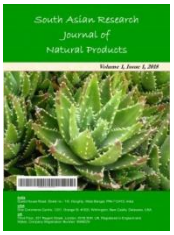

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Phytochemistry and Bioactivity of *Annona reticulata* L. (Annonaceae): A Mini-review

Koto-Te-Nyiwa Ngbolua[1,2*], Clément L. Inkoto[1], Gédéon N. Bongo[1], Lengbiye E. Moke[1], Lufuluabo G. Lufuluabo[3], Colette Masengo Ashande[2], Damien S. T. Tshibangu[3], Dorothée D. Tshilanda[3] and Pius T. Mpiana[3]

[1]Department of Biology, Faculty of Science, University of Kinshasa, P.O.Box 190 Kinshasa XI, Democratic Republic of the Congo.
[2]Department of Environmental Sciences, University of Gbadolite, P.O.Box 111 Gbadolite, Province of Nord-Ubangi, Democratic Republic of the Congo.
[3]Department of Chemistry, Faculty of Science, University of Kinshasa, P.O.Box Kinshasa XI, Democratic Republic of the Congo.

Authors' contributions

This work was carried out in collaboration between all authors. Authors KTNN and PTM designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors LGL, DDT and DSTT managed the analyses of the study. Authors CLI, GNB, LEM and CMA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To provide knowledge on phytochemistry and bioactivity of *Annona reticulata*.
Study Design: Multidisciplinary advanced bibliographic surveys, utilization of ChemBioDraw software package and dissemination of the resulted knowledge.
Place and Duration of Study: Faculty of Science, University of Kinshasa and Department of Environmental Science, University of Gbadolite, the Democratic Republic of the Congo, between October 2017 and January 2018.

**Corresponding author: Email: jpngbolua@unikin.ac.cd, ngbolua@gmail.com;*

Methodology: A literature search was conducted to obtain information about the phytochemistry and pharmacognosy of *A. reticulata* from various electronic databases (PubMed, PubMed Central, Science Direct and Google scholar). The scientific name of this plant species was used as a keyword for the search, along with the terms phytochemistry and pharmacognosy. The chemical structures of the *A. reticulata* naturally occurring compounds were drawn using ChemBioDraw Ultra 12.0 software package.
Results: Results revealed that this plant is traditionally used as stimulant or pain reliever. This plant is reported to possess various biological properties like anti-oxidant, antimicrobial, anti-inflammatory, antihelmintic, antipyretic, antihyperglycemic, analgesic, wound healing, antisickling and cytotoxic effects. These properties are due to the presence of numerous naturally occurring phytochemicals like tannins, alkaloids, phenols, glycosides, flavonoids and steroids.
Conclusion: The present review can, therefore, help inform future scientific research towards the development of novel drugs of relevance from *A. reticulata* to improve human health and wellbeing. Especially drug candidates for cancer treatment or external use like wound healing medicines.

Keywords: Annona reticulate; primary health care; phyto-constituents; pharmacognosy; model system.

1. INTRODUCTION

1.1 Background

According to the World Health Organization (WHO), 80% of the population living in developing countries relies on traditional medicine for their primary health care needs [1].

In Democratic Republic of the Congo (DRC), medicinal plants represent the key product for both urban and rural populations for their health care needs because the costs of conventional drugs are often unaffordable. These medicinal plants have found to have therapeutic value for fighting against major health problems [2-7]. *Annona reticulata* Lin. is a small tree which belongs to Annonaceae family and is considered as one of the plants traditionally used to treat various ailments such as dysentery, diabetes mellitus, heart stroke, epilepsy, parasite and worm infestations, constipation, haemorrhage, dysuria, fever, ulcer and cancer. Nearly 119 different species of the *Annona* genus (Annonaceae) are identified among which most of them are shrubs and trees. Its common name is Custard apple or Bullock's heart or Ramphal plant and it is related closely to *A. squamosa* and *A. cherimola* [8,9]. It was reported that *A. reticulata* fruits are considered as a good tonic, enrich blood, used as an expectorant, increases muscular strength, cooling, lessens burning sensation and tendency to biliousness, sedative to heart and relieves vomiting and are as well used as expectorant [8]. The bark is a powerful astringent and is used as a tonic while leaves are used as anti-helminthic medicine [10,11,12]. The bark decoction is taken as a tonic and also as a remedy for diarrhea and dysentery. The leaf decoction is given as a vermifuge while crushed leaves are used against ulcers. The unripe dried fruit is also employed to treat diarrhea and dysentery [13,14]. It possesses as well antiparasitic, insecticide, antidiarrheic and antidysenteric properties but also the anti-hyperglycemic, analgesic, cytotoxic, anti-profilatory and CNS depressant activities were reported.

