# A Review on Annona squamosa L.: Phytochemicals and Biological Activities

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# A Review on *Annona squamosa* L.: Phytochemicals and Biological Activities

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Abstract: *Annona squamosa* L. (Annonaceae) is a fruit tree with a long history of traditional uses. *A. squamosa* is an evergreen plant mainly located in tropical and subtropical regions. Srikayas, the fruits of *A. squamosa*, are extensively used to prepare candies, ice creams and beverages. A wide range of ethno-medicinal uses has been related to different portions of *A. squamosa*, such as tonic, apophlegmatisant, cool medicine, abortient and heart sedative. Numerous research projects on *A. squamosa* have found that it has anticancer, anti-oxidant, antidiabetic, antihypertensive, hepatoprotective, antiparasitic, antimalarial, insecticidal, microbicidel and molluscicidal activities. Phytochemistry investigations on *A. squamosa* have considered annonaceous acetogenins (ACGs), diterpenes (DITs), alkaloids (ALKs) and cyclopeptides (CPs) as the main constituents. Until 2016, 33 DITs, 19 ALKs, 88 ACGs and 13 CPs from this species were reported. On the basis of the multiple researches on *A. squamosa*, this review strives to integrate available information on its phytochemicals, folklore uses and bioactivities, hoping to promote a better understanding of its medicinal values.

*Keywords*: *Annona squamosa*; Annonaceae Acetogenins; Biological Activities; Bioactive Compounds; Review.



## Introduction

Apart from the critical role of photosynthesis, plants can also be manufactured as natural products. Natural products have been used to help human sustain its health since the start of medicine. Over the past centenary, the phytochemicals and active constituents in plants have played a pivotal role in pharmaceutical discovery. The importance of the bioactive materials of plants in medicine and agriculture has stimulated significant interest in the

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bioactivities of substances (Moghadamtousi *et al.*, 2013). Despite investigations in a restricted range of plant species, all established wisdoms are relatively inadequate concerning their underlying role in nature. Therefore, the reasonable developments of natural products necessitate overall investigations on the bioactivities of these plants and their key phytochemicals (Moghadamtousi *et al.*, 2014). In the pharmaceutical field, plants with a long history in enthno-medicine are a vast resource of active phytoconstituent, which provides medicinal and health benefits against numerous ailments and disease (Li *et al.*, 2015; Moghadamtousi *et al.*, 2015; Xiao *et al.*, 2015). One of such plants with extensive traditional usage is *A. squamsoa*. In this review, we summarize the phytochemicals and bioactivities of *A. squamosa*.



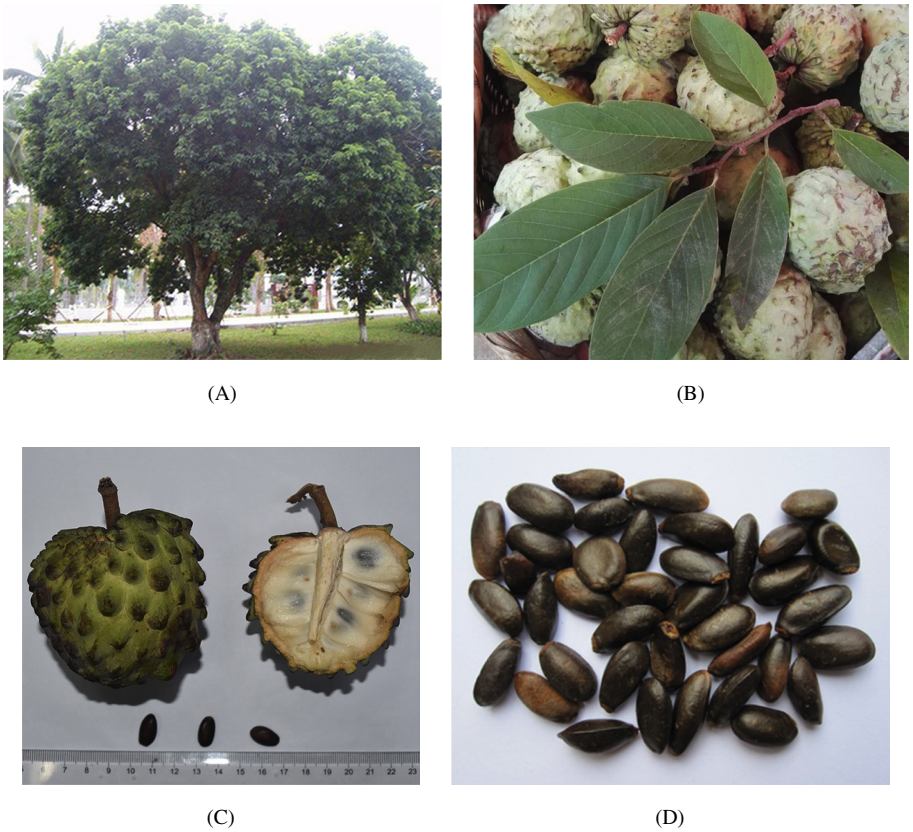
## Botanical Description and Distribution

*Annona squamosa* L., which is commonly known as sugar apple, custard apple, sweet sop, sweet apres and sitaphal, is a member of *Annonaceae* family, comprising approximately 135 genera and 2300 species (Raj *et al.*, 2009; Srivastava *et al.*, 2011). The birthplace of *A. squamosa* is not clear. It is a semi-deciduous tree widely distributed in tropical South America and in the West Indies. The Spaniards probably carried seeds from the New World to the Philippines and the Portuguese were assumed to introduce the sugar apple to southern India before 1590 (Morton, 1987). Nowadays, it is cultivated in tropical and sub-tropical regions worldwide (Ngiefu *et al.*, 1977; Yang *et al.*, 2009a).

*A. squamosa* is an ever-green tree reaching 3–8 m in height. Leaf oblong lanceolate or lanceolate, 6–17 cm long and 3–5 cm wide, alternately arranged on short petioles; bark thin, gray; flower greenish, fleshy, drooping, extra-axillary, more on leafy shoot than on the older wood and tending to open as the shoot elongates; fruit can be round, heart-shaped, ovate or conical, 5–10 cm in diameter, with many round protuberance; seeds 1.3–1.6 cm long, oblong, smooth, shiny, blackish or dark brown (Fig. 1) (Chen *et al.*, 2011a).

## Ethnopharmacology

All portions of *A. squamosa* tree, which is similar to other species within the same genus, are widely used as ethnical medicine against various ailments and human diseases, especially for cancer and parasitism (Gajalakshmi *et al.*, 2011). In Ayurveda, srikayas, the fruits of *A. squamosa*, are reported to be good tonic. It was stated that srikayas have the capacity to enrich blood and to increase muscle strength. It can also be used as apophlegmatisant and can help cool, relieve burning perception and tendency to biliousness. In addition, srikayas are sedative to the heart and alleviate vomiting (Vijayalakshmi and Nithiya, 2015). The seeds are deemed to be abortient and good at eliminating lice in hair according to Yunani medicine. Seed yields oil and resin, which act as a decontaminant, and mixed with gram-flour, are good for hair wash (Gajalakshmi *et al.*, 2011). In the south of China, seed extraction was used as a folkloric remedy for "malignant sores" (cancer) (Wu, 2004). Seeds are powerful irritant of conjunctiva and thus can trigger ulcers in the eye. Several research studies in our laboratory cured cornea injury with seeds. Leaves are made into poultice to



(A) (B)

(C) (D)

Figure 1. *Annona squamosa* L. (A); appearance of leaves (B), fruits (C) and seeds (D).



heal boils and ulcers, and leaf infusion is proved efficacious in treating prolapse in children. A cataplasm, made from bruised leaves with salt, is applied for extraction of guinea-worms (Gowdhami *et al.*, 2014). In Cuban medicine, leaves are taken to lower uric acid levels. Leaves, bark, and unripe fruit were used for diarrhea and dysentery (Kirtikar and Basu, 1918). Folkloric record presented the use of *A. squamosa* as an insecticidal, an anticancer agent, antidiabetic, anti-oxidant, antilipidimic and anti-inflammatory agent, which have been confirmed by recent investigations.

## Phytochemistry

Extensive phytochemical evaluations on different portions of *A. squamosa* plant have shown the presence of various phytochemicals and constituents, including diterpenes (DITs), alkaloids (ALKs), annonaceous acetogenins (ACGs), cyclopeptides (CPs) and essential oils. The chemical structures of major compounds isolated from *A. squamosa* L. are shown in Figs. 2–5. Until February 2016, 33 DITs, 19 ALKs, 88 ACGs and 13 CPs were isolated from this species.

