Journal of Pharmacognosy and Phytochemistry

Available online at www.phytojournal.com

E-ISSN: 2278-4136
P-ISSN: 2349-8234
www.phytojournal.com
JPP 2021; 10(1): 40-51
Received: 15-11-2020
Accepted: 21-12-2020

Mahunakpon NG Gnanga
Inter-Regional University of Industrial Engineering Biotechnologies and Applied Sciences, Unité de formation en Ingénierie des Procédés de Production, Laboratoire de Pharmacologie et Toxicologie, Benin

Assogba Gabin Assanhou
Université d'Abomey Calavi, Faculté des Sciences de la Santé, Unité de formation et de recherche en Pharmacie, Laboratoire de Pharmacie Galénique et de Biopharmacie, Benin

Habib Ganfon
Université d'Abomey Calavi, Faculté des Sciences de la Santé, Unité de formation et de recherche en Pharmacie, Laboratoire de Pharmacognosie et de Phytothérapie, Benin

Engelbert J Agbokponto
Université d'Abomey Calavi, Faculté des Sciences de la Santé, Unité de formation et de recherche en Pharmacie, Laboratoire de Chimie Organique et Pharmaceutique, Benin

Fernand A Gbaguidi
Université d'Abomey Calavi, Faculté des Sciences de la Santé, Unité de formation et de recherche en Pharmacie, Laboratoire de Chimie Organique et Pharmaceutique, Benin

Virgile AHYI
Inter-Regional University of Industrial Engineering Biotechnologies and Applied Sciences, Unité de formation en Ingénierie des Procédés de Production, Laboratoire de Pharmacologie et Toxicologie, Benin

Corresponding Author:
Assogba Gabin Assanhou
Université d'Abomey Calavi, Faculté des Sciences de la Santé, Unité de formation et de recherche en Pharmacie, Laboratoire de Pharmacie Galénique et de Biopharmacie, Benin

Annona muricata L. and *Annona squamosa* L. (Annonaceae): A review of their traditional uses and anticancer activities

Mahunakpon NG Gnanga, Assogba Gabin Assanhou, Habib Ganfon, Engelbert J Agbokponto, Fernand A Gbaguidi and Virgile AHYI

DOI: https://doi.org/10.22271/phyto.2021.v10.i1a.13287

Abstract
Over the past century, research on cancer has increased due to the importance of the disease as sixth leading cause of mortality worldwide. Several medicines, methods and strategies have been used to cure the disease. However, the problematic of drug resistance faced by researchers and physicians before different cancer types remains a big challenge. Therefore, basic plant research has produced new bioactive compounds with promising prospects in this regard. Phytotherapy appears then as a potential alternative for the discovery of new drugs in the fight against cancer and its drug resistance.

Keywords: *Annona muricata L.*; *Annona squamosa L.;* bioactive compounds; anticancer activities

1. Introduction
Sixth cause of death in human population since 2016 behind infections, cancer is one of the diseases that continues to progress statistically [1]. Radiation therapy, chemotherapy and surgery remain ineffective treatments while herbal remedies become the best mean because of their less harmful side effects on non-target human cells and the biological environment [2]. Traditional African medicines have aroused growing interest as potential sources of new medicines with a wide range of biological and pharmacological activities. In a pharmaceutical context, plants with high use in ethno-medicine are a rich source of active phytoconstituents known to improve health against a wide range of diseases and infections [3]. Plants that are used in traditional medicine include *Annona muricata* and *Annona squamosa*. Belonging to the Annonaceae family, they have been widely used in Beninese traditional medicine for the treatment of cancer and tumors [4]. In this review, we describe the botany, distribution and ethnomedicinal use of these plants. Then we summarize the phytochemistry, anticancer activities and possible mechanisms of actions of *A. muricata* and *A. Squamosa* against cancer.

2. Botanical Description and Distribution
2.1 *Annona muricata* L.
Annona muricata L., commonly known as Soursop (*English*), Graviola (*Brazilian Portuguese*), Soursop (*French*), Guanábana (*Spanish*), is part of the Annonaceae family of around 130 genera and 2,300 species [5, 6]. *A. muricata* is native from the warmest tropical regions of South America and North America but is now widely dispersed in all tropical and subtropical parts of the earth, including Africa, Southeast Asia and the Caribbean [7]. Different parts of this plant are used to treat several diseases in Benin. *A. muricata* is an evergreen, terrestrial, upright tree up to 5–8 m tall and composed of a covered and rounded canopy with large, dark green silky leaves. The edible fruits of the tree are large, human heart-shaped and green in color, and the diameter varies from 15 cm to 20 cm (Figure 1) [8].

2.2 *Annona squamosa* L.
Annona squamosa L. commonly known as sugar or candy apple and English apple belongs to the Annonaceae family [9]. *A. Squamosa* is native from the tropical regions of the America and the West India. It is now the most widely cultivated of all *Annona* species grown for its fruits in the tropics and warmer subtropics, including Africa, Asia, South America, Central America and North America [10]. It is a small semi-deciduous tree 3 to 7 m high, with a wide and open crown or with irregularly spreading branches, with pale green leaves. The edible sweet fruits of the tree are round, heart-shaped and pale green in color and vary in diameter between 5 and 10 cm (Figure 2) [10].

Remember that plant stress lowers the active components of the plant. Plant stress is a condition considered to be detrimental to plant growth. Transporting the plants to the state of the goods produce many quantities of secondary metabolite, which are used as medicine.

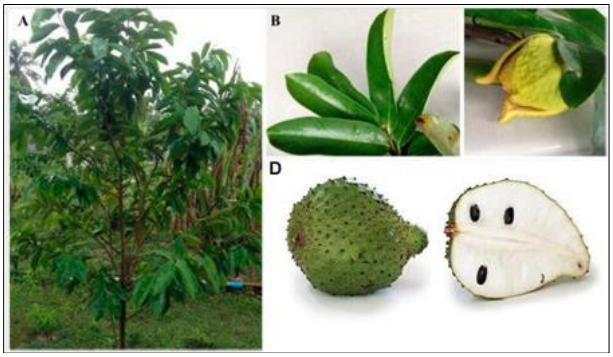


Fig 1: (A) *Annona muricata* L. tree; (B) leaves; (C) flowers and (D) fruits

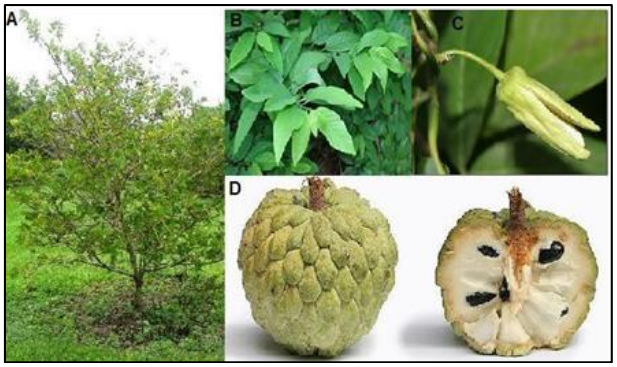


Fig 2: (A) *Annona squamosa* L. tree; (B) leaves; (C) flowers and (D) fruits

3. Ethnomedicinal Uses

All parts of the *A. muricata* and *A. Squamosa* tree are widely used as traditional remedies for a range of human ailments and illnesses, in particular cancer and parasitic infections. The fruit is used as a natural medicine against cancer, neuralgia, malaria, diarrhea, dysentery, rheumatism, fever, arthritis, parasites, dysentery, rashes and worms. It is also consumed by mothers to improve postpartum milk production. The leaves are used to treat cystitis, diabetes, headaches and insomnia. The crushed seeds are said to have anthelmintic activities against worms, external and internal parasites. The leaves of *A. Muricata* are used as ethnomedicine for tumors and cancer [4]. The anti-inflammatory, hypoglycemic, sedative, relaxant effects of smooth muscles, hypotensive and antispasmodic are also accredited on the leaves, barks and roots of *A. Muricata* [5, 7]. Aside from its ethnomedicinal use, the fruits are widely used for the preparation of drinks, candies, ice creams, shakes and syrups [12, 13].