The present review aims to give updated information on the phytochemistry and pharmacognosy of this useful medicinal plant species.

1.2 Botany and Geographical Distribution

A. reticulata is a small tree of about 6.0-7.5 m in height having glabrous and numerous lateral branches. Its leaves are oblong, cylindrical, and membranous and rounded at the basis. The upper surface of leaves is glabrous and the lower one is made of very few spreading hairs while the stem is cylindrical with lenticels having very short coffee colored hairs. Two to four flowers may be present on lateral pedicels and its fruits are edible, somewhat heart shaped, rough and yellow in color which change to yellowish red while ripening. Seeds are smooth and blackish in color [9,15].

A. reticulata is a plant species native to India, West Indies and tropical regions of America, widely distributed in tropical and subtropical regions [16]. Nowadays, the plant is widely cultivated and naturalized as a fruit consuming plant and deciduous tree in Africa and Asia [17-19].

Fig. 1. Plant of *Annona reticulata* [20]

2. METHODOLOGY

A literature search was conducted to obtain information about the phytochemistry and pharmacognosy of *A. reticulata* from various electronic databases (PubMed, PubMed Central, Science Direct and Google scholar). The scientific name of this plant species was used as the keyword for the search, along with the terms phytochemistry and pharmacognosy. The chemical structures of the *A. reticulata* naturally occurring compounds were drawn using ChemBioDraw Ultra 12.0 software package.

3. RESULTS AND DISCUSSION

3.1 Microscopic Features of *A. reticulata*

Microscopic study of *A. reticulata* powder revealed the presence of paracytic stomata from the lower surface of the leaves, fragment of fibers with narrow lumen, multicellular trichome filled with tannin content from the epidermal surface, microrosette crystals of calcium oxalate pitted stone cells with wide lumen and annular vessels from vascular bundle [20]. While the microscopic features of *A. senegalensis* revealed the presence of fibers, parenchyma with numerous starch grains, secretory and secreting hairs as well as fragments of punctuated vessels. It is clear that *Annona* species have particular histological characteristics, and fibers are found both species [21]. Seeing the usefulness of a species in traditional medicine, it is necessary to report on its microscopic features while carrying out the standardization for which the determination of histological elements of drugs for the elaboration of monographs has proven to be paramount for detecting falsifications [21]. Therefore, we encourage researchers to carry out micrographic analyses of other Annona species knowing that this genus has a great potential activity.

3.2 Phytochemistry

Many phyto-constituents were identified from different parts of *A. reticulata*. The leaves contain secondary metabolites like alkaloids, steroids, flavonoids, tannins, glycosides, phenolic compounds, amino acids, carbohydrates and proteins [10,20]. The stem bark contains tannins; alkaloid and phenolic compounds while the root contains acetogenin, alkaloids, flavonoids, tannins, carbohydrates and proteins. The plant was also found to be rich in minerals like Ca, P, K, Mg, Na, Cl, S, Mn, Zn, Fe, Cu, Se, Co, Ni and Cr [10]. Some phytochemicals of pharmacological relevance were characterized including kaurane and kaurene diterpenoids, isoquinoline, benzylisoquinoline, aporphine, pyrimidine-carboline alkaloids, dopamine and bioactive acetogenins [22,23].

The Table 1 gives the name of 19 biologically active compounds isolated from leaves, bark or roots of *A. reticulata*, their pharmacological action and the model system used.

The Fig. 2 gives the chemical structures of secondary metabolites isolated from *A. reticulata* L.

3.3 Bioactivity of *A. reticulata*

3.3.1 Antioxidant and antibacterial activities

Recent findings revealed that the root bark of *A. reticulata* possess the antioxidant activity in a laboratory test using DPPH free radical scavenging and H_2O_2 scavenging assays. The extract of this plant species showed an interesting inhibitory effect against *Bacillus subtilis, Escherichia coli* and *Candida blankii*. The maximum zone of inhibition against these microbial stains was obtained with n-butanol, chloroform and acetone soluble fractions. Methanol extracts and chloroform fraction displayed also potent antimicrobial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa* [28].