*Diterpenes*

DITs are widely extensive in different parts of *A. squamosa*, excepting in seeds and leaves. For the time being, 34 DITs have been isolated from this species, majority of which are ent-kaurane DITs (Fig. 2). Several DITs isolated from barks showed promising antitumor activities against lung and ovarian cancer cells (Sun *et al.*, 2012).

*Alkaloids*

ALKs are a class of early reported compounds from *A. squamosa*. But only 19 alkaloids (Fig. 3) were isolated from *A. squamosa.* Most of them were aporphine ALKs and are

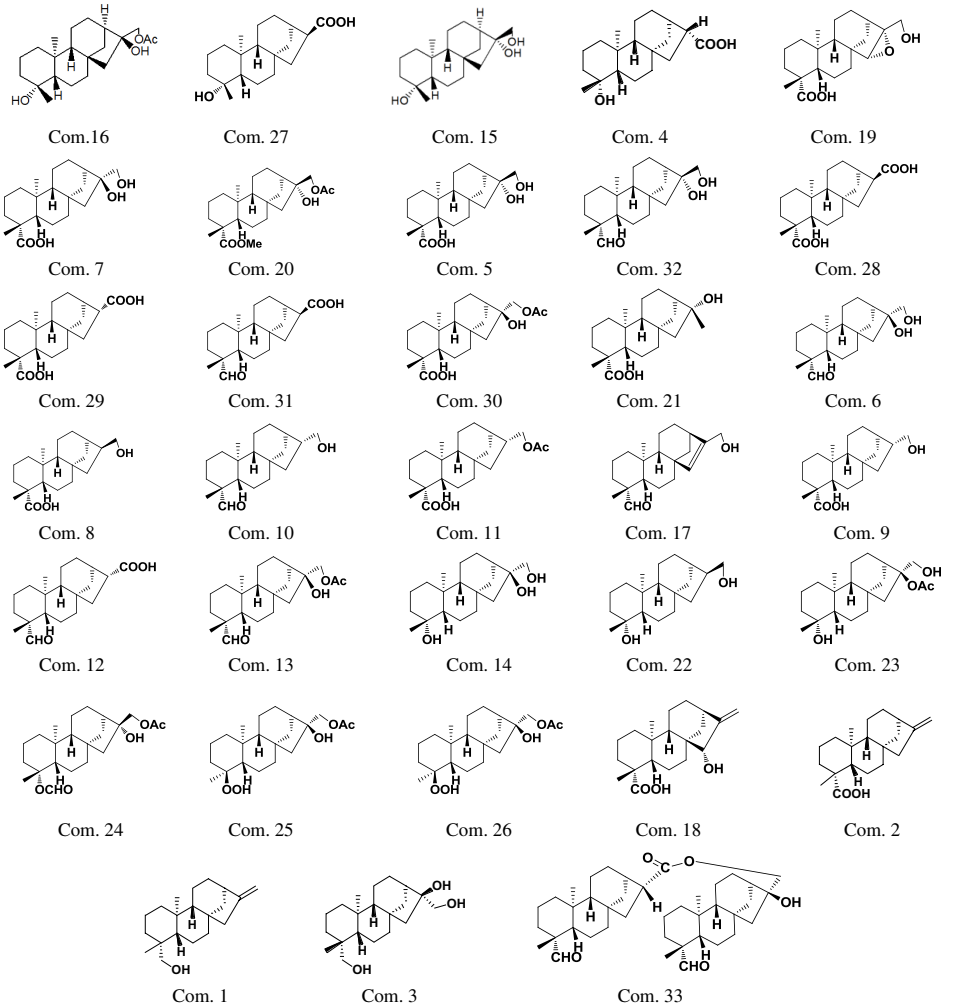



Figure 2. Chemical structures of diterpenoids isolated from *A. squamosa*.

isolated from leaves or stems of this plant. ALKs from *A. squamosa* were considered as the bioactive constituents with antihypertensive, antispasmodic, antihistaminic and bronchodilatory activities (Kirtikar and Basu, 1918).

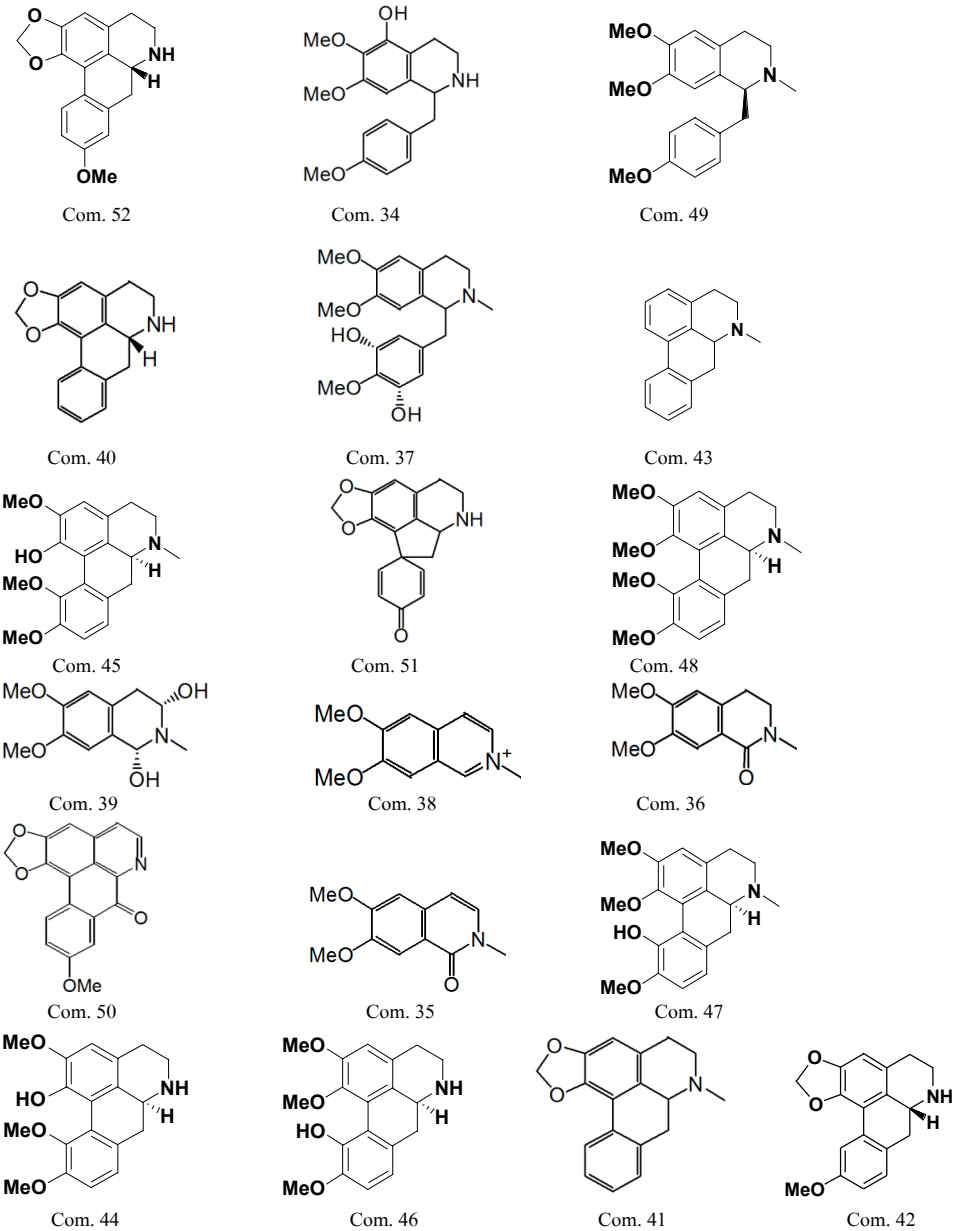



Figure 3. Chemical structures of ALKs isolated from *A. squamosa*.

*Annonaceous Acetogenins*

ACGs isolated exclusively from *Annonaceae* species constitute a series of natural products (Zafra-Polo *et al.*, 1996; Bermejo *et al.*, 2005) that are extensively distributed throughout tropical and sub-tropical parts of the world. ACGs are a unique class of C-35/C-37 natural products derived from unbranched C-32/C34 fatty acids in polyketide pathway.