4. Phytochemistry

Huge phytochemical assessments on different parts of the *A. muricata* plant have shown the presence of various phytoconstituents and compounds, including alkaloids (ALKs) [6, 14], megastigmanes (MGs) [15], flavonoltriglycosides (FTGs) [16], phenolics (PLs) [17],cyclopeptides (CPs) and essential oils [18, 19]. However, *Annona* species, including *A. muricata* and *A. Squamosa*, have been shown to be generally the main source of acetogenin compounds (AGEs) [20]. The presence of different major minerals such as Fe, Ca, Na, Cu, K and Mg suggest that continuous consumption of the *A. muricata* fruit can help to provide nutrients and essential elements to the human body [21].

Phytochemical research reveals that acetogenins are the main components of the Annonaceae family. Over 100 annonaceae acetogenins reported have been isolated from the leaves, bark, seeds, roots and fruits [3]. AGEs are a distinctive class of secondary metabolites C-35/C37 obtained from long chain fatty acids (C-32/C34) in the polyketide pathway. They are normally characterized by a fusion of fatty acids with a C-2 2-propanol unit which forms an α, β- unsaturated methyl-substituted γ-lactone [22]. Since the discovery of *Uvaria accuminata* uvaricin in 1982, more than 500 AGEs have been characterized in different parts of the Annonaceae plants family [23, 24]. Due to the special structures and extensive biological activities, AGEs have aroused significant scientific interest in recent years. Various biological activities have been reported for AGEs, including antimalarial, pest and pesticide activities [22, 25]. However, the biological activities of AGEs are mainly characterized by toxicity against cancer cells and inhibitory effects against the mitochondrial complex I (NADH mitochondrial: ubiquinone oxidoreductase) [26, 27]. Phytochemical examinations and biological research on various parts of the *A. muricata* plant have made it possible to identify a wide range of AGE compounds, as summarized in Table 2. The main chemical structures of the main acetogenins are illustrated in Figure 3.

5. Anticancer activities

5.1 *Annona muricata*

Several studies have reported significant antiproliferative effects of different isolated plant extracts and AGEs to various cancer cell lines [28 -30]. However, few of these studies have explained the underlying mechanism of action (Table 1).

Table 1: Anticancer studies on *A. muricata*

Plant Part	Subject of Study	Effect
Ethyl acetate extract of the leaves	lung A549 cancer cells	mitochondrial-mediated apoptosis, cell cycle arrest at Gi phase
Ethyl acetate extract of the leaves	colon HT-29 and HCT-116 cancer cells	mitochondrial-mediated apoptosis, cell cycle arrest at Gi phase, suppression of migration and invasion
Water extract of the leaves	rat's prostate	reduction of prostate size
Ethanolic extract of the leaves	breast tissues of mice	prevention of DMBA-induced DNA damage
Ethanolic extract of the leaves	DMBA/croton oil induced mice skin papillomagenesis	suppression of tumor initiation and promotion
Ethanolic extract of the leaves	DMH induced colon cancer	reduction of ACF formation
Ethanolic extract of the leaves	K562 chronic myeloid leukemia cells	induction of apoptosis
Leaves boiled in water	metastatic breast cancer	stabilization of disease
Ethyl acetate of the leaves	azoxymethane induced colon cancer	reduction of ACF formation
Ethyl acetate of the leaves	colon HT-29 cancer cells	bioassay-guided isolation of annomuricin E and its apoptosis inducing effect

Recent *in vitro* studies have been performed to determine the mechanism of action of ethyl acetate extract from *A. Muricata* leaves against colon cancer cells (HT-29 and HCT-116) and lung cancer cells (A549). The leaf extract could activate apoptosis in colon and lung cancer cells via the mitochondria-mediated pathway. This antiproliferative effect was associated with stopping the cell cycle in the G1 phase [31, 32]. In addition, the migration and invasion of cancer cells from the colon were significantly inhibited by the leaf extract. Activation of caspase 3 by the ethanolic extract of the leaves has also shown an apoptosis-inducing effect in K562 myeloid leukemia cells [30]. George VC *et al*., in 2012, also confirmed the presence of pharmacologically active antineoplastic compounds in the n-butanol leaf extract of *A. muricata* [30].

Another research focused on fractionation guided by the bioactivity of the leaves of *A. muricata L.* (Annonaceae) resulted in the isolation of two new Annonaceous acetogenins, muricoreacin (1) and murihexocin C (2). Compounds 1 and 2 showed significant cytotoxicity against six human tumor cell lines with selectivities for the prostate adenocarcinoma (PC-3) and pancreatic carcinoma (PACA-2) cell lines [33].

Rieser MJ *et al*., have shown that cis-announacin extracted from seeds of *A. Muricata* was selectively cytotoxic against colon adenocarcinoma cells (HT-29) and was 10,000 times more potent than adriamycin [34].

The components extracted from the leaves of *A. Muricata* were tested against the HeLa and PC3 cell lines. The HeLa cells treated with 75 µg of crude leaf extract of *A. Muricata* have shown 80% inhibition of cancer. *A. Muricata* has a wide range of powerful anti-cancer agents called acetogenins, which play a key role in different types of cancer. Acetogenins are powerful inhibitors of NADH oxidase from the plasma membrane of cancer cells [35].

A 2011 study demonstrated that a *A. Muricata* fruit extract significantly regulates the expression of the epidermal growth factor receptor (EGFR) gene and inhibits the growth of breast cancer cells [36]. *A. Muricata* extracts have been effective against the growth of adriamycin resistant human breast adenocarcinoma (MCF-7 / Adr) by blocking cancer cell access to ATP and inhibiting the actions of the glycoprotein in plasma membrane [37]. It also inhibited the expression of HIF-1α, NF-κB, glucose transporters and glycolytic enzymes, resulting in a decrease in glucose absorption and ATP production in pancreatic cancer cells [38].

The phenolic compounds in *A. Muricata* have also demonstrated the potential for free radical recovery from human breast carcinoma cells [30] and promyelocytic leukemia cells [39]. The muricin acetogenin isolates J, K and L have antiproliferative effects against human prostate cancer cells, with the strongest effect of muricin K [40].

In the colon and lung cancer cell lines, the ethanolic extract of graviola caused the cell cycle to be stopped in the G1 phase by upregulating the Baxand downregulating the Bcl-2 proteins [41, 42].

Recent *in vitro* and *in vivo* studies have been performed using the *A. muricata* aqueous leaves extract against the benign prostatic hyperplasia (BPH-1) and rat prostate cell line. The results demonstrated a suppressive effect on BPH-1 cells with an IC50 value of 1.36 mg / mL after 72 h with upregulation of Bax and downregulation of Bcl-2 at the mRNA level. The size of the rat's prostate was reduced after two months of treatment with a dose of 30 and 300 mg / mL ofthe extract [43]. This promising anti-tumor effect also reported an *in vivo* study on cell proliferation induced by 7,12-dimethylbenzene anthracene (DMBA) in the mammary tissues of mice. The protective effect against DNA damage induced by DMBA indicates that oral administration of the *A. muricata* leaves may have protective effects on the development of breast carcinogenesis [44].

The leaves, even at the low dose of 30 mg / kg, inhibited the initiation and promotion stage of cutaneous papilloma genesis in mice, activated respectively by DMBA and croton oil [45]. *Moghadamtousi et al*, [46] have also studied the *in vivo* chemo preventive potential of ethyl acetate extract from the *A. muricata* against foci of azoxymethane-induced colonic aberrant crypt foci (ACF) in rats. Oral distribution of the extract at two doses (250 and 500 mg / kg) for 60 days substantially reduced ACF formation in rats, as evidenced by the methylene blue staining of the colorectal samples. The authors justified the use of *A. muricata* sheets in ethnomedicine against cancer and highlighted annomuricin E as one of the compounds contributing to anticancer activity. An immunohistochemical examination showed that this activity was accompanied by an upregulation of Bax and a downregulation of Bcl-2. This significant decrease in ACF formation has also been reported for the ethanolic extract of the leaves against colon cancer triggered by 1,2-dimethylhydrazine (DMH) [47]. Another research was followed by an *in vitro* study guided by biological tests against HT-29 cells, which led to the isolation of annomuricin E. This EFA showed mitochondrial-dependent apoptosis activity against colon cancer cells with an IC50 value of 1.62 ± 0.24 µg / mL after 48 h [46].