3.3.2 Anti-hyperglycemic activity

Rahman et al. [17] reported the antihyperglycemic effect of methanolic extract of

A. reticulata leaves using oral glucose tolerance test. This activity was dose-dependent and statistically significant. In the same line, Soumya et al. [29] reported as well the anti-hyperglycemic activity of *A. reticulata* using a rat model. The activity was strong with the extract than with Streptozocin.

3.3.3 Analgesic and Anti-inflammatory activities

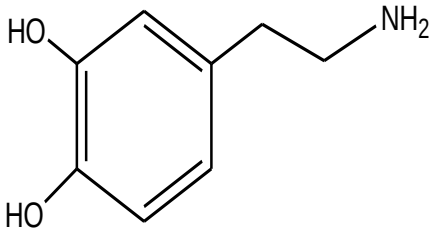
Ndiaye et al. [13] reported that the anti-inflammatory activity of the leaf extracts of *A. reticulata* is occurring by inhibition/reduction of the development of carrageenan-induced rat paw oedema. The results also revealed that the effect of the hexanolic extract was lower than the one of the aqueous extract. It was suggested that the anti-inflammatory compounds of *A. reticulata* leaves would have rather a polar character thus justifying the traditional use of the aqueous extract of this plant species to prevent the inflammation by traditional healers. Kaurenoic acid isolated from the bark of *A. reticulata* exhibited analgesic and anti-inflammatory activities. The activity of this biologically active compound was blocked by naloxone in both analgesic models [30].

3.3.4 Anthelmintic activity

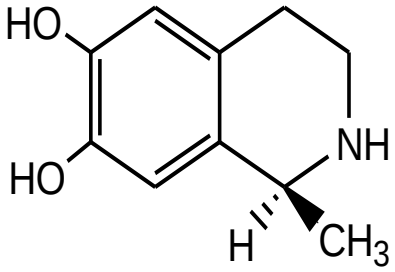
The anthelmintic activity of the leaves of *A. reticulata* was screened using earthworm *Pherentima posthuma* as model system. The total ethanolic extract was sequentially fractionated by petroleum ether, chloroform, ethyl acetate and ethanol. The ethanol fraction revealed less time to produce paralysis which indicated the ethanol fraction had more pronounced activity than other fractions [31].

Table 1. Model system used, pharmacological action and plant part of 19 biologically active compounds isolated from *A. reticulata* L

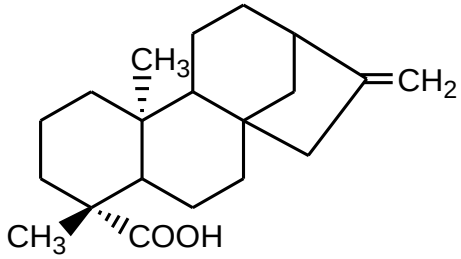
Authors	Plant parts	Biologically active compounds	Model system used	Pharmacological action
[24]	Leaves	annonaretin A kaurenoic acid 16α-hydro-19-al-ent-kauran-17-oic acid 16α-hydro-ent-kauran-17,19-dioic acid Taraxerol β-sitosterol 6β-hydroxystigmast-4-en-3-one 17-acetoxy-16β-ent-kauran-19-oic acid 24 (2S)-di-O-methylquiritigenin	RAW 264.7 cells	Inhibition of LPS-induced iNOS-dependent NO production
[25]	Bark	Rolliniastin-2 Bullatacin	Swiss albino mice	Central analgesic activity using the hot plate method
[26]	Root	Neoannonin Liriodenine Reticuline Norushinsunine	Cancer cell lines (A-549, K-562, HeLa, MDA-MB, Vero)	Antiproliferative activity
[27]	Bark	Reticulatacin Adriamycin (-)-kau-16en-19-oic acid Methyl 16a,l7-dihydro-(-)-kauran-19-oate	Human tumor cell lines (BST, A-549, MCF-7, HT-29)	Cytotoxic activity