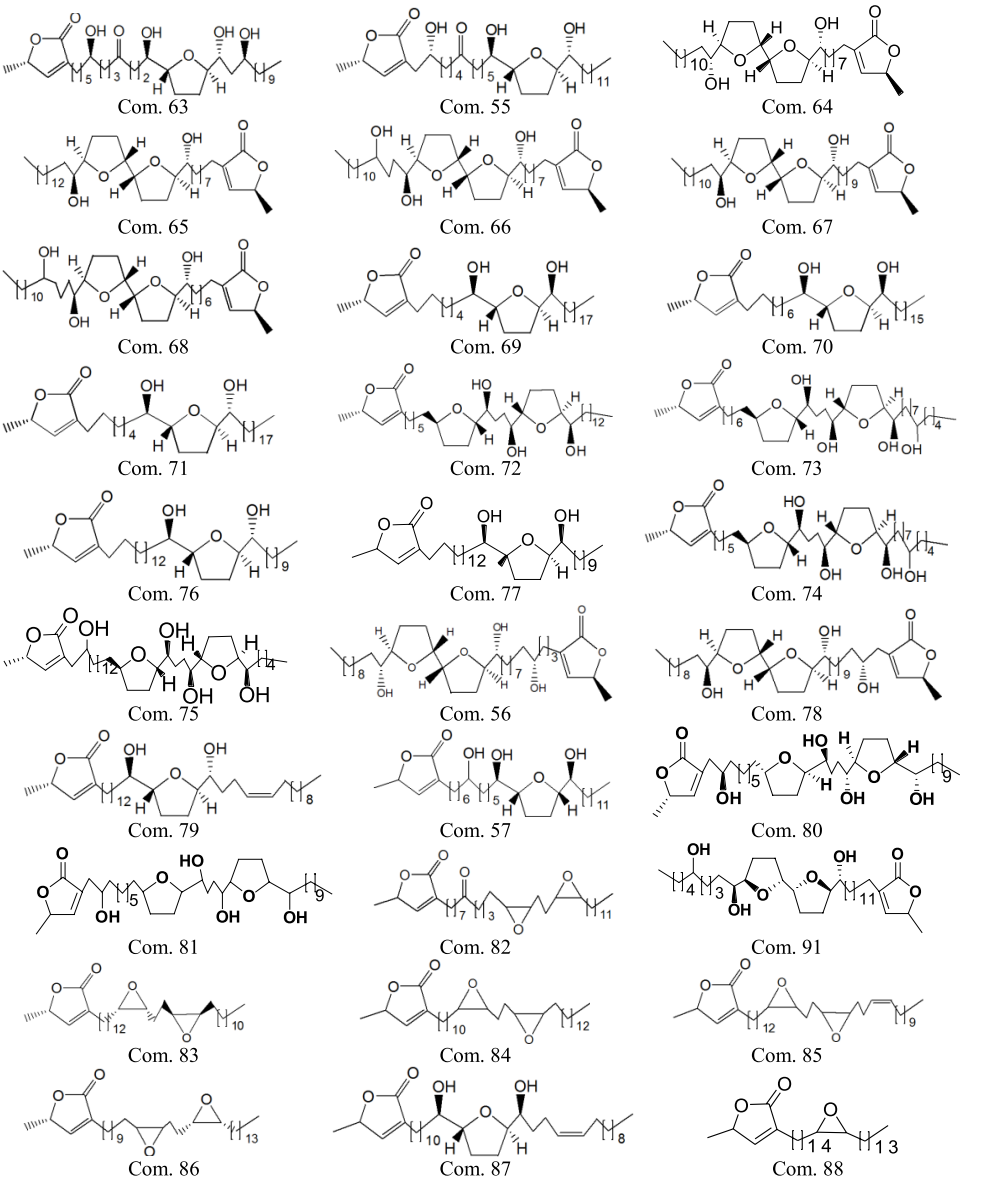



Figure 4. Chemical structures of ACGs isolated from *A. squamosa*.

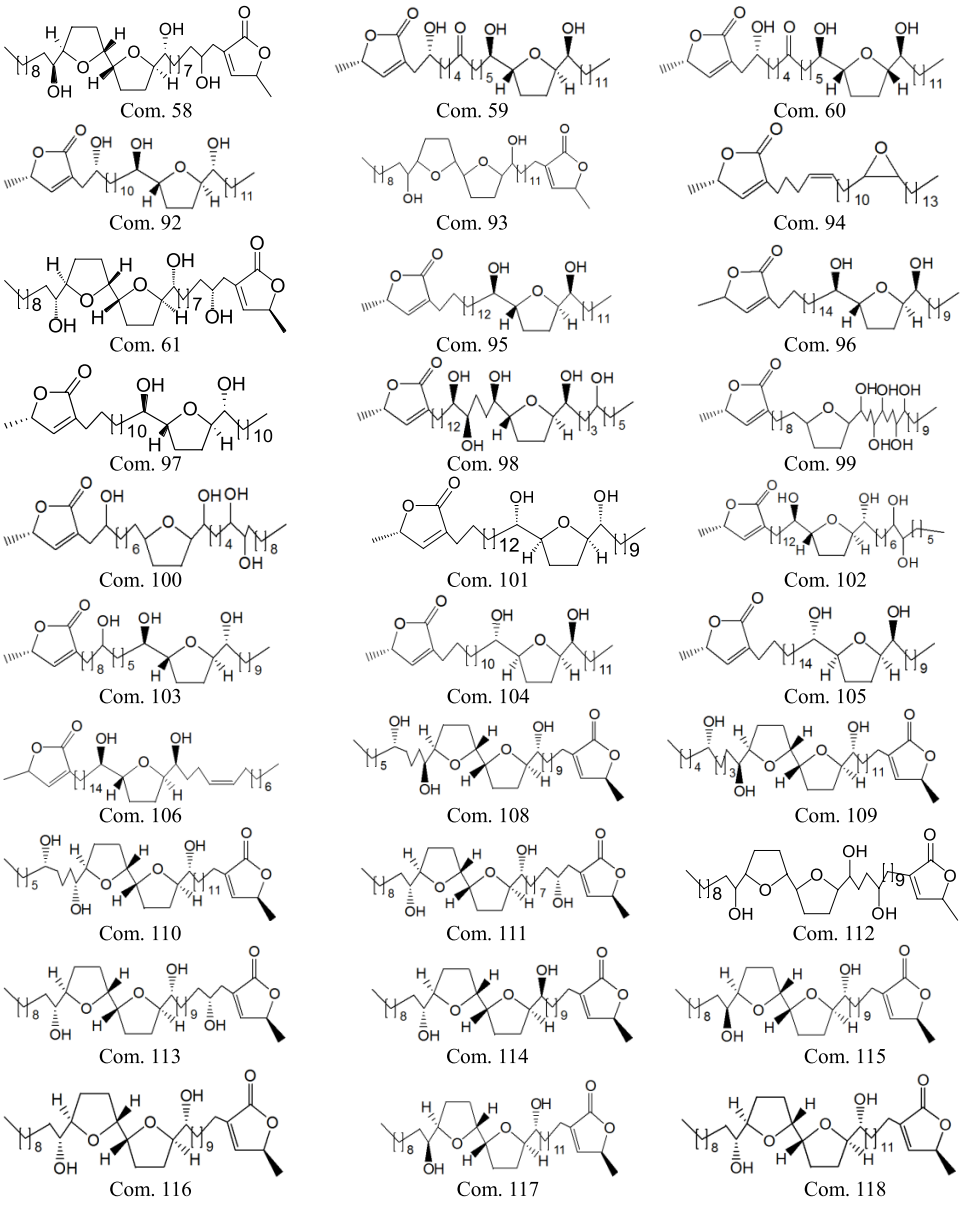



Figure 4. (*Continued*)