Anti-cancer research on *A. muricata* was not only limited to *in vitro* and *in vivo* analysis. A case study of a 66-year-old woman with metastatic breast cancer found that taking boiled leaves in water and Xeloda had stabilized the disease [48].

These important anti-cancer and anti-tumor activities indicated for the *A. muricata* leaves have led to tablet formulations of the ethyl acetate-soluble parts of the leaves, which contain ACGs that can be used as adjuvant therapy for cancer [49].

5.2 *Annona squamosa*

Annona squamosa L. (Annonaceae), commonly known as an English apple, mainly used for its edible fruit, is also recognized for its many medicinal properties [9].Four new announced acetogenins (ACGs), squamocin-I (1), II (2) and III (3) and squamoxinone-D (4), as well as seven known ACGs (5-11), were isolated from the seeds from A squamosa. Compounds 1-4 were analyzed for their cytotoxicity against the human cancer cell lines Hep G2, SMMC 7721, BEL 7402, BGC 803 and H460. Compound 1 demonstrated better potency than the positivecontrol, while compound 3 showed selective cytotoxicity against H460 with an IC50 value of 0.0492 µg / ml [50].

Wang *et al*. focused on the anticancer potential of the organic and aqueous extracts of leaf of *A. Squamosa* L. The crude and ethyl acetate extracts were found to possess significant anticancer activity only against human epidermoid carcinoma KB-3-1 and colon cancer HCT-116 cell lines [2].

In a study to identify promising plant candidates against adult human T-cell leukemia / lymphoma, 245 extracts from 182 plants belonging to 61 families were tested against two T- cell lines infected with HTLV-I (MT-1 and MT- 2). Extracts from the aerial parts of A. Reticulata and *A. Squamosa* have shown the most potent inhibitory activity [51].

Another study investigated the constituents of the *A. Squamosa* and evaluated their anti-tumor activities. Eleven

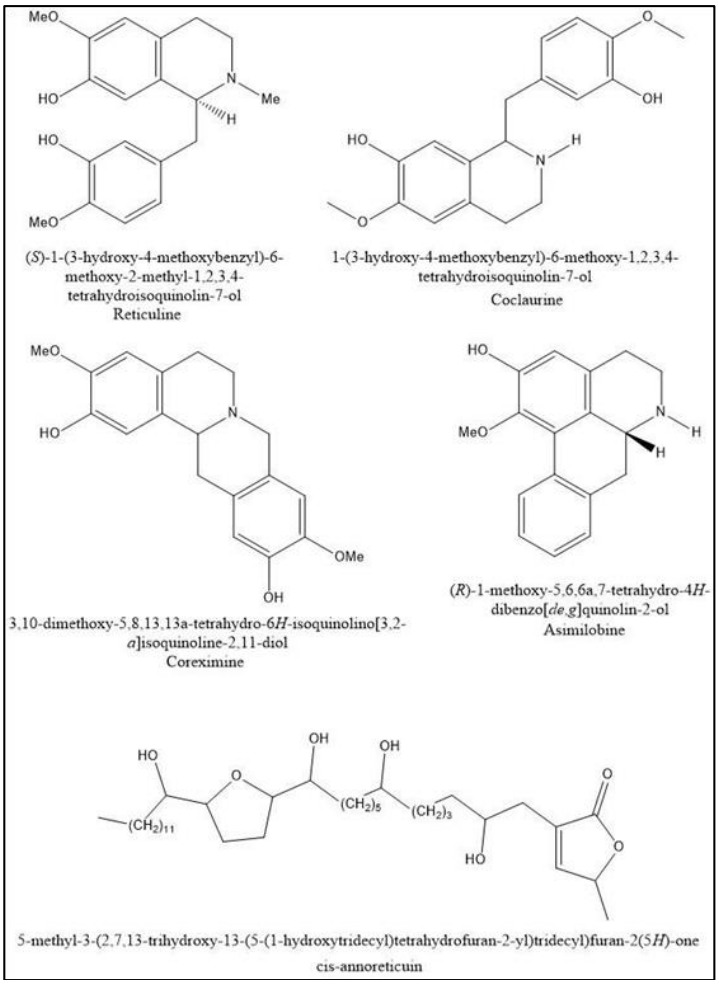
compounds were obtained from the 95% EtOH extract. The structures were determined as: annosquamosin C(1), 15, 16-epoxy-17-hydroxy-ent-kau-ran-19-oic acid (2), 16, 17-dihydroxyent-kau-ran-19-oic acid(3), annosquamosin A(4), ent-kaur-16-en-19-oic acid (5), 19-nor-ent-kauran4-ol-17-oic acid (6),16-hydroxy ent-kau ran-19-oic acid (7), ent- 15beta-hydroxy-kaur-16-en-19-oic acid (8), annosquamosin B (9), ent-16beta, 17-dihydroxykauran-19-al (10), 16, 17-dihydroxy-entkauran-19-oic acid methyl ester (11). Compounds 1,2,3,5,9 showed different inhibitory activities against 95-D lung cancer cells, but the effect of compound 5 was strongest with the IC50 value of 7.78 μM/L. Compounds 2, 5, 9 showed inhibitory activities against A2780 ovarian cancer cells. The effects of compounds 2 and 9 were strong with IC50 values of 0.89, 3.10 μM/L respectively [52].

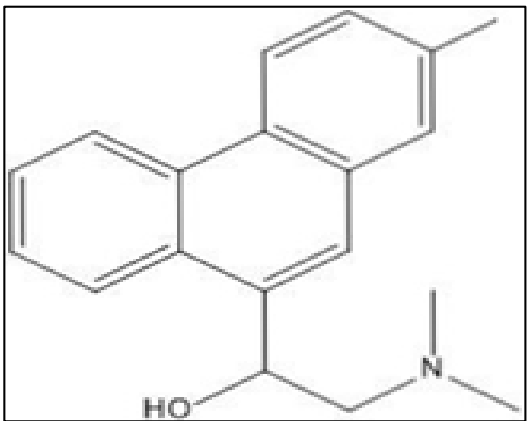
The study by Chen *et al*., demonstrated the anti-tumor activity of *A. Squamosa* seeds against human hepatoma cells *in vitro* and *in vivo*. Two major annonaceous acetogenins; 12, 15-cis-squamostatin-A and bullatacin were characterized by HPLC. The seed extract showed significant anti-tumor activity against four human tumor cell lines, notably against MCF-7 (IC500.25 μg/ml) and Hep G2 (IC50 0.36 μg/ml) cells *in vitro*. The extract inhibited the growth of H (22) tumor cells in mice with a maximum inhibitory rate of 69.55% by oral administration. These results indicate a potential for developing the extract as a novel hepatoprotective drug. In addition, an ethnopharmacological investigation revealed that the seeds of *A. Squamosa* L. have been used in southern China as a folk remedy to treat "malignant wounds" (cancer) [53]. New acetogins of the mono-tetrahydrofuran cycle, originating from the bark of *A. Squamosa*, have shown selective cytotoxic activity against the human pancreatic tumor cell line, PACA-2, with a potency 10 to 100 times greater than that of adriamycin [54].

Another study identified squamotacin from extracts of the bark of *A. Squamosa* as a new announced bioactive acetogenin with cytotoxic selectivity for the human prostate tumor cell line (PC-3) with a power of more than 100 million times that of adriamycin [55].