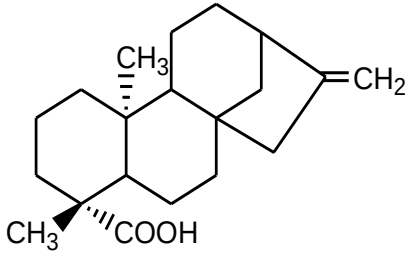
Dopamine



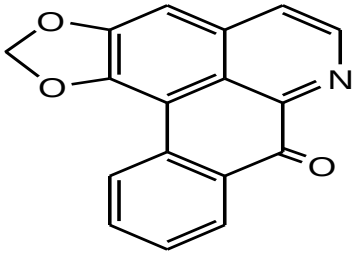
Salsolinol



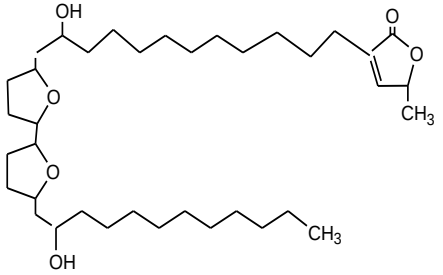
Diterpenes (e)-kau-16-en-19-oic acid



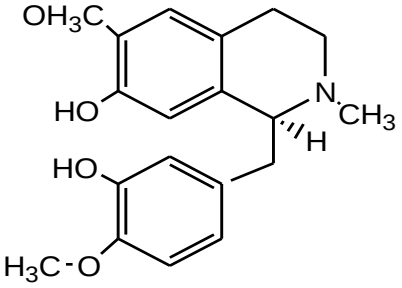
Diterpenes (e)-kau-16-en-19-oic acid



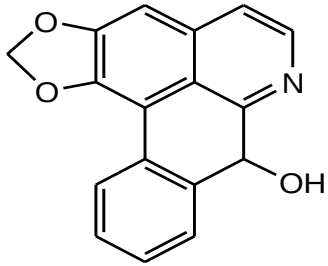
Liriodenine



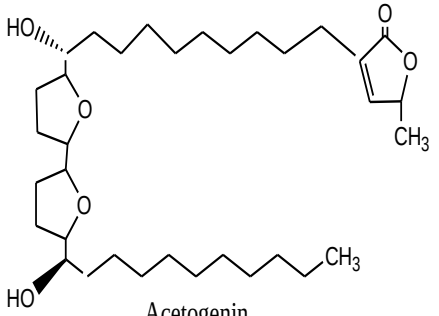
Acetogenin neoannonin



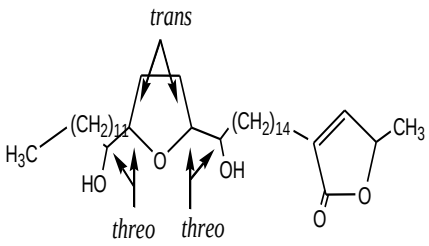
Reticuline



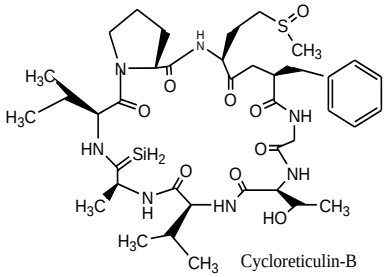
Norushinsunine



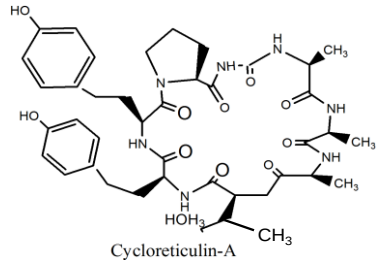
Acetogenin



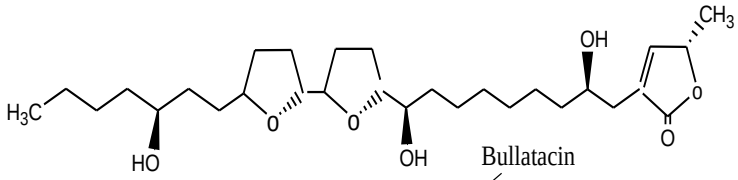
Reticulatacin



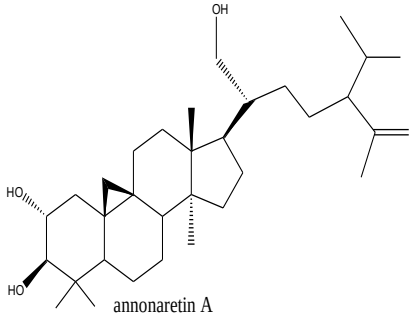
Cycloreticulin-B



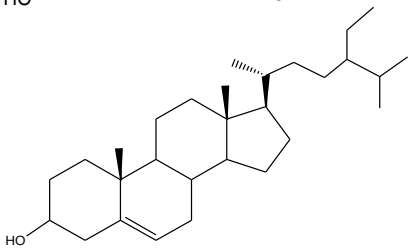
Cycloreticulin-A



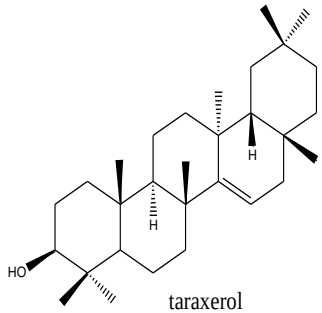
Bullatacin



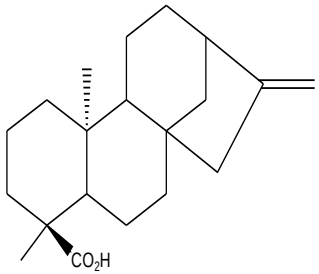
annonaretin A



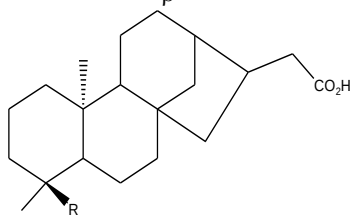
β -sitosterol



taraxerol

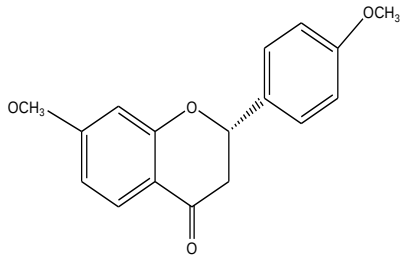


kaurenoic acid

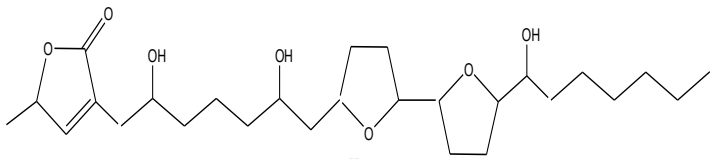


5 R = CHO 16 α -hydro-19-al-ent-kauran-17-oic acid

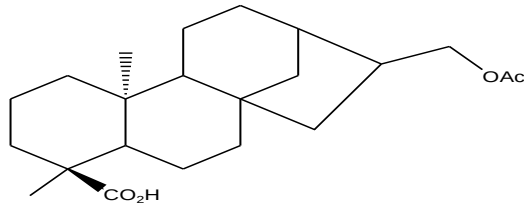
8 R = CO_2H 16 α -hydro-ent-kauran-17,19-dioic acid