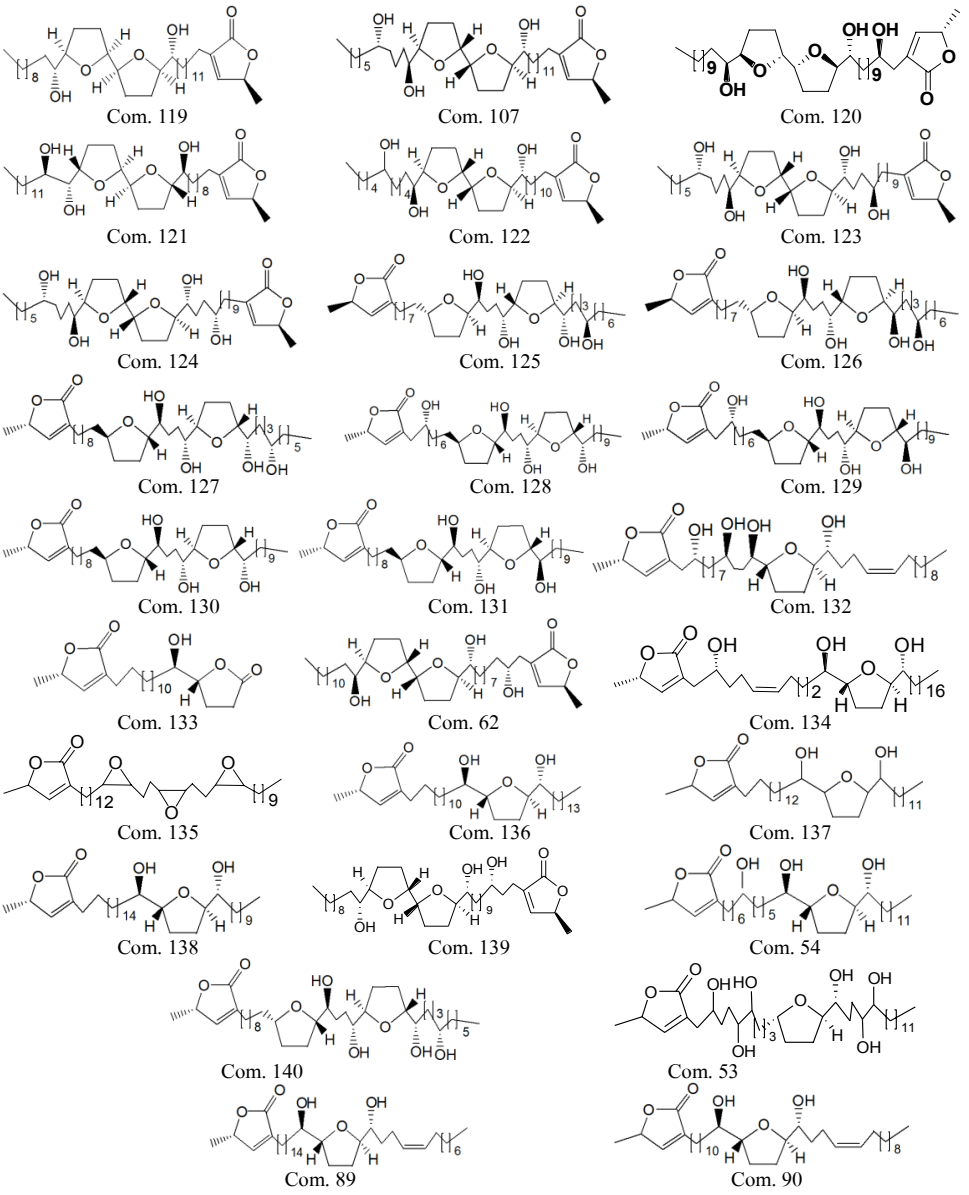



Figure 4. (*Continued*)

The common skeleton is characterized by a long fatly chain ending in a α,β-unsaturated γ-methyl-γ-lactone (Kojima and Tanaka, 2009). Since the first ACG (uvaricin) was isolated from *uvaria accuminata* in 1982, more than 500 ACGs have been discovered from different parts of species in *Annoneceae* family (McLaughlin, 2008). In recent years, ACGs have attracted extensive scientific interest, due to their specific structures and significant

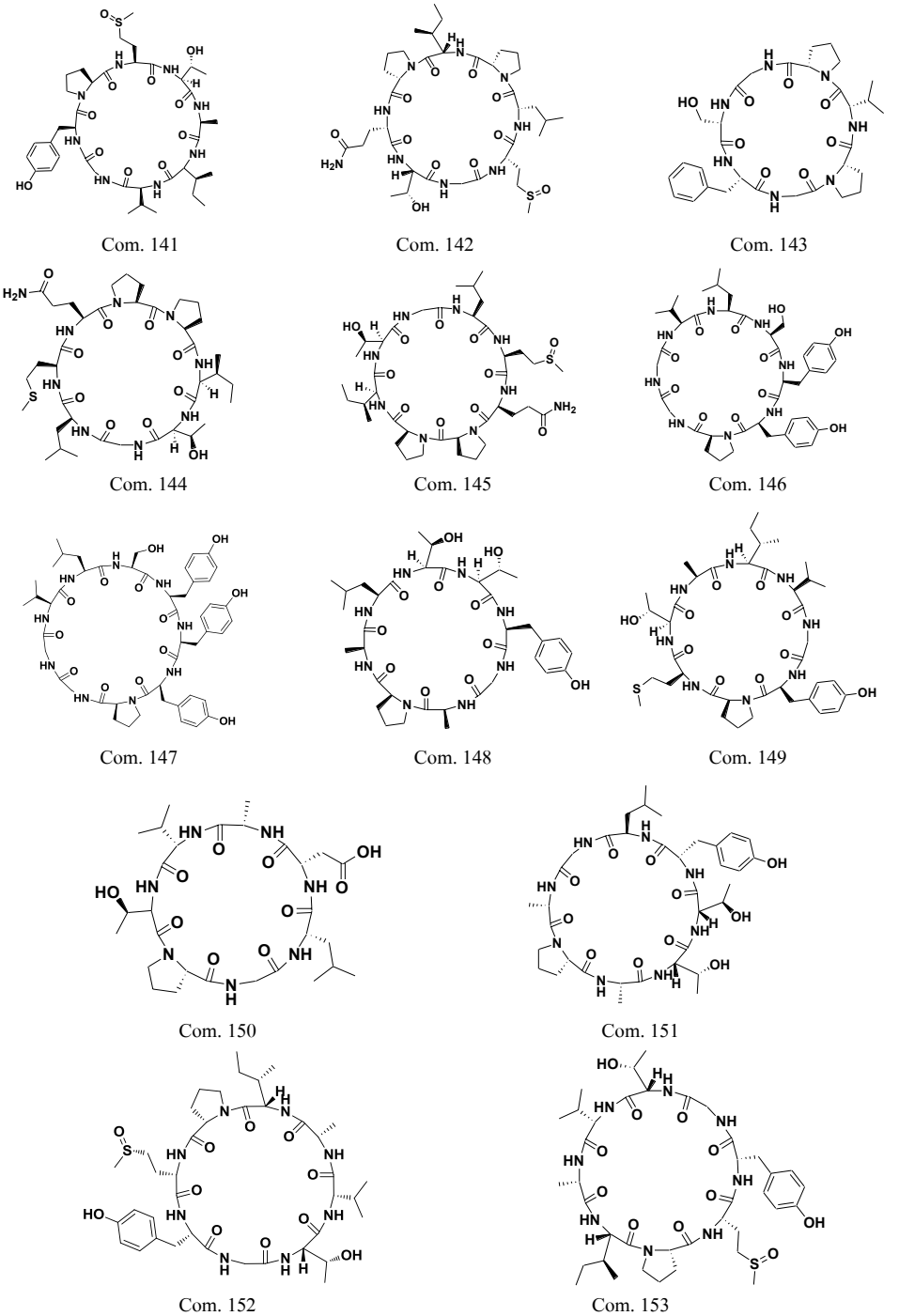



Figure 5. Chemical structures of CPs isolated from *A. squamosa*.