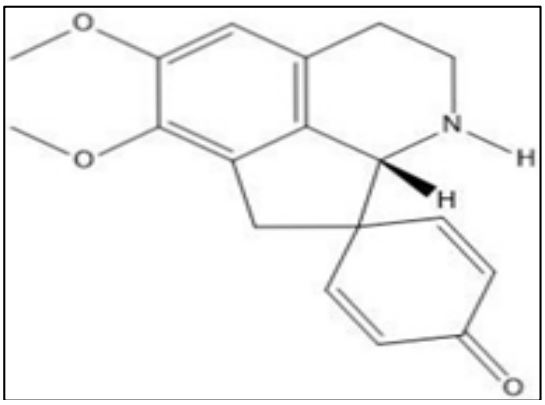
6. Toxicology

Mycotoxins are secondary fungal metabolites that can cause harmful effects in humans and animals. In 1999, research published in the Lancet Journal examined the possible relationship between the consumption of tropical fruits and the impact of atypical parkinsonism in the French West Indies [57]. Hence, AGEs are proposed as environmental neurotoxins responsible for neurodegenerative disorders, including atypical Guadeloupe parkinsonism. Research by Bonneau *et al.* have shown that the fruit of *A. muricata* with annonacin as the primary AGE may be a potential risk factor for neurodegeneration [59]. In rat striatal neurons, annonacin decreases the ATP reserve and interrupts the transport of mitochondria to the cell, which causes cellular disturbances in the tau protein and leads to a number of characteristics similar to neurodegenerative diseases [58]. It is estimated that if someone ingests a soursop fruit or its nectar daily, after one year, the total amount of annonacin consumed is sufficient to trigger brain damage in rats by intravenous infusion [60]. Globally, there are more than 300 mycotoxins [56], but none of them have been associated with the use *A. Muricata* and *A. Squamosa.* However,, the intake of products from Annonaceae species must be done with caution to avoid any neurotoxic damage.

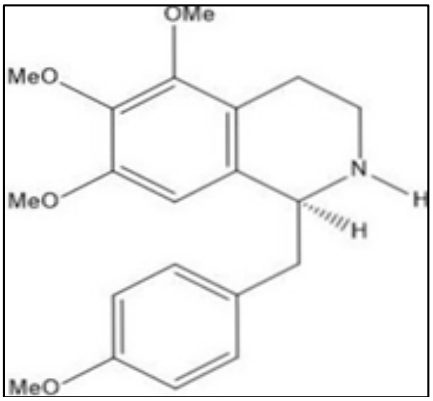


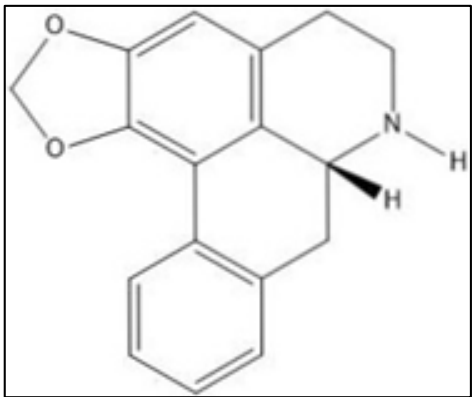


-(dimethylamino)-1-(2-methoxyphenanthren-9- yl) ethan- 1-ol Atberospamuune

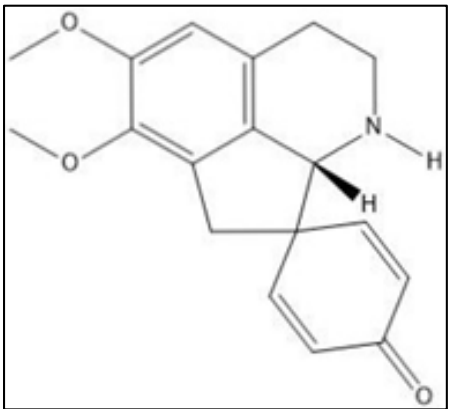


(*R*)-S'.6'-dimethoxy-2 '.3'.7'.8a'-tetrahydro-l 'H sp to[eyclohexane-1.8'-cydopenta [u1tsoqumolme] -2.5-Dien-1-one Stephanne

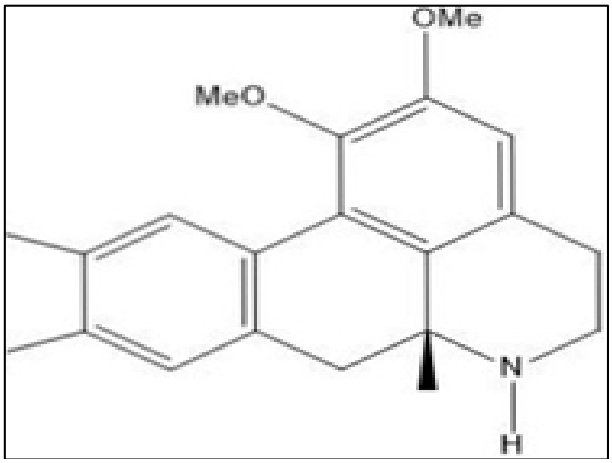




(S)-5, 6, 7-trimetboxy-1-(4-ethoxybenzyl)-1.2,3,4-tetrahydro isoquinoline Anomurine

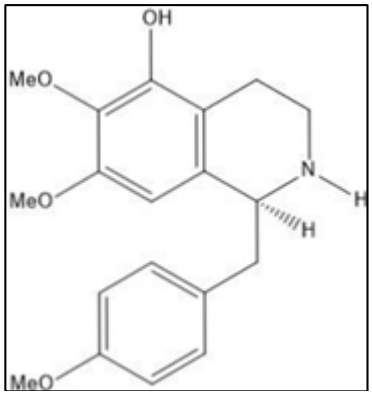


(R)-S'.6'-dimethoxy-2 '.3'.7'.8a'-tetrahydro-l 'H sp to [eyclohexane-1.8'-cydopenta[u1tsoqumolme] -2.5-Dien-1-one Stephanne

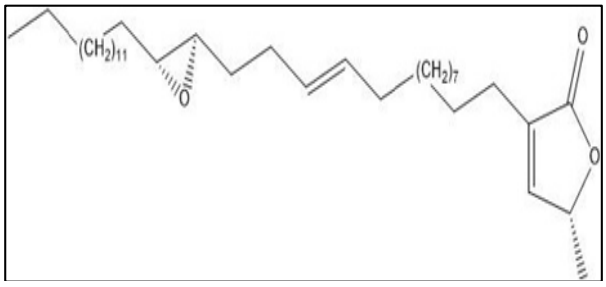


tetrahydroisoquino lin-5-ol Anomuricm e<

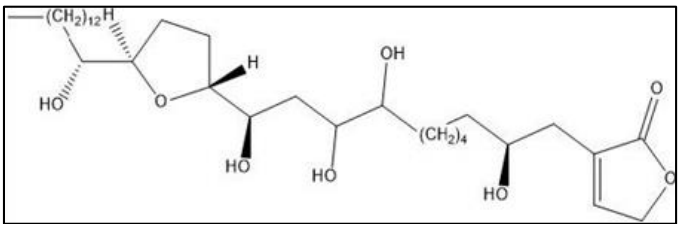
(R)-U-dimethoxy- S,6.6a.7-tetrahydro-4H- [1.3)dioxolo [4'.5':4.5] benzo [1.2-g] benzo[*de*)quinolone Nomuciferine



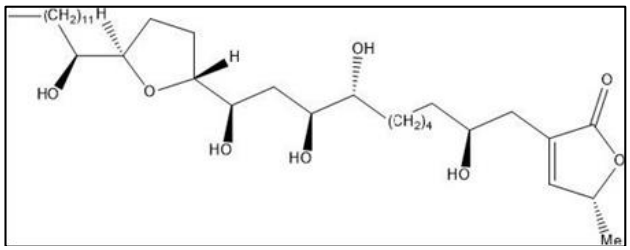
(S)-6.7-dimethoxy-1-(4 -methoxybenzy l)-1, 2, 3, 4 –