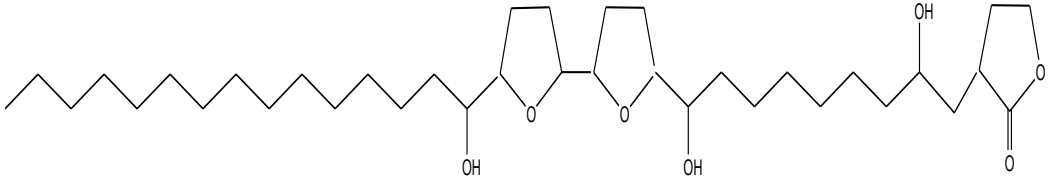
(2S)-di-O-methylquiritigenin



Bullatacin



17-acetoxy-16β -ent-kauran-19-oic acid 24



Rolliniastin -2

Fig. 2. Chemical structures of secondary metabolites of *Annona reticulata* L. [12]

3.3.5 Antipyretic activity

The crude aqueous extract of *A. reticulata* leaves was reported to have an antipyretic activity at a dose of 200 $mg.kg^{-1}$ and 400 $mg.kg^{-1}$ respectively by inhibiting hyperpyrexia induced by injecting 20% aqueous suspension of Brewer's yeast subcutaneously in rats [32].

3.3.6 Anticancer activity

Compounds like acetogenins (bullatacin, cis-/trans-isomurisolenin, cis-/trans-bullatacinone, annoreticulin, annoreticulin-9-one, cis-/trans-murisolinone and squamocin) isolated from the seed of *A. reticulata* cause cell death in various cancer cell lines by inhibiting the mitochondrial NADH-ubiquinone oxido-reductase (complex I of the respiratory chain) [33].

3.3.7 Antisickling activity

The anthocyanins extracted from the leaves of *A. reticulata* exhibited strong antisickling activity *in vitro* by inhibiting the reversal of sickle erythrocytes in hypoxic conditions created and by preventing the polymerization of hemoglobin S [34].