**Table 1. Chemical Compounds Isolated from *A. squamosa***

| No. | Plant Part | Compounds | Class | Biological Activity | References |
|---|---|---|---|---|---|
| 1 | Fruits | *ent*-kaur-16-en-19-ol | DIT | | (Wu *et al.*, 1996) |
| 2 | Fruits | *ent*-kaur-16-en-19-oic acid | DIT | Toxicity against lung 95-D and ovarian A2780 cancer cells | (Wu *et al.*, 1996; Zhou *et al.*, 2013) |
| 3 | Fruits | *ent*-kaurane-16β, 17, 19-triol | DIT | | (Wu *et al.*, 1996) |
| 4 | Fruits | 4α-hydroxy-19-nor-*ent*-kauran-17-oic-acid | DIT | | (Wu *et al.*, 1996) |
| 5 | Fruits, Stems | 16α,17-dihydroxy-*ent*-kauran-19-oic acid | DIT | | (Wu *et al.*, 1996; Chen *et al.*, 2015) |
| 6 | Fruits, Pericarp | *ent*-16β,17-dihydroxykauran-19-al | DIT | | (Wu *et al.*, 1996; Chen *et al.*, 2015) |
| 7 | Fruits | 16β,17-dihydroxy-*ent*-kauran-19-oic acid | DIT | Anti-inflammatory activities | (Wu *et al.*, 1996; Yeh *et al.*, 2005) |
| 8 | Fruits, Stems | 17-hydroxy-16α-*ent*-kauran-19-oic acid | DIT | | (Wu *et al.*, 1996; Yang *et al.*, 2002) |
| 9 | Fruits, Stems | 17-hydroxy-16β-*ent*-kauran-19-oic acid | DIT | | (Wu *et al.*, 1996; Yang *et al.*, 2002) |
| 10 | Fruits, Stems | 17-hydroxy-16β-*ent*-kauran-19-al | DIT | Inhibitory effects on platelet aggregation | (Wu *et al.*, 1996; Yang *et al.*, 2002) |
| 11 | Fruits | 17-acetoxy-16β-*ent*-kauran-19-oic acid | DIT | | (Wu *et al.*, 1996) |
| 12 | Fruits | 19-formyl-*ent*-kauran-17-oic acid | DIT | | (Wu *et al.*, 1996) |
| 13 | Fruits, Barks | Annosquamosin A | DIT | | (Wu *et al.*, 1996; Sun *et al.*, 2012) |
| 14 | Fruits, Barks, | Annosquamosin B | DIT | Toxicity against lung 95-D and ovarian A2780 cancer cells | (Wu *et al.*, 1996; Sun *et al.*, 2012) |
| 15 | Barks | (4α-)19-nor-*ent*-kaurane-4,16,17-triol | DIT | | (Zhou *et al.*, 2013) |
| 16 | Barks | (4α,16α)-17-(acetyloxy)-19-nor-*ent*-kaurane-4,16-diol | DIT | | (Zhou *et al.*, 2013) |
| 17 | Barks | 17-hydroxy-*ent*-kaur-15-en-19-al | DIT | Toxicity against lung 95-D and ovarian A2780 cancer cells | (Zhou *et al.*, 2013) |
| 18 | Barks | *ent*-15β-hydroxy-kaur-16-en-19-oic acid | DIT | | (Sun *et al.*, 2012) |
| 19 | Barks | 15,16-epoxy-17-hydroxy-*ent*-kauran-19-oic acid | DIT | Toxicity against lung 95-D and ovarian A2780 cancer cells | (Sun *et al.*, 2012) |
| 20 | Barks | 16α, 17-dihydroxy-*ent*-kauran-19-oic acid methyl ester | DIT | Toxicity against lung 95-D and ovarian A2780 cancer cells | (Sun *et al.*, 2012; Zhou *et al.*, 2013) |
| 21 | Barks | 16-α-hydroxykauranoic acid | DIT | | (Sun *et al.*, 2012) |
| 22 | Barks, Stems | Annosquamosin C | DIT | Toxicity against lung 95-D cancer cells | (Yang *et al.*, 2002; Zhou *et al.*, 2013) |
| 23 | Stems, Pericarp | Annosquamosin D | DIT | | (Yang *et al.*, 2002; Chen *et al.*, 2015) |

**Table 1. (*Continued*)**

| No. | Plant Part | Compounds | Class | Biological Activity | References |
|---|---|---|---|---|---|
| 24 | Stems | Annosquamosin E | DIT | | (Yang *et al.*, 2002) |
| 25 | Stems | Annosquamosin F | DIT | | (Yang *et al.*, 2002) |
| 26 | Stems | Annosquamosin G | DIT | | (Yang *et al.*, 2002) |
| 27 | Stems | 4α-hydroxy-19-nor-*ent*-kauran-17-oic-acid | DIT | | (Yang *et al.*, 2002) |
| 28 | Stems | 16α-hydro-*ent*-kauran-17,19-dioic acid | DIT | | (Yang *et al.*, 2002) |
| 29 | Stems | 16β-hydro-*ent*-kauran-17,19-dioic acid | DIT | | (Yang *et al.*, 2002) |
| 30 | Stems, Pericarp | 16β-hydroxy-17-acetoxy-*ent*-kauran-19-oic acid | DIT | | (Yang *et al.*, 2002; Chen *et al.*, 2015) |
| 31 | Stems | 16α-hydro-19-al-*ent*-kauran-17-oic acid | DIT | | (Yang *et al.*, 2002) |
| 32 | Stems | 16α,17-dihydroxy-*ent*-kauran-19-al | DIT | Toxicity against lung 95-D and ovarian A2780 cancer cells | (Yang *et al.*, 2002; Zhou *et al.*, 2013) |
| 33 | Stems | Annomosin A | DIT | | (Yang *et al.*, 2002) |
| 34 | Stems | (+)-anomuricine | ALK | | (Yadav *et al.*, 2011) |
| 35 | Stems | N-methyl-6,7-dimethoxyisoquinolone | ALK | Immune stimulating activity | (Yadav *et al.*, 2011; Soni *et al.*, 2012) |
| 36 | Stems | N-methylcorydaldine | ALK | | (Yadav *et al.*, 2011) |
| 37 | Stems | 5-((6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-methoxybenzene-1,3-diol | ALK | | (Jayendra and Kumar, 2013) |
| 38 | Stems | 6,7-dimethoxy-2-methylisoquinol | ALK | | (Jayendra and Kumar, 2013) |
| 39 | Stems | (1R,3S)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-1,3-diol | ALK | | (Jayendra and Kumar, 2013) |
| 40 | Stems, Leaves | Anonaine | ALK | | (Bhakuni *et al.*, 1972) |
| 41 | Stems, Leaves | Roemerine | ALK | Enhance the cytotoxic response | (You *et al.*, 1995) |
| 42 | Stems, Leaves | Norlaureline | ALK | | (Bhakuni *et al.*, 1972) |
| 43 | Stems, Leaves | Aporphine | ALK | | (Bhakuni *et al.*, 1972) |
| 44 | Stems, Leaves | Norcorydine | ALK | | (Bhakuni *et al.*, 1972) |
| 45 | Stems, Leaves | Corydine | ALK | | (Bhakuni *et al.*, 1972) |
| 46 | Stems, Leaves | Norisocorydine | ALK | | (Bhakuni *et al.*, 1972) |
| 47 | Stems, Leaves | Isocorydine | ALK | | (Bhakuni *et al.*, 1972) |

**Table 1.** (*Continued*)

| No. | Plant Part | Compounds | Class | Biological Activity | References |
|---|---|---|---|---|---|
| 48 | Stems, Leaves | Glaucine | ALK | | (Bhakuni *et al.*, 1972) |
| 49 | Stems, Leaves | (+)-O-methylarmepavine | ALK | Immune stimulating activity | (Soni *et al.*, 2012) |
| 50 | Stems, Leaves | Lanuginosine | ALK | Immune stimulating activity | (Soni *et al.*, 2012) |
| 51 | Stems, Leaves | Dienone | ALK | | (Bhakuni *et al.*, 1972) |
| 52 | Leaves | (−)-xylopine | ALK | Inhibiting anococcygeus muscle contraction induced by phenylephrine | (Bhaumik *et al.*, 1979; Liu *et al.*, 1989) |
| 53 | Leaves | Murihexocin C | ACG | Toxicity against human colon carcinoma Col 2 cell line | (Mazahery *et al.*, 2009) |
| 54 | Barks | 4-Deoxyannoreticuin | ACG | | (Hopp *et al.*, 1998) |
| 55 | Barks | Annoreticuin-9-one | ACG | | (Hopp *et al.*, 1998) |
| 56 | Barks | Bullacin B | ACG | | (Hopp *et al.*, 1998) |
| 57 | Barks | cis-4-deoxyannoreticuin | ACG | | (Hopp, 1997) |
| 58 | Barks | Molvizarin | ACG | | (Hopp, 1997) |
| 59 | Barks | Mosin B | ACG | | (Hopp, 1997) |
| 60 | Barks | Mosin C | ACG | | (Hopp, 1997) |
| 61 | Barks | Parviflorin | ACG | | (Hopp, 1997) |
| 62 | Barks | Squamotacin | ACG | Toxicity against breast cancer (MDR MCF-7/A) cells | (Hopp, 1997; Oberlies *et al.*, 1997) |
| 63 | Seeds | Annoglaxin | ACG | | (Li *et al.*, 2010) |
| 64 | Seeds | Annosquacin A | ACG | | (Chen *et al.*, 2012a) |
| 65 | Seeds | Annosquacin B | ACG | Toxicity against lung A549/Taxol cancer cells | (Chen *et al.*, 2012a; Yuan *et al.*, 2015) |
| 66 | Seeds | Annosquacin C | ACG | | (Chen *et al.*, 2012a) |
| 67 | Seeds | Annosquacin D | ACG | Toxicity against lung A549/Taxol cancer cells | (Chen *et al.*, 2012a; Yuan *et al.*, 2015) |
| 68 | Seeds | Annosquacin-I | ACG | Toxicity against lung A549, breast MCF-7, liver HepG2 cancer cells | (Chen *et al.*, 2011b) |
| 69 | Seeds | Annosquamin A | ACG | Toxicity against lung A549/Taxol cancer cells | (Chen *et al.*, 2012a; Yuan *et al.*, 2015) |