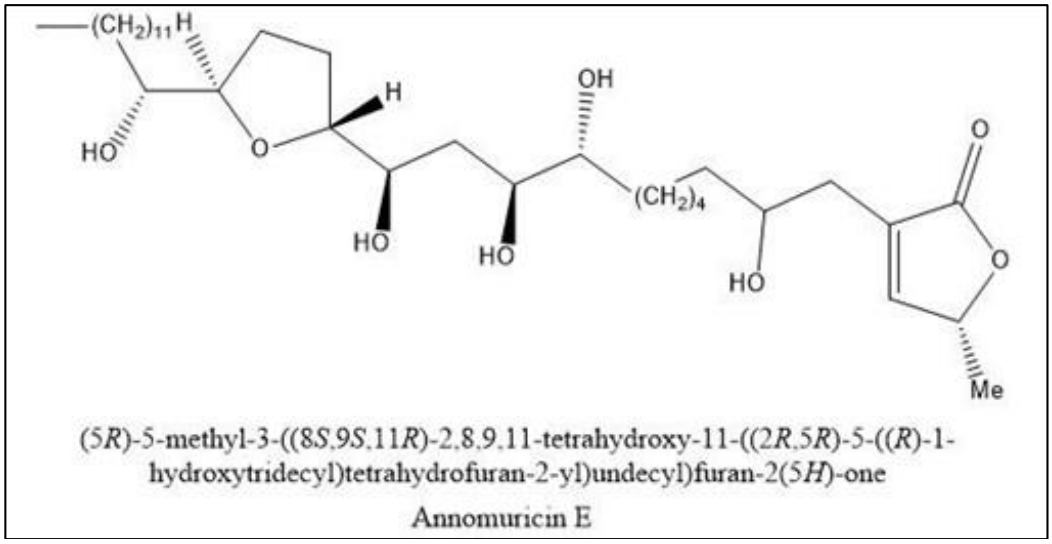
(R)-5-methyl-3· ((E)-14-((2RJR)-3-tetrad ecyloxiran-2-yl) tetJadec-11-en-l-yl) furan-2(5H) -ooe Sabadelin



(5R)-5-methyi-3-((2S.IIR)-2, 8, 9, 11-tetrahydroxy- II-((2R.5R)-5-((R)-l hydroxy tetradecyl) tetrahydrofuran-2-yl) undecyl) furan-2(5H)-one Annomuricin A

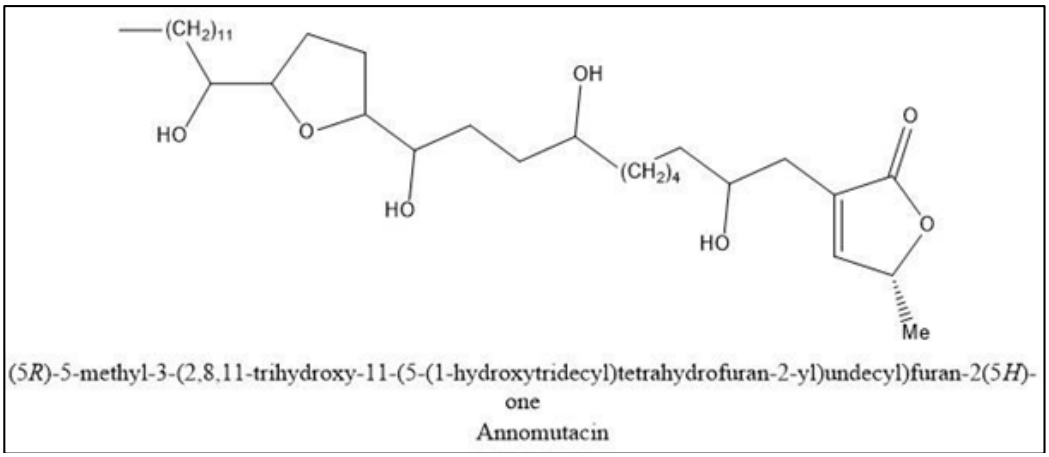


(R)-5-methyl-3-((2S.8S.9S.l lR)-2.8.9.ll-tetrahydroxy-ll-((2R .5R)-5-((S)-l hydroxytridecyl) tetrallydrofuran-2-yl) undecyl) furan-2(5H)-one



(5*R*)-5-methyl-3-((8*S*,9*S*,11*R*)-2,8,9,11-tetrahydroxy-11-((2*R*,5*R*)-5-((*R*)-1-hydroxytridecyl)tetrahydrofuran-2-yl)undecyl)furan-2(5*H*)-one

Annomuricin E



(5*R*)-5-methyl-3-(2,8,11-trihydroxy-11-(5-(1-hydroxytridecyl)tetrahydrofuran-2-yl)undecyl)furan-2(5*H*)-one

Annomutacin

Fig 3: Chemical structures of some compounds isolated from *Annona muricata* [3].

Table 2: Chemical compounds isolated from *Annona muricata*.
AGE: annonaceous acetogenin; ALK: alkaloid; CP: cyclopeptide; FTG: flavonoltriglycoside; MG: megastigmane; PL: phenolic [3]

Plant Part	Compound	Class	Biological Activity
Fruits	annonaine	ALK	anti-depressive
Fruits	nornuciferine	ALK	anti-depressive
Fruits	asimilobine	ALK	anti-depressive
Fruits	epomusenin-A	AGE	-
Fruits	epomusenin-B	AGE	-
Fruits	epomurinin-A	AGE	-
Fruits	epomurinin-B	AGE	-
Fruits	*cis*-annoreticuin	AGE	-
Fruits	muricin J	AGE	toxicity against prostate PC-3 cancer cells
Fruits	muricin K	AGE	toxicity against prostate PC-3 cancer cells
Fruits	muricin L	AGE	toxicity against prostate PC-3 cancer cells
Fruits	cinnamic acid derivative	PL	-
Fruits	coumaric acid hexose	PL	-
Fruits	5-caffeoylquinic acid	PL	-

Fruits	dihydrokaempferol-hexoside	PL	-
Fruits	*p*-coumaric acid	PL	-
Fruits	caffeic acid derivative	PL	-
Fruits	dicaffeoylquinic acid	PL	-
Fruits	feruloylglycoside	PL	-
Fruits	4-feruloyl-5-caffeoylquinic acid	PL	-
Fruits	*p*-coumaric acid methyl ester	PL	-
Leaves	annomuricin A	AGE	toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells
Pericarp	annomuricin A	AGE	toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells
Leaves	annomuricin B	AGE	toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells
Leaves	annomuricin C	AGE	toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells
Leaves	annomuricin E	AGE	toxicity against pancreatic MIA PaCa-2 and colon HT-29 cancer cells
Leaves	annomutacin	AGE	toxicity against lung A549 cancer cells
Leaves	(2,4-*cis*)-10*R*-annonacin-A-one	AGE	toxicity against lung A549 cancer cells
Leaves	(2,4-*trans*)-10*R*-annonacin-A-one	AGE	toxicity against lung A549 cancer cells
Leaves	annohexocin	AGE	toxicity against brine shrimp and different cancer cells
Leaves	muricapentocin	AGE	toxicity against pancreatic MIA PaCa-2 and colon HT-29 cancer cells
Leaves	(2,4-*cis*)-isoannonacin	AGE	-
Leaves	(2,4-*trans*)-isoannonacin	AGE	-
Seeds	(2,4-*trans*)-isoannonacin	AGE	-
Leaves	muricatocin A	AGE	toxicity against lung A549 cancer cells
Leaves	muricatocin B	AGE	toxicity against lung A549 cancer cells
Leaves	muricatocin C	AGE	toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells
Leaves	gigantetronenin	AGE	
Seeds	gigantetronenin	AGE	-
Leaves	annonacin A	AGE	-
Seeds	annonacin A	AGE	-
Pericarp	annonacin A	AGE	-
Leaves	annopentocin A	AGE	toxicity against pancreatic MIA PaCa-2 cancer cells
Leaves	annopentocin B	AGE	toxicity against lung A549 cancer cells
Leaves	annopentocin C	AGE	toxicity against lung A549 cancer cells
Leaves	*cis*-annomuricin-D-one	AGE	toxicity against lung A549, colon HT-29 and pancreatic MIA PaCa-2 cancer cells
Leaves	*trans*-annomuricin-D-one	AGE	toxicity against lung A549, colon HT-29 and pancreatic MIA PaCa-2 cancer cells
Leaves	murihexocin A	AGE	toxicity against different cancer cells
Leaves	murihexocin B	AGE	toxicity against different cancer cells
Leaves	murihexocin C	AGE	toxicity against different cancer cells
Leaves	muricoreacin	AGE	toxicity against different cancer cells
Leaves	*cis*-corossolone	AGE	toxicity against human hepatoma cells
Leaves	annocatalin	AGE	toxicity against human hepatoma cells
Leaves	annocatacin B	AGE	toxicity against human hepatoma cells
Leaves	anonaine	ALK	neurotoxic
Leaves	isolaureline	ALK	-
Leaves	xylopine	ALK	-
Leaves	quercetin 3-*O*-a-rhamnosyl-(1→6)-β-sophoroside	FTG	-
Leaves	gallic acid	FTG	-
Leaves	epicatechine	FTG	-
Leaves	quercetin 3-*O*-rutinosid	FTG	-
Leaves	quercetin 3-*O*-neohispredoside	FTG	-
Leaves	quercetin 3-*O*-robinoside	FTG	-
Leaves	catechine	FTG	-
Leaves	chlorogenic acid	FTG	-
Leaves	argentinine (1-*N*,*N*- dimethylethanyl-4,6-dimethoxy-3,8-dihydroxy-phenanthrene)	FTG	-
Leaves	kaempferol 3-*O*-rutinoside	FTG	-
Leaves	quercetin 3-*O*-glucoside	FTG	-
Leaves	quercetin	FTG	-
Leaves	kaempferol	FTG	-

