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

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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 Benin 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.

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 as ethnomedicine for tumors and cancer [1]. 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 generally be 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-saturated methyl-substituted γ-lactone [22]. Since the discovery of *Uvaria acuminate* 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.

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 G1 phase |
| Ethyl acetate extract of the leaves | colon HT-29 and HCT-116 cancer cells | mitochondrial-mediated apoptosis, cell cycle arrest at G1 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 | azoxy methane 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 |

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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 a 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 Bax and 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 of the 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., 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 squamoxinine-D (4), as well as seven known ACGs (5-11), were isolated from the seeds of 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 activity against colon cancer cells with an IC50 value of 0.0492 μg / ml after 48 h [47].

In vivo studies have been performed using the A. squamosa leaves extract against the skin papillomas in rats. The leaves, even at the low dose of 30 mg / kg, significantly inhibited the growth of papillomas and reduced the size of the papillomas. The ethanolic extract of the leaves resulted in the decrease in glucose absorption and ATP production in pancreatic cancer cells [38].

In a study to identify promising plant candidates against adult 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-kaur-19-oic acid (2), 16, 17-dihydroxy-ent-kaur-19-oic acid (3), annosquamosin A(4), ent-kaur-16-en-19-oic acid (5), 19-nor-ent-kauran-4-ol-17-oic acid (6), 16-hydroxy ent-kaur ran-19-oic acid (7), ent-15beta-hydroxy-kaur-16-en-19-oic acid (8), annosquamosin B (9), ent-16beta, 17-dihydroxykauran-19-ol (10), 16, 17-dihydroxy-ent-kauran-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 (IC50 0.25 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 acetogens 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 [50], 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) ethanol-1-ol
Atherospanumune

(R)-S'.6'-dimethoxy-2',3',7',8a'-tetrahydro-1'H spiro[cyclohexane-1,8'-cyclopenta[1]naphthalene]-2,5-Dien-1-one Stephanne

(S)-5, 6, 7-trimethoxy-1-(4-ethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline Anomurine

(R)-S'.6'-dimethoxy-2',3',7',8a'-tetrahydro-1'H spiro[cyclohexane-1,8'-cyclopenta[1]naphthalene]-2,5-Dien-1-one Stephanne

(R)-U-dimethoxy-7,6,6a,7-tetrahydro-4H-[1,3]dioxolo[4',5':4,5]benzo[1,2-g]benzo[g][1,2]quinoline Nomuciferine

(S)-6,7-dimethoxy-1-(4-methoxybenzyl)-1, 2, 3, 4-

(R)-5-methyl-3-((E)-14-((2RJR)-3-tetradecyloxiran-2-yl) tetradec-11-en-1-yl) furan-2(5H)-ooe Sabadelin
(5R)-5-methyl-3-((2S,9R,11S)-2, 8, 9, 11-tetrahydroxy-11-((2R,5R)-5-((R)-1-hydroxy tetradecyl) tetrahydrofuran-2-yl) undecyl) furan-2(5H)-one Annomuricin A