**Table 1. (*Continued*)**

| No. | Plant Part | Compounds | Class | Biological Activity | References |
|---|---|---|---|---|---|
| 70 | Seeds | Annosquamin B | ACG | Toxicity against hepatoma H22 and lung A549/Taxol cancer cells | (Chen *et al.*, 2012a, 2013; Yuan *et al.*, 2015) |
| 71 | Seeds | Annosquamin C | ACG | | (Chen *et al.*, 2012a) |
| 72 | Seeds | Annosquatin A | ACG | | (Chen *et al.*, 2012a) |
| 73 | Seeds | Annosquatin B | ACG | Toxicity against hepatoma H22, breast MCF-7, lung A549 cancer cells | (Chen *et al.*, 2012a, 2013) |
| 74 | Seeds | Annosquatin-I | ACG | Toxicity against lung A549, breast MCF-7, liver HepG2 cancer cells | (Chen *et al.*, 2011b) |
| 75 | Seeds | Annosquatin-II | ACG | Toxicity against lung A549, breast MCF-7, liver HepG2 cancer cells | (Chen *et al.*, 2011b) |
| 76 | Seeds | Annotemoyin-1 | ACG | Antibacterial activities; toxicity against lung A549/Taxol cells | (Rahman *et al.*, 2005; Yuan *et al.*, 2015) |
| 77 | Seeds | Annotemoyin-2 | ACG | Antibacterial activities | (Rahman *et al.*, 2005; Ndob *et al.*, 2009) |
| 78 | Seeds | Bullatacin/squamocin G/annonareticin | ACG | Toxicity against hepatoma H22, breast MDR MCF-7/Adr and leukemia L1210 cancer cells and nematicidal activities | (Araya, 2004; Chen *et al.*, 2011b; Dang *et al.*, 2011; Chen *et al.*, 2013) |
| 79 | Seeds | bullatencin | ACG | | (Ndob *et al.*, 2009) |
| 80 | Seeds | Cherimolin-1 | ACG | | (Yu *et al.*, 2005) |
| 81 | Seeds | Cherimolin-2 | ACG | | (Yu *et al.*, 2005) |
| 82 | Seeds | Corepoxylone | ACG | | (Ndob *et al.*, 2009) |
| 83 | Seeds | Diepomuricanin A | ACG | | (Ndob *et al.*, 2009) |
| 84 | Seeds | Diepomuricanin B | ACG | | (Ndob *et al.*, 2009) |
| 85 | Seeds | Dieporeticenin | ACG | | (Ndob *et al.*, 2009) |
| 86 | Seeds | Dieposabadelin | ACG | | (Ndob *et al.*, 2009) |
| 87 | Seeds | Dotistenin | ACG | | (Ndob *et al.*, 2009) |
| 88 | Seeds | Epoxyrolin B | ACG | | (Li *et al.*, 2010) |
| 89 | Seeds | Glabrencin B | ACG | | (Ndob *et al.*, 2009) |
| 90 | Seeds | Lepirenin | ACG | | (Ndob *et al.*, 2009) |

**Table 1.** (*Continued*)

| No. | Plant Part | Compounds | Class | Biological Activity | References |
|---|---|---|---|---|---|
| 91 | Seeds | Motrilin | ACG | Toxicity against breast cancer (MDR MCF-7/Adr) cells | (Oberlies *et al.*, 1997) |
| 92 | Seeds | Murisolin | ACG | | (Li *et al.*, 2010) |
| 93 | Seeds | Neo-desacetyluvaricin | ACG | | (Li *et al.*, 2010) |
| 94 | Seeds | Neo-epoxyrolin | ACG | | (Li *et al.*, 2010) |
| 95 | Seeds | Reticulatain-1 | ACG | | (Ndob *et al.*, 2009) |
| 96 | Seeds | Reticulatain-2 | ACG | | (Ndob *et al.*, 2009) |
| 97 | Seeds | Solamin | ACG | | (Chen *et al.*, 2012a) |
| 98 | Seeds | Squadiolin A | ACG | | (Liaw *et al.*, 2008) |
| 99 | Seeds | Squadiolin B | ACG | | (Liaw *et al.*, 2008) |
| 100 | Seeds | Squadiolin C | ACG | | (Liaw *et al.*, 2008) |
| 101 | Seeds | cis-annotemoyin 1 | ACG | | (Liaw *et al.*, 2008) |
| 102 | Seeds | Squafosacin B | ACG | | (Liaw *et al.*, 2008) |
| 103 | Seeds | Squafosacin C | ACG | | (Liaw *et al.*, 2008) |
| 104 | Seeds | Squafosacin F | ACG | | (Liaw *et al.*, 2008) |
| 105 | Seeds | Squafosacin G | ACG | | (Liaw *et al.*, 2008) |
| 106 | Seeds | Squamocenin | ACG | | (Ndob *et al.*, 2009) |
| 107 | Seeds | Squamocin | ACG | Antibacterial activities and nematicidal activities | (Rahman *et al.*, 2005; Dang *et al.*, 2011) |
| 108 | Seeds | Squamocin B | ACG | | (Araya, 2004) |
| 109 | Seeds | Squamocin C | ACG | Toxicity against leukemia L1210 cells | (Araya, 2004) |
| 110 | Seeds | Squamocin D | ACG | | (Araya, 2004) |
| 111 | Seeds | Squamocin E | ACG | | (Araya, 2004) |
| 112 | Seeds | Squamocin F | ACG | | (Araya, 2004) |
| 113 | Seeds | Squamocin H | ACG | Toxicity against leukemia L1210 cells, nematicidal activities | (Araya, 2004; Dang *et al.*, 2011) |
| 114 | Seeds | Squamocin I | ACG | Toxicity against leukemia L1210 cells | (Araya, 2004) |
| 115 | Seeds | Squamocin J | ACG | Toxicity against leukemia L1210 cells | (Araya, 2004) |
| 116 | Seeds | Squamocin K | ACG | | (Araya, 2004) |

**Table 1.** (*Continued*)

| No. | Plant Part | Compounds | Class | Biological Activity | References |
|---|---|---|---|---|---|
| 117 | Seeds | Squamocin L | ACG | Toxicity against leukemia L1210 cells | (Araya, 2004; Xu *et al.*, 2012) |
| 118 | Seeds | Squamocin M | ACG | | (Xu *et al.*, 2012) |
| 119 | Seeds | Squamocin N | ACG | | (Jayendra and Kumar, 2013) |
| 120 | Seeds | Squamocin-I | ACG | Toxicity against human tumor cells | (Miao *et al.*, 2015) |
| 121 | Seeds | Squamocin-II | ACG | Toxicity against human tumor cells | (Miao *et al.*, 2015) |
| 122 | Seeds | Squamocin-III | ACG | Toxicity against human tumor cells | (Miao *et al.*, 2015) |
| 123 | Seeds | Squamocin-O1 | ACG | | (Araya *et al.*, 2002) |
| 124 | Seeds | Squamocin-O2 | ACG | | (Araya *et al.*, 2002) |
| 125 | Seeds | Squamostanin A | ACG | Toxicity against colon HCT, lung A549 and prostate PC-3 cancer cells | (Yang *et al.*, 2009b) |
| 126 | Seeds | Squamostanin B | ACG | Toxicity against colon HCT, lung A549 and prostate PC-3 cancer cells | (Araya, 2004; Yang *et al.*, 2009b) |
| 127 | Seeds | Squamostatin A | ACG | | (Chen *et al.*, 2011b) |
| 128 | Seeds | Squamostatin B | ACG | | (Araya, 2004) |
| 129 | Seeds | Squamostatin C | ACG | | (Li *et al.*, 2010) |
| 130 | Seeds | Squamostatin D | ACG | Toxicity against leukemia L1210 cancer cells | (Araya, 2004; Chen *et al.*, 2011b) |
| 131 | Seeds | Squamostatin E | ACG | Toxicity against leukemia L1210 cancer cells | (Araya, 2004) |
| 132 | Seeds | Squamosten A | ACG | | (Araya, 2004) |
| 133 | Seeds | Squamostolide | ACG | | (Xie *et al.*, 2003) |
| 134 | Seeds | Squamoxinone-D | ACG | Toxicity against human tumor cells | (Miao *et al.*, 2015) |
| 135 | Seeds | Tripoxyrollin | ACG | | (Tormo *et al.*, 1999) |
| 136 | Seeds | Uvariamicin I | ACG | | (Tormo *et al.*, 1999) |
| 137 | Seeds | Uvariamicin II | ACG | | (Ndob *et al.*, 2009; Chen *et al.*, 2012a) |
| 138 | Seeds | Uvariamicin III | ACG | | (Ndob *et al.*, 2009; Chen *et al.*, 2012a) |
| 139 | Seeds | Uvarigrandin A | ACG | | (Chen *et al.*, 2011b) |
| 140 | Seeds | 12,15-cis-squamostatin A | ACG | Toxicity against lung A549/Taxol cells | (Xu *et al.*, 2012; Yuan *et al.*, 2015) |