Leaves	annonamine	ALK	-
Leaves	(*S*)-norcorydine	ALK	-
Leaves	(R)-4'-*O*-methylcoclaurine	ALK	-
Leaves	(*R*)-*O*,*O*-dimethylcoclaurine	ALK	-
Leaves	annoionol A	MG	-
Leaves	annoionol B	MG	-
Leaves	annoionol C	MG	-
Leaves	annoionoside	MG	-
Leaves	vomifoliol	MG	-
Leaves	roseoside	MG	-
Leaves	turpinionoside A	MG	-
Leaves	citroside A	MG	-
Leaves	blumenol C	MG	-
Leaves	(+)-epiloliolide	MG	-
Leaves	loliolide	MG	-
Leaves	(1*S*,2*S*,4*R*)-*trans*-2-hydroxy-1,8-cineole β-D-glucopyranoside	MG	-
Leaves	(*Z*)-3-hexenyl β-D-glucopyranoside	MG	-
Leaves	rutin	MG	-
Leaves	kaempferol 3-*O*-rutinoside	MG	-
Leaves	kaempferol 3-*O*-robinobioside	MG	-
Leaves	kaempferol 3-*O*-P-D-(2''-*O*-β-D-glucopyranosyl,6''-*O*-α-L-rhamnopyranosyl)glucopyranoside	MG	-
Roots	montecristin	AGE	-
Roots	cohibin A	AGE	-
Roots	cohibin B	AGE	-
Roots	*cis*-solamin	AGE	-
Roots	*cis*-panatellin	AGE	-
Roots	*cis*-uvariamicin IV	AGE	-
Roots	*cis*-uvariamicin I	AGE	-
Roots	*cis*-reticulatacin	AGE	-
Roots	*cis*-reticulatacin-10-one	AGE	-
Roots	chatenaytrienin 1	AGE	-
Roots	chatenaytrienin 2	AGE	-
Roots	chatenaytrienin 3	AGE	-
Roots	muridienin 3	AGE	-
Roots	muridienin 4	AGE	-
Roots	muricadienin	AGE	-
Roots	coronin	AGE	-
Roots, Fruits	sabadelin	AGE	-
Seeds	murisolin	AGE	-
Seeds	muricatacin	AGE	toxicity against lung A549, breast MCF7, colon HT-29 cancer cells
Seeds	annonacin	AGE	neurotoxic, molluscicidal, inhibitor of mitochondrial complex I
Leaves	annonacin	AGE	neurotoxic, molluscicidal, inhibitor of mitochondrial complex I
Pericarp	annonacin	AGE	neurotoxic, molluscicidal, inhibitor of mitochondrial complex I
Seeds	corossolone	AGE	toxicity against oral KB cancer cells and brine shrimp larva, antileishmanial
Leaves	corossolone	AGE	toxicity against oral KB cancer cells and brine shrimp larva, antileishmanial
Seeds	corossolin	AGE	toxicity against oral KB cancer cells and brine shrimp larva
Seeds	solamin	AGE	toxicity against oral KB cancer and normal kidney VERO cells
Roots	solamin	AGE	toxicity against oral KB cancer and normal kidney VERO cells
Leaves	solamin	AGE	toxicity against oral KB cancer and normal kidney VERO cells
Seeds	corepoxylone	AGE	-
Seeds	annonacin-10-one	AGE	-
Leaves	annonacin-10-one	AGE	-
Seeds	isoannonacin	AGE	molluscicidal, anticancer
Seeds	isoannonacin-10-one	AGE	-
Seeds	goniothalamicin	AGE	molluscicidal
Leaves	goniothalamicin	AGE	molluscicidal

Seeds	gigantetrocin	AGE	-
Seeds	gigantetrocin A	AGE	toxicity against colon HT-29 cancer cells
Leaves	gigantetrocin A	AGE	toxicity against colon HT-29 cancer cells
Seeds	gigantetrocin B	AGE	toxicity against colon HT-29 cancer cells
Seeds	muricatetrocin A	AGE	toxicity against colon HT-29 cancer cells
Leaves	muricatetrocin A	AGE	toxicity against colon HT-29 cancer cells
Seeds	muricatetrocin B	AGE	toxicity against colon HT-29 cancer cells
Leaves	muricatetrocin B	AGE	toxicity against colon HT-29 cancer cells
Seeds	epomuricenin A	AGE	-
Leaves	epomuricenin A	AGE	-
Seeds	epomuricenin B	AGE	-
Leaves	epomuricenin B	AGE	-
Seeds	annomuricatin A	CP	-
Seeds	annocatacin A	AGE	toxicity against human hepatoma cells
Seeds	annomuricatin C	CP	-
Seeds	*cis*-annonacin	AGE	crown gall tumor inhibition, toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells
Seeds	*cis*-annonacin-10-one	AGE	crown gall tumor inhibition, toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells
Seeds	*cis*-goniothalamicin	AGE	crown gall tumor inhibition, toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells
Seeds	arianacin	AGE	crown gall tumor inhibition, toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells
Seeds	javoricin	AGE	crown gall tumor inhibition, toxicity against brine shrimp, A549, breast MCF-7 and colon HT-29 cancer cells
Seeds	murihexol	AGE	-
Seeds	donhexocin	AGE	-
Seeds	cohibin C	AGE	-
Seeds	cohibin D	AGE	-
Seeds	muricatenol	AGE	-
Seeds	2,4-*cis*-gigantetrocinone	AGE	-
Seeds	2,4-*trans*-gigantetrocinone	AGE	-
Seeds	2,4-*trans*-isoannonacin-10-one	AGE	-
Seeds	annomontacin	AGE	-
Seeds	longifolicin	AGE	toxicity against human hepatoma cells
Seeds	muricin A	AGE	toxicity against human hepatoma cells
Seeds	muricin B	AGE	toxicity against human hepatoma cells
Seeds	muricin C	AGE	toxicity against human hepatoma cells
Seeds	muricin D	AGE	toxicity against human hepatoma cells
Seeds	muricin E	AGE	toxicity against human hepatoma cells
Seeds	muricin F	AGE	toxicity against human hepatoma cells
Seeds	muricin G	AGE	toxicity against human hepatoma cells
Seeds	muricin H	AGE	toxicity against human hepatoma cells
Seeds	muricin I	AGE	toxicity against human hepatoma cells
Seeds	*cis*-annomontacin	AGE	toxicity against human hepatoma cells
Seeds and Leaves	annonacinone	AGE	-
Seeds	xylomaticin	AGE	-
Seeds	*N*-fatty acyl tryptamines	ALK	-
Seeds	annoreticuin-9-one	AGE	-
Stem barks	epoxymurin A	AGE	-
Stem barks	epoxymurin B	AGE	-
Leaves	reticuline	ALK	-
Roots,	reticuline	ALK	-
Stems	reticuline	ALK	-
Barks	reticuline	ALK	-
Leaves	coclaurine	ALK	-
Roots,	coclaurine	ALK	-
Stems	coclaurine	ALK	-
Barks	coclaurine	ALK	-
Leaves	coreximine	ALK	-
Roots,	coreximine	ALK	-
Stems	coreximine	ALK	-
Barks	coreximine	ALK	-
Leaves	atherosperminine	ALK	-

Roots,	atherosperminine	ALK	-
Stems	atherosperminine	ALK	-
Barks	atherosperminine	ALK	-
Leaves	stepharine	ALK	-
Roots,	stepharine	ALK	-
Stems	stepharine	ALK	-
Barks	stepharine	ALK	-
Leaves	anomurine	ALK	-
Roots,	anomurine	ALK	-
Stems	anomurine	ALK	-
Barks	anomurine	ALK	-
Leaves	anomuricine	ALK	-
Roots,	anomuricine	ALK	-
Stems	anomuricine	ALK	-
Barks	anomuricine	ALK	-

7. Conclusion

A. muricata and *A. Squamosa* are highly coveted tropical trees with a long history of traditional use and a wealth of phytochemical investigations. In addition to being an important source of food and an indigenous medicinal plant, they have been shown to have a wide range of biological activities. Among all the studies on these plants, the most promising activities happen to be their anticancer activity. New *in vitro*, *in vivo* and clinical studies on the biological activities of *A. muricata* and *A. Squamosa* are necessary in order to better understand how these herbal medicines can serve as a starting point of the bioprospecting for new anti-cancer lead compounds.