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

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

**Table 2**: Chemical compounds isolated from *Annona muricata*.

| Plant Part | Compound       | Class  | Biological Activity                        |
|------------|----------------|--------|--------------------------------------------|
| Fruits     | annonaine      | ALK    | anti-depressive                            |
| Fruits     | normuciferine  | 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 | 4-feruloyl-5-cafeoylquinic acid | PL | - |
| Fruits | 4-feruloylglycoside | PL | - |
| Fruits | feruloylglycoside | PL | - |
| Fruits | dicafeoylquinic acid | PL | - |
| Fruits | caffeic acid derivative | PL | - |
| Fruits | p-coumaric acid | PL | - |
| Fruits | dihydrokaempferol-hexoside | PL | - |
| Pericarp | kaempferol | - | - |
| Leaves | quercetin 3-O-glucoside | FTG | - |
| Leaves | quercetin 3-O-rutinoside | FTG | - |
| Leaves | quercetin 3-O-neohispredoside | FTG | - |
| Leaves | quercetin 3-O-robinoside | FTG | - |
| Leaves | quercetin 3-O-rhamnosyl-1-β-D-glucoside | FTG | - |
| Leaves | quercetin 3-O-neohispredoside | FTG | - |
| Leaves | quercetin 3-O-neohispredoside | FTG | - |
| Leaves | quercetin 3-O-robinoside | FTG | - |
| Leaves | quercetin 3-O-rutinoside | FTG | - |
| Leaves | quercetin 3-O-glucoside | FTG | - |
| Leaves | quercetin | FTG | - |
| Leaves | kaempferol | FTG | - |
| Leaves | argentinine (1-N,N-dimethylethylamino-4,6-dimethoxy-3,8-dihydroxy-phenanthrene) | FTG | - |
| Leaves | kaempferol 3-O-rutinoside | FTG | - |
| Leaves | chlorogenic acid | FTG | - |
| Leaves | epicatechin | FTG | - |
| Leaves | gallic acid | FTG | - |
| Leaves | aucubin | FTG | - |
| Leaves | isolaureline | ALK | - |
| Leaves | xylopine | ALK | - |
| Leaves | quercetin | FTG | - |
| Leaves | quercetin 3-O-glucoside | FTG | - |
| Leaves | quercetin | FTG | - |
| Leaves | quercetin 3-O-robinoside | FTG | - |
| Leaves | quercetin | FTG | - |
| Leaves | kaempferol | FTG | - |
| Leaves | argentinine | FTG | - |
| Leaves | quercetin 3-O-glucoside | FTG | - |
| Leaves | quercetin 3-O-robinoside | FTG | - |
| Leaves | quercetin | FTG | - |
| Leaves | kaempferol | FTG | - |
| Leaves       | annonamine        | ALK | - |
|-------------|-------------------|-----|---|
| Leaves      | (S)-norcorydine   | ALK | - |
| Leaves      | (R)-4'-O-methylcoclaurine | ALK | - |
| Leaves      | (R)-O,D-dimethylcoclaurine | ALK | - |
| Leaves      | annononol A       | MG  | - |
| Leaves      | annononol B       | MG  | - |
| Leaves      | annononol C       | MG  | - |
| Leaves      | annonioside       | 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      | (15,25,4R)-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       | muricatacin       | AGE | - |
| Seeds       | annonacin         | AGE | toxicity against lung A549, breast MCF7, colon HT-29 cancer cells |
| Seeds       | annonacin         | AGE | neurotoxic, molluscidal, inhibitor of mitochondrial complex I |
| Leaves      | annonacin         | AGE | neurotoxic, molluscidal, inhibitor of mitochondrial complex I |
| Pericarp    | annonacin         | AGE | neurotoxic, molluscidal, inhibitor of mitochondrial complex I |
| Seeds       | 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, antileishmanial |
| Seeds       | solamin           | AGE | toxicity against oral KB cancer cells 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 | - |
| Seeds       | isoonanonacn      | AGE | molluscidal, anticancer |
| Seeds       | isoonanonacn-10-one | AGE | - |
| Seeds       | goniotalamicin    | AGE | molluscidal |
| Leaves      | goniotalamicin    | AGE | molluscidal |
| Part       | Compound                                      | Description                                                                 |
|------------|-----------------------------------------------|-----------------------------------------------------------------------------|
| Seeds      | gigantetrocin                                 | toxicity against colon HT-29 cancer cells                                     |
| Leaves     | gigantetrocin                                 | toxicity against colon HT-29 cancer cells                                     |
| Seeds      | gigantetrocin B                               | toxicity against colon HT-29 cancer cells                                     |
| Leaves     | gigantetrocin B                               | toxicity against colon HT-29 cancer cells                                     |
| Seeds      | muriacetetrocin A                             | toxicity against colon HT-29 cancer cells                                     |
| Leaves     | muriacetetrocin A                             | toxicity against colon HT-29 cancer cells                                     |
| Seeds      | muriacetetrocin B                             | toxicity against colon HT-29 cancer cells                                     |
| Leaves     | muriacetetrocin B                             | toxicity against colon HT-29 cancer cells                                     |
| Seeds      | epomuricenin A                               | toxicity against colon HT-29 cancer cells                                     |
| Leaves     | epomuricenin A                               | toxicity against colon HT-29 cancer cells                                     |
| Seeds      | epomuricenin B                               | toxicity against colon HT-29 cancer cells                                     |
| Leaves     | epomuricenin B                               | toxicity against colon HT-29 cancer cells                                     |
| Seeds      | annomuricatin A                              | toxicity against human hepatoma cells                                       |
| Seeds      | annomuricatin C                              | toxicity against human hepatoma cells                                       |
| Seeds      | cis-annomontacin                             | crown gall tumor inhibition, toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells |
| Seeds      | cis-annomonancin-10-one                      | crown gall tumor inhibition, toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells |
| Seeds      | cis-goniothalaminic                          | crown gall tumor inhibition, toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells |
| Seeds      | ariancin                                     | crown gall tumor inhibition, toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells |
| Seeds      | javoricin                                    | crown gall tumor inhibition, toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells |
| Seeds      | murihexol                                    | toxicity against human hepatoma cells                                       |
| Seeds      | donhexocin                                   | toxicity against human hepatoma cells                                       |
| Seeds      | cohibin C                                    | toxicity against human hepatoma cells                                       |
| Seeds      | cohibin D                                    | toxicity against human hepatoma cells                                       |
| Seeds      | muriacetanol                                 | toxicity against human hepatoma cells                                       |
| Seeds      | 2,4-cis-gigantetrocinone                     | toxicity against human hepatoma cells                                       |
| Seeds      | 2,4-trans-gigantetrocinone                   | toxicity against human hepatoma cells                                       |
| Seeds      | 2,4-trans-isoaionanancin-10-one              | toxicity against human hepatoma cells                                       |
| Seeds      | annomuricatin                                | toxicity against human hepatoma cells                                       |
| Seeds      | longifolicin                                 | toxicity against human hepatoma cells                                       |
| Seeds      | muricin A                                    | toxicity against human hepatoma cells                                       |
| Seeds      | muricin B                                    | toxicity against human hepatoma cells                                       |
| Seeds      | muricin C                                    | toxicity against human hepatoma cells                                       |
| Seeds      | muricin D                                    | toxicity against human hepatoma cells                                       |
| Seeds      | muricin E                                    | toxicity against human hepatoma cells                                       |
| Seeds      | muricin F                                    | toxicity against human hepatoma cells                                       |
| Seeds      | muricin G                                    | toxicity against human hepatoma cells                                       |
| Seeds      | muricin H                                    | toxicity against human hepatoma cells                                       |
| Seeds      | muricin I                                    | toxicity against human hepatoma cells                                       |
| Seeds      | cis-annomontacin                             | toxicity against human hepatoma cells                                       |
| Seeds and Leaves | annonacinone                      | toxicity against human hepatoma cells                                       |
| Seeds      | xylomacticin                                 | toxicity against human hepatoma cells                                       |
| Seeds      | N-fatty acyl tryptamines                     | toxicity against human hepatoma cells                                       |
| Seeds      | annoreticuin-9-one                           | toxicity against human hepatoma cells                                       |
| Stem barks | epoxymurin A                                | toxicity against human hepatoma cells                                       |
| Stem barks | epoxymurin B                                | toxicity against human hepatoma cells                                       |
| Leaves     | reticuline                                   | toxicity against human hepatoma cells                                       |
| Roots      | reticuline                                   | toxicity against human hepatoma cells                                       |
| Stems      | reticuline                                   | toxicity against human hepatoma cells                                       |
| Barks      | reticuline                                   | toxicity against human hepatoma cells                                       |
| Leaves     | cochlaurine                                  | toxicity against human hepatoma cells                                       |
| Roots      | cochlaurine                                  | toxicity against human hepatoma cells                                       |
| Stems      | cochlaurine                                  | toxicity against human hepatoma cells                                       |
| Barks      | cochlaurine                                  | toxicity against human hepatoma cells                                       |
| Leaves     | coreximine                                   | toxicity against human hepatoma cells                                       |
| Roots      | coreximine                                   | toxicity against human hepatoma cells                                       |
| Stems      | coreximine                                   | toxicity against human hepatoma cells                                       |
| Barks      | coreximine                                   | toxicity against human hepatoma cells                                       |
| Leaves     | atherosperminine                             | toxicity against human hepatoma cells                                       |
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 anticancer 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
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