**Table 1. (*Continued*)**

| No. | Plant Part | Compounds | Class | Biological Activity | References |
|---|---|---|---|---|---|
| 141 | Seeds | Annosquamosin A | CP | | (Li *et al.*, 1997) |
| 142 | Seeds | Cherimolacyclopeptide B | CP | | (Yang *et al.*, 2008) |
| 143 | Seeds | Cyclosquamosin A | CP | | (Morita *et al.*, 1999) |
| 144 | Seeds | Cyclosquamosin B | CP | Vasorelaxant effect | (Morita *et al.*, 1999, 2006) |
| 145 | Seeds | Cyclosquamosin C | CP | | (Morita *et al.*, 1999) |
| 146 | Seeds | Cyclosquamosin D | CP | Anti-inflammatory activities | (Morita *et al.*, 1999; Yang *et al.*, 2008) |
| 147 | Seeds | Cyclosquamosin E | CP | | (Morita *et al.*, 1999; Yang *et al.*, 2008) |
| 148 | Seeds | Cyclosquamosin F | CP | | (Morita *et al.*, 1999) |
| 149 | Seeds | Cyclosquamosin G | CP | | (Morita *et al.*, 1999) |
| 150 | Seeds | Cyclosquamosin H | CP | | (Yang *et al.*, 2008) |
| 151 | Seeds | Cyclosquamosin I | CP | | (Yang *et al.*, 2008) |
| 152 | Seeds | Squamin A | CP | | (Yang *et al.*, 2008) |
| 153 | Seeds | Squamin B | CP | | (Yang *et al.*, 2008) |

bioactivities. Numerous biological activities have been reported for ACGs, including insecticidal, antiparasitical and fungicidal activities (Zafra-Polo *et al.*, 1998; Alali *et al.*, 1999). However, the biological activities of ACGs are primary characterized as cytotoxic against cancer cells and as inhibitory against the mitochondrial complex I (NADH-ubiquinone oxidoreductase) (Tormo *et al.*, 1999; Chih *et al.*, 2001). Phytochemical investigations and pharmacological studies on different part of *A. squamosa* leaded to the identification of serial ACG compounds, as summarized in Table 1. The chemical structures of major ACGs are shown in Fig. 3.

### *Cyclic Peptides*

Cyclic peptides are described as a unique family of cyclic proteins in which this principle of topological simplicity is not obtained. This cyclotide family of proteins is abundant in *Rubiaceae* and *Violaceae* family plants and contains not only a unique amide head to tail cyclized peptide backbone, but also incorporate a cystine knot in which an embedded ring in the structure is formed by two disulfide bones. These combined features of the cyclic cystine knot produce a unique protein fold that is topologically complex and has exceptional chemical and biological stability (Craik *et al.*, 1999). The folkloric use of *A. squamosa*, as an insecticidal, an antitumor agent, antidiabetic, anti-oxidant, anti-lipidimic and anti-inflammatory agent, has been characterized due to the presence of the cyclic peptides (Gajalakshmi *et al.*, 2011). CPs were also reported in literature on *A. squamosa* which note several effective pharmacological activities. These cyclic peptides are displayed in Fig. 4.

### *Essential Oil*

GC-MS analyses on leaf oil of *A. squamosa*, which was collected from North Indian Plains showed the presence of mostly sesquiterpenes, with the major compounds being β-Caryophyllene and germacrene D (Garg and Gupta, 2005). A study on *A. squamosa* collected from Brazil found the major identified compounds were (E)-caryophyllene (27.4%), germacrene D (17.1%) and bicyclogermacrene (10.8%) in leaf oil (Meira *et al.*, 2015). Another investigation on *A. squamosa* bark oil identified the significant volatile oil constituting of caryophyllene oxide (29.38%), kaur-16-ene (19.13%), germacrene D (11.44%), bisabolene (4.48%) and 1H-Cycloprop(e)azulene (3.46%) (Chavan *et al.*, 2006). The fruit pulp essential oil was found to contain a high concentration of monoterpenes, including pinene, sabinene and limonene (Andrade *et al.*, 2001).

## Biological Activities

### *Anticancer Activity*

Plenty of studies on extracts of different parts and the isolated ACGs from this plant indicated the significant antiproliferative activities against various cancer cell lines. However, few investigations illustrated the underlying mechanism of anticancer action

**Table 2. Anticancer Studies on *A. squamosa***

| Plant Part | Subject of Studies | Effect | Reference |
|---|---|---|---|
| Aqueous extract of the seeds | Ascites BC-8 cancer cells | Generation of free radicals and induction of apoptosis | (Pardhasaradhi *et al.*, 2004) |
| Aqueous and organic extract of the seeds | Breast MCF-7 and erythroleukemia K-562 | Induction of ROS generation and reduction of glutathione levels | (Pardhasaradhi *et al.*, 2005) |
| Total annonaceous ACGs from the seeds | $H_{22}$-bearing mice and hep-atocarcinoma Bel-7402 cells | Induction of apoptosis, arresting oncocytes at $G_1$ phase and increasing the activities of Caspase-3 | (Yang *et al.*, 2015) |
| Isolated ACGs from the leaves | Colon carcinoma Col 2 cell line | Isolated of Murihexocin C and its apoptosis inducing effect | (Mazahery *et al.*, 2009) |

(Table 2). Recent metabolic studies were performed *in vivo* by our team to determine the mechanism of total ACGs from seeds against hepatic cancer cells (H22). This portion was able to induce apoptosis through the mitochondrial-mediated pathway. In addition, *in vitro* studies were performed to illustrate the mechanism of the anticancer effect of isolated ACGs. Annosquacin B, an isolated ACG from seeds, was able to restrain the proliferation of multi-drug resistant MCF-7 cell, which was associated with cell cycle arrest in the G1 phase. All detailed reports about the research above will be published soon. The structure-activity relationships of ACGs against different cancer cells and multi-drug resistant cancer cells were performed *in vitro* (Chen *et al.*, 2013; Yuan *et al.*, 2014, 2015). The results revealed that different types of ACGs show different inhibitory activities against different cancer cells.

Recently a study on different extractions from *A. squamosa* against the S180 tumor bearing mice concluded that the main antitumor and toxic compounds may exist in the seeds (Deng *et al.*, 2012). *In vivo* studies were performed on the aqueous and organic extracts of seeds against a rat histiocyte tumor cell line, AK-5. The results showed that both extracts caused a significant tumor cell apoptosis with enhanced caspase-3 activity, caused the downregulation of anti-apoptotic genes Bcl-2 and $Bcl_{XL}$, and thus would enhance the generation of intracellular reactive oxygen species (ROS). In addition, DNA fragmentation and annexin-V staining confirmed that the apoptosis in tumor cell is induced by extracts through the oxidative stress (Pardhasaradhi *et al.*, 2004). Further *in vitro* studies showed that the aqueous and the organic extract of the seeds could induce apoptosis in MCF-7 and K-562 cells. Treatment of MCF-7 and K-562 cells with both extracts resulted in nuclear condensation, DNA fragmentation, the induction of ROS generation and reduced intracellular glutathione levels. In addition, down regulation of Bcl-2 and PS externalization by Annexin-V staining suggested that the extracts induce apoptosis in MCF-7 and K-562 cells through oxidative stress (Pardhasaradhi *et al.*, 2005). The extract of seeds even at the dose of 18 mg/kg inhibited the growth of $H_{22}$ hepatoma cells in mice with an inhibitory rate of 69.55% and no side effects were observed (Chen *et al.*, 2012b).