Author's contribution

All manuscript was written through the contribution of all the authors and they have given approval to the final version.

Conflict of interest

None

8. References

1. World Health Organization (WHO), United Nation, 2016. [En ligne]. Available: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. [Accès le 19 Novembre 2019].
2. Wang De-Shen, Rizwani, Ghazala Guo, Huiqin Ahmed, Mansoor Ahmed, Maryam Hassan. Rui-Hua, *Annona squamosa* Linn: Cytotoxic activity found in leaf extract against human tumor cell lines, Pakistan J of pharm. Sci 2014;27:1559-1563.
3. Moghadamtousi SZ, Fadaeinasab M, Nikzad S, Mohan G, Ali HM, Kadir HA. *Annona muricata* (Annonaceae): A Review of Its Traditional Uses, Isolated Acetogenins and Biological Activities, Int. J Mol Sci 2015;16(7):15625-15658.
4. Adewole SO, Ojewole JA. Protective effects of *Annona muricata* Linn, (Annonaceae) leaf aqueous extract on serum lipid profiles and oxidative stress in hepatocytes of streptozotocin-treated diabetic rats, Afr J Tradit Complement Altern Med 20086(1):30-41.
5. Mishra S, Ahmad S, Kumar N, Sharma BK, *Annona muricata* (the cancer killer): A review. Glob. J Pharm. Res 2013;2:1613-1618.
6. Leboeuf M, Cavé A, Bhaumik P, Mukherjee B et R. Mukherjee, The phytochemistry of the Annonaceae.,» Phytochemistry 1980;21:2783-2813.
7. Adewole S *et al*. Caxton-Martins, Morphological changes and hypoglycemic effects of *Annona muricata* Linn. (Annonaceae) leaf aqueous extract on pancreatic B-cells of streptozotocin-treated diabetic rats., Afr. J. Biomed. Res 2009;93(9):173-187 (ISSN: 1119-5096).
8. De Souza R, Benassi E, da Silva R, Afonso S et al. Scarminio, Enhanced extraction yields and mobile phase separations by solvent mixtures for the analysis of metabolites in *Annona muricata* L. Leaves., J Sep. Sci 2009;32(23-24):4176-4185.
9. Ponrasu T *et al*. Suguna, Efficacy of *Annona squamosa* on wound healing in streptozotocin-induced diabetic rats., Int Wound J 2012;9(6):613-23.
10. Morton J. Sugar Apple. In: Fruits of warm climates. Julia F. Morton, Miami, FL 1987, 69–72.
11. Chukwuma Ogbaga C, Habib-ur-Rehman Athar, The need to incorporate fast and slow relaxation kinetic parameters into photosynthesis-measuring systems, Scientific African 2019;4:e00106, ISSN 2468-2276.
12. Jaramillo-Flores M *et al*. Hernandez-Sanchez, Thermal diffusivity of soursop (*Annona muricata* L.) pulp., J Food Eng 2000,139-143. ISSN 0260-8774.
13. Wu FE, Gu ZM, Zeng L *et al*. Two new cytotoxic monotetrahydrofuran Annonaceous acetogenins, annomuricins A and B, from the leaves of *Annona muricata*., J Nat Prod 199558(6):830-836.
14. Yang C, Gundala SR, Mukkavilli R, Vangala S, Reid MD, Aneja R. Synergistic interactions among flavonoids and acetogenins in Graviola (*Annona muricata*) leaves confer protection against prostate cancer. Carcinogenesis. 2015;36(6):656-665.
15. Matsushige A, Matsunami K, Kotake Y, Otsuka H, Ohta S. Three new megastigmanes from the leaves of *Annona muricata*. J Nat Med 2012;66(2):284-291.
16. Nawwar M, Ayoub N, Hussein S *et al*., A flavonol triglycoside and investigation of the antioxidant and cell stimulating activities of *Annona muricata* Linn. Arch Pharm Res 2012;35(5):761-767.
17. Jiménez Víctor, Gruschwitz Maike, Schweiggert, Ralf Carle, Reinhold, Esquivel, Patricia. Identification of phenolic compounds in soursop (*Annona muricata*) pulp by high-performance liquid chromatography with diode array and electrospray ionization mass spectrometric detection. Food Res. Int 2014;65Part A:42-46.
18. Pélissier Y, Marion C, Kone D, Lamaty G, Menut C, Bessière J. Volatile Components of *Annona muricata* L., J Essent. Oil Res 1994;6(4):411-414.
19. Kossouoh C, Moudachirou M, Adjakidje V, JC. Chalchat et G. Figuérédo, Essential oil chemical composition of *Annona muricata* L. Leaves from Benin., J Essent. Oil Res 2007;19(4):307-309.