3.3.8 Wound healing activity

A. reticulata was reported to possess several medicinal properties including wound healing effects in Wistar Albino rat model. An Ointment containing *A. reticulata* seed extract (10 g), grape seed extract (3 g), ghee (4 g), honey (2 g) and neem oil (2 g) was formulated. The test formulation revealed faster wound closure and wound contraction in treated rats. The formulation was suggested to act by suppressing infection in wounds because of its high antibacterial compounds content like tannins, but additionally, regular dressings and changing of sugar on the wound which maintain an osmolarity that is inhibitory to bacteria [32].

3.3.9 Antiproliferative activity

The ethanol and aqueous extracts of roots of *A. reticulata* revealed *in vitro* antiproliferative effect against cancer lines like *A-549* (human lung carcinoma), *K-562* (human chronic myelogenous leukemia bone marrow), *HeLa* (human cervix) and *MDA-MB* (human adenocarcinoma mammary gland) and Vero cells (cells are one of the most common normal mammalian continuous cell lines used in research) using MTT [3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide] colorimetric assay. These results suggest that *A. reticulata* can be used as a chemo-preventive agent in cancer therapy [26].

3.3.10 Antiulcer activity

Antiulcer properties of aqueous extract of *A. reticulata* leaves were investigated using ethanol and indomethacin-induced ulcer model in rats. Ulcer was induced using 50% alcohol or indomethacin (10 $mg.kg^{-1}$). Significant dose-dependent reduction in ulcer index was observed in rats treated with extract (100 $mg.kg^{-1}$ and 200 $mg.kg^{-1}$) and reference standard drug (famotidine: 3 $mg.kg^{-1}$) [35].

3.3.11 Antiplasmodial activity

Extracts from *A. muricata* and *A. reticulata* were tested *in vitro* against *Plasmodium falciparum*. The anti-malarial activity was attributed to gallic acid (IC_{50} of 3.32 µg/mL and Selective index > 10). These results support traditional claims for *A. muricata* and *A. reticulata* in the treatment of malaria. According to the low cytotoxicity displayed, these plant species were proposed by the authors as promising starting points for anti-malarial phytochemicals discovery [36]. However, a study on the antimalarial effectiveness and safety of ethanolic crude extracts of *A. senegalensis* growing in Democratic Republic of the Congo using two malaria parasites strains (*P. falciparum FcM29 & P. yoelii subsp nigeriensis*) and their cytotoxicity towards leukaemia P-388 cell lines revealed that the antiplasmodial activities are moderate *in vitro* and weak *in vivo*. The crude extract displayed also toxic effect towards P-388 cells (weak selective index) [37].

The risk factors of using this plant species are high and require research future directions. So, the wide use of *Annona* genus in Folk Medicine could constitute a great risk of population poisoning. The observed cytotoxic effect of the leaves of plant species in this genus could be due to the presence of aporphine alkaloid. Indeed, authors [38] reported that (-)-roemerine isolated from the leaves of *A. senegalensis* enhances the cytotoxic response mediated by vinblastine in multidrug-resistant KB-V1 cells.

A recent study showed that the fruit of *A. muricata* with annonacin as a major annonaceous acetogenin (AAG) may be a potential risk factor for neurodegeneration due to

being a major source of exposure to AAGs. However, AAGs like squamocin and annonacin are reported as inhibitors of the first complex (NADH-CoQ_{10} reductase) in the mitochondrial respiratory chain and act as environmental neurotoxins responsible for human atypical Parkinsonism [39]. These phytotoxins are found in leaves, fruits and seeds of the plant species belonging to *Annona* genus [40]. Such plant genus is a good candidate for the development of anticancer drugs. Their use per os as phytomedicines could be done with moderation by traditional healers and at a low dose, especially in rural areas where the cost of conventional medicines is very high for poor population. It is also interesting to develop drugs from Annona genus for external use like wound healing medicines.

4. CONCLUSION

Medicinal plant species are rich in secondary metabolites of pharmaceutical relevance. The advantages of their therapeutic uses in various ailments are their safety besides being economical, effective and their availability. The present mini-review was undertaken with the aim of providing highlight and updated information on the medically and scientific evidence supporting the multiple uses of *A. reticulata* in Traditional Medicine.

Chemically, this plant contains a wide range of secondary metabolites as well as minerals which could be responsible for different reported therapeutic activities. Therefore, *A. reticulata* could be of considerable interest for the development of plant-based new anticancer drugs for human health and wellbeing according to it richness in annonaceous acetogenin. Plant species from Annona genus are also good drug candidates for external use like wound healing medicines.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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