Recently, Wang *et al.* (2014) examined the anticancer potential of the aqueous extract and ethyl acetate extract of the *A. squamosa* leaves against various cancer cell lines through MTT assay. The comprising result showed that the ethyl acetate extract had significant anticancer activities on human epidermoid carcinoma cell line KB-3-1 and colon cancer cell line HCT-116 with IC 50 value of $13.66 \pm 0.73$ µg/mL and $1.37 \pm 0.64$ µg/mL.

Antitumor studies on *A. squamosa* were not only limited to *in vivo* and *in vitro* researches. 86 cases of non-small cell lung cancer were treated with "Bujing Jiedu" (*Cordyceps sinensis* and seeds of *A. squamosa*), compared with the chemical therapy group. The result presented that 1-year and 2-year overall survival was similar to the chemotherapy group. In comparison to chemotherapy patients, patients in "Bujing Jiedu" group had higher quality of life (Johns *et al.*, 2011; Qing, 2012).

### *Antidiabetic and Hypolipidemic Activity*

The chronic disease of diabetic mellitus afflicts a large proportion of people all over the world. Therefore, an effective traditional plant assisted therapy would be very advantageous to decrease the prevalence of diabetic complications and to improve the quality of patients' life. Due to the traditional use of *A. squamosa* against diabetes, several studies were performed to evaluate the potential *in vivo*. Shirwaikar *et al.* (2004b) reported that the daily oral administration of streptozotocin induced in diabetic rats with the alcohol extract of *A. squamosa* leaves (250 mg/kg) for 12 days increased their fasting plasma glucose concentration from 186.75 mg/dL to 121.04 mg/dL. In addition, the aqueous extract at the same dose significantly reduced the concentration from 175.20 mg/dL to 94.11 mg/dL with liver glycogen levels and pancreatic TBARS levels decreasing (Shirwaikar *et al.*, 2004c).

Based on the traditional application of *A. squamosa* against diabetes, other similar studies were performed to examine the aqueous extract of *A. squamosa* leaves against STZ-induced diabetes in rats and reported the same prospective antidiabetic activities (Kaleem *et al.*, 2006, 2008). This activity was explained by its anti-oxidant and hypoglycemic capacities, as well as protective effects against pancreatic β-cell (Gupta *et al.*, 2008). The anti-oxidant activity of *A. squamosa* is demonstrated in next paragraph. Diabetic wounds are defined as chronic wounds or lesions that take a long time to heal or fail to heal (Wysocki, 1996). The *A. squamosa* ethanolic extract was found to having beneficial effects on enhancing the rates of epithelialisation and wound contraction with the formation of glycosaminoglycans and collagen during wound healing (Ponrasu and Suguna, 2012, 2014).

### *Anti-oxidant Activity*

The immoderate generation of intracellular ROS, as a precursor of oxidative stress, would subsequently stimulate metabolic deficiency and cellular death through biochemical and physiological lesions (Chance *et al.*, 1979). The identification of anti-oxidants from natural products has triggered great interests in the pharmaceutical field for an outstanding role in

nullifying the destructive effects of ROS (Wang *et al.*, 2015; Das *et al.*, 2016; Ma *et al.*, 2016). ABTS, DPPH and nitric oxide radical tests on the ethanolic extract of *A. squamosa* leaves revealed the marked anti-oxidative activity accompanied with the moderate scavenging activity of superoxide radicals and antilipid peroxidation potential (Shirwaikar *et al.*, 2004a). Extracts of different parts from *A. squamosa* were shown to have good anti-oxidant capacity (Seema *et al.*, 2008; Mariod *et al.*, 2012). The anti-oxidant potential of each extract from *A. squamosa* leaves was determined by scavenging activity and by reducing the power of free radicals. The results obtained from *in vitro* studies of anti-oxidant activities clearly suggested that the methanol, chloroform, and aqueous extract of *A. squamosa* leaves possess anti-oxidant activities (Kalidindi *et al.*, 2015). The wine prepared from *A. squamosa* fruits were also revealed to have good anti-oxidant capacity (Jagtap and Bapat, 2015). There were several anti-oxidative phytochemicals isolated from *A. squamosa* (Panda and Kar, 2007, 2015). All the studies above strongly suggested that as a natural source, *A. squamosa* have the potential of being an anti-oxidant.

### *Anti-Inflammatory and Analgesic Activity*

Inflammation and soreness occur as a result of the first line defense against injuries and offer the primary signs in the diagnosis of many diseases (Singh *et al.*, 2012). A lot of medicinal plants available worldwide are helpful in the treatment of pain and inflammation (Huang *et al.*, 2016; Sui *et al.*, 2016). *A. squamosa* is one of these plants. Intra-peritoneal treatment in rats with ethanolic extraction of *A. squamosa* leaf (100 mg/kg) significantly reduced the carrageenan-induced edema in rat paws by 47.16%, exhibiting its anti-inflammatory activities (Singh *et al.*, 2012). Nevertheless, oral administration in the same model of the petroleum ether extract of *A. squamosa* bark demonstrated higher inhibition percentage with lower dose (Chavan *et al.*, 2011). Both extracts showed significant suppression of abdominal writhing induced with acetic acid and the inhibition of pain induced with thermal stimulus, exhibiting powerful antinociceptive activities (Chavan *et al.*, 2011; Singh *et al.*, 2012). The same assays showed the anti-inflammatory and analgesic activities of several phytochemicals isolated from *A. squamosa*, which were shown to be induced through the suppression of TNF-α and IL-6 proteins (Chavan *et al.*, 2010, 2011; Wu *et al.*, 2014). Ulcers, as a development of inflammation, could also be suppressed by *A. squamosa*. Comparing with the control group, a significant decrease of CAT, GSH and Gpx appeared through the treatment of *A. squamosa* leaf aqueous extract. The leaf aqueous extract at dose 300 mg/kg for 4 weeks had the ability of counteracting ulcerative colitis that was induced by acetic acid (Ibrahim *et al.*, 2015). These findings demonstrated the anti-inflammatory and analgesic activities of *A. squamosa* and its traditional use as antiulcerative.

### *Antihypertensive Activity*

While a fraction of total ALKs from sugar apple was reported to be antihypertensive (Husain, 1992). Morita *et al.* (2006) found that the extract of from the seeds of *A. squamosa*

showed vasorelaxant effect on rat aorta. Further search for bioactive compounds targeting aortic smooth muscle, cyclosquamosin B (cyclic peptide), which was isolated from seeds showed a hypotensive effect on rat aorta (Morita *et al.*, 2006). This effect was suggested to have been induced through the peripheral mechanisms involving the inhibition of voltage-dependent $Ca^{2+}$-channels (VDC).

### *Hepatoprotective Activity*

Natural remedies from medicinal plants are considered as an effective and safe alternative treatment for liver toxicity. A study was performed *in vivo* to determine the hepatoprotective potential of the alcoholic extract of *A. squamosa* leaves. This study was conducted on DEN-induced liver injury in mice, and the levels of total and direct bilirubin were measured in oral treatment at the dose of 5 g/kg of the leaf extract for 30 days. The histopathological pattern of treatment group showed a minimal inflammation with moderate portal triaditis and their lobular architecture is normal (Raj *et al.*, 2009). Saleem *et al.* (2008) investigated the effect of alcoholic and water extract of sugar apple against isoniazid (INH) + rifampicin (RIF) induced rats. The results revealed that the extracts were not able to revert completely hepatic injury induced by INH + RIF, and they could reduce toxicity of these drugs in liver. This would be helpful to plan the strategy of therapy of hepatic problems using products from this plant.

### *Antiparasitic Activity*

Protozoal diseases are a major type of global problem affecting millions of people worldwide. The most prominent and widely distributed infections are due to protozoal of genus *Leishmania*, *Trypanosoma* and *Plasmodium*, causing leishmaniasis, sleeping sickness as well as Chagas disease and malaria, respectively (Glaser and Holzgrabe, 2016). The development of resistance empirically discovered drugs represents a major hindrance to treatment of protozoal diseases. Furthermore, in case of long-term usage, toxicity and several side effects have made available treatments more unsatisfactory (Moghadamtousi *et al.*, 2015). Natural extracts are good and safe alternatives due to their low toxicity to mammal. As a natural agent, *A. squamosa* has been subjected to various pathogenic parasites to ascertain its cytotoxicity (Table 3). The essential oils from *A. squamosa* showed inhibitory activity against *Trypanosoma cruzi*. Trypanocidal activity