20. Rupprecht J, Hui YH et J. McLaughlin, Annonaceous acetogenins: A review., J. Nat. Prod./Int. J Mol. Sci 1990/2015;53(2):237-278.
21. Gyamfi K, Sarfo D, Nyarko B, Akaho E, Serfor-Armah Y, Ampomah - Amoako E. Assessment of elemental content in the fruit of graviola plant, *Annona muricata*, from some selected communities in Ghana by instrumental neutron activation analysis., Elixir Food Sci 2011;41:5671-5675.
22. Alali FQ, Liu XX, McLaughlin JL. Annonaceous acetogenins: recent progress. J Nat Prod 1999;62(3):504-540.
23. Tempesta M, Kriek G *et al*. Bates, Uvaricin, a new antitumor agent from Uvaria accuminata (Annonaceae)., J Org. Chem 1982;47(16):3151-3153.
24. McLaughlin JL, Paw paw and cancer: annonaceous acetogenins from discovery to commercial products. J Nat Prod 2008;71(7):1311-1321.
25. Zafra-Polo MC, Figadere Gallardo B, T Tormo JR *et al*., Natural acetogenins from Annonaceae, synthesis and mechanisms of action, UN Food and Agri Org 1998; 48(7):1087-1117.
26. Zafra-Polo M, González M, Estornell E, Sahpaz S *et al*. Cortes, Acetogenins from Annonaceae, inhibitors of mitochondrial complex I., Phytochemistry 1996;42(2):253-271.
27. Chih HW, Chiu HF, Tang KS, Chang FR, et. Wu YC. Bullatacin, a potent antitumor annonaceous acetogenin, inhibits proliferation of human hepatocarcinoma cell line 2.2.15 by apoptosis induction., Life Sci 2001;69(11):1321-1331.
28. Jaramillo M, Arango G, Gonzalez M, Robledo S *et al*. Velez, Cytotoxicity and antileishmanial activity of *Annona muricata* pericarp., Fitoterapia 2000;71(2):183-186.
29. Arroyo J, Prashad M, Vásquez Y, Li E *et al*. Tomás, Actividad citotóxica *in vitro* de la mezcla de *Annona muricata* y krameria lappacea sobre células cancerosas de glándula mamaria, pulmóny sistema nervioso central (in Spanish)., Rev. Perú. Med. Exp. Salud Publica 2005;22(4):247-253. ISSN 1726-4634.
30. George V, Kumar D, Rajkumar V, Suresh P, Kumar R *et al*. Quantitative assessment of the relative antineoplastic potential of the n-butanolic leaf extract of *Annona muricata* linn. In normal and immortalized human cell lines., Asian Pac. J Cancer Prev 2012;13:699-704.
31. Astirin O, Artanti A, Fitria M, Perwitasari E *et al*. Prayitno, Annonaa *muricata* linn leaf induce apoptosis in cancer cause virus., J. Cancer Ther 2013;4:1244-1250.
32. Gavamukulya Y, Abou-Elella F, Wamunyokoli F *et al*. AEl-Shemy, Phytochemical screening, anti-oxidant activity and *in vitro* anticancer potential of ethanolic and water leaves extracts of *Annona muricata* (graviola)., Asian Pac J Trop Med., 2014;7S1:S355-S363.
33. Kim G, Zeng L, Alali F, Rogers L *et al*. Wu, Sastrodihardjo, S. Muricoreacin and murihexocin C, mono-tetrahydrofuran acetogenins, from the leaves of *Annona muricata*., McLaughlin J.L. Phytochemistry 1998;49(2):565-571.
34. Rieser M, Gu Z, Fang X, Zeng L *et al*. Wood, McLaughlin, J.L. Five novel mono- tetrahydrofuran ring acetogenins from the seeds of *Annona muricata*. J Nat Prod 1996;59(2):100-108.
35. Paul J, Gnanam R, Jayadeepa R *et al*. Arul, Anti cancer activity on Graviola, an exciting medicinal plant extract vs various cancer cell lines and a detailed computational study on its potent anti-cancerous leads., Curr Top Med Chem 2013;13(14):1666-1673.
36. Dai Y, Hogan S *et al*. Schmelz, Selective growth inhibition of human breast cancer cells by graviola fruit extract *in vitro* and *in vivo* involving downregulation of EGFR expression., Nutr Cancer 2011;63(5):795-801.
37. Oberlies N, Chang C *et al*. McLaughlin, Structure-activity relationships of diverse Annonaceous acetogenins against multidrug resistant human mammary adenocarcinoma (MCF-7/Adr) cells., J Med Chem 1997;40(13):2102-2106.
38. Torres M, Rachagani S *et al*. Purohit, Graviola: a novel promising naturalderived drug that inhibits tumorigenicity and metastasis of pancreatic cancer cells *in vitro* and *in vivo* through altering cell metabolism., Cancer Lett 2012;323(1):29-40.
39. Pieme C, Kumar S *et al*. Dongmo, Antiproliferative activity and induction of apoptosis by *Annona muricata* (Annonaceae) extract on human cancer cells., BMC Complement Altern Med 2014;14(1):516.
40. Sun S, Liu J *et al*. Kadouh, Three new anti-proliferative Annonaceous acetogenins with mono-tetrahydrofuran ring from graviola fruit (*Annona muricata*)., Bioorg Med Chem Lett 2014;24(12):2773-2776.
41. Moghadamtousi S, Kadir H *et al*. Paydar, *Annona muricata* leaves induced apoptosis in A549 cells through mitochondrial-mediated pathway and involvement of NF-kappaB., BMC Complement Altern Med 2014;14:299.
42. Moghadamtousi S, Karimian H *et al*. Rouhollahi, *Annona muricata* leaves induce G(1) cell cycle arrest and apoptosis through mitochondria-mediated pathway in human HCT- 116 and HT-29 colon cancer cells., J Ethnopharmacol 2014;156:277-289.
43. Asare G, Afriyie D, Ngala R, Abutiate H, Doku D, Mahmood S *et al*. Rahman, Antiproliferative activity of aqueous leaf extract of *Annona muricata* L. On the prostate, BPH-1 cells, and some target genes., Integr. Cancer Ther 2015;14:65-74.
44. Minari J *et al*. Okeke, Chemopreventive effect of *Annona muricata* on DMBAinduced cell proliferation in the breast tissues of female albino mice., Egypt. J Med. Hum. Genet 2014;15:327–334.
45. Hamizah S, Roslida A, Fezah O, Tan K, Tor Y *et al*. Tan, Chemopreventive potential of *Annona muricata* L leaves on chemically-induced skin papillomagenesis in mice., Asian Pac. J Cancer Prev 2012;13:2533-2539.
46. Moghadamtousi S, Rouhollahi E, Karimian H, Fadaeinasab M, Firoozinia M, Abdulla M *et al*. Kadir, The chemopotential effect of *Annona muricata* leaves against azoxymethane-induced colonic aberrant crypt foci in rats and the apoptotic effect ofacetogenin annomuricin E in HT-29 cells: A bioassay-guided approach., PLoS One 2015;10(4):e0122288..
47. Eggadi V, Gundamedi S, Sheshagiri S, Revoori S, Jupally V *et al*. Kulandaivelu, Evaluation of anticancer activity of *Annona muricata* in 1,2dimethyl hydrazine induced colon cancer., World Appl. Sci. J 2014;32:444-450.
48. Hansra D, Silva O, Mehta A *et al*. Ahn, Patient with metastatic breast cancer achieves stable disease for 5 years on graviola and xeloda after progressing on multiple lines of therapy., Adv. Breast Cancer Res 2014;3:84-87.

49. Elisya Y, Kardono L *et al*. Simanjuntak, Tablet formulation of the ethyl acetate soluble extract of soursop (*Annona muricata* L.) leaves., Asian J Appl. Sci 2014;2323-329.
50. Y M, Xu X, Yuan F, Shi Y, Chen Y, Chen J X Li, *et al*. Four cytotoxic annonaceous acetogenins from the seeds of *Annona squamosa*., Nat Prod Res 2015;16:1-7.
51. Nakano D, Ishitsuka K, Kamikawa M, Matsuda M, Tsuchihashi R, Okawa M, Okabe H *et al*. Screening of promising chemotherapeutic candidates from plants against human adult T-cell leukemia/lymphoma (III)., J Nat Med 2013;67(4):894-903.
52. Sun L, Zhu H, Gan L, Mo J, Feng F *et al*. Zhou, Constituents from the bark of *Annona squamosa* and their anti-tumor activity., Zhongguo Zhong Yao Za Zhi 2012;37(14):2100-2104.
53. Chen Y, Xu S, Chen J, Wang Y, HQ X, NB F *et al*. Antitumor activity of *Annona squamosa* seeds extract containing annonaceous acetogenin compounds., J Ethnopharmacol 2012;142(2):462-466.
54. Hopp D, Zeng L, Gu Z, Kozlowski J *et al*. McLaughlin, Novel monotetrahydrofuran ring acetogenins, from the bark of *Annona squamosa*, showing cytotoxic selectivities for the human pancreatic carcinoma cell line, PACA-2. J Nat Prod 1997;60(6):581-586.
55. Hopp D, Zeng L, Gu Z *et al*. McLaughlin, Squamotacin: an annonaceous acetogenin with cytotoxic selectivity for the human prostate tumor cell line (PC3). J Nat Prod 1996;59(2):97-99.
56. Lukwago F, Mukisa M, Atukwase A, Kaaya A, Tumwebaze S, Mycotoxins contamination in foods consumed in Uganda: A 12-year review (2006–18), Scientific African 2019;3:e00054, ISSN 2468-2276.
57. Caparros-Lefebvre D, Elbaz A *et al*. Group, Possible relation of atypical parkinsonism in the french west indies with consumption of tropical plants: A case-control study., Lancet 1999;354:281–286.
58. Escobar-Khondiker M, Höllerhage M, Muriel MP, Champy P, Bach A, Depienne C *et al*. Yagi, Annonacin, a natural mitochondrial complex I inhibitor, causes tau pathology in cultured neurons., J Neurosci 2007;27:7827-7837.
59. Bonneau N, le Ven J, Schmitz-Afonso I, Guérineau V, ba Ndob I *et al*., Annonaceous acetogenins as environmental neurotoxins: Human exposure from edible annona fruits., Planta Med 2012;78:PH25.
60. Champy P, Melot A, Guérineau Eng V, Gleye C, Fall D, Höglinger GM *et al*. Laurens, Quantification of acetogenins in *Annona muricata* linked to atypical parkinsonism in guadeloupe., Mov. Disord 2005;20:1629-1633.