind that only pure isolated compounds are appropriate as lead compounds for drug design, it is important that the pharmacological screening aimed at developing new drug molecules from the plant shift away from crude extracts and fractions to pure isolated compounds. Some of medical conditions for which the plant is efficacious in both ethnomedicinal practice and pharmacological

evaluation in the laboratory as revealed by this review still have unmet needs in terms of treatment outcome. This makes *C. barteri* worthy of optimal exploitation in the search of better therapeutic options to address the unmet needs in the treatment of these medical conditions. Also, some preliminary neurobehavioral studies suggest that the plant has some psycho-activity [56-58]. This understanding therefore warrants a drug design approach that will minimize the central nervous system-related side-effects during drug development. Furthermore, the mortalities observed in the toxicological studies presented following intraperitoneal route of administration of extract of the plant were not observed with the oral route. This suggests that the plant extract is safer when administered through the oral route. Hence, the apparent safety of the plant parts in ethnomedicinal practice is therefore not surprising, given that the oral route is the route of administration in ethnomedicinal use of the plant. Additionally, there is a need for chronic toxicity studies of the extracts and pure isolates from the plant in order to put the toxicity profile in proper perspective, more so, as parts of the plant have been found to be effective in chronic condition such as epilepsy both in ethnomedicine and preliminary pharmacological investigations [33, 34, 49, 50]. More research efforts should also be directed at exploring it potential as a food additive given that it is used in soups due to the taste and aroma its impacts on soups. Similarly, the physico-chemical properties of the seeds should also be extensively explored with a view to developing food and pharmaceutical adjuvant from the plant [31].

CONCLUSIONS

This review highlighted evidences and overview on the state of knowledge as well as future directions on research on *C. barteri.* As a consequence, it pointed for further investigation of the potentials of *C. barteri* for drug development using constituents of the plant for possible development of lead molecules that will help find better therapeutic options for several diseases. Thus, it is our sincere hope that this review will serve as useful guide in application the medicinal properties of *C. barteri* for the purpose of drug development.

Ethical approval: The conducted research is not related to either human or animal use.

Conflict of interest: Authors declare no conflict of interest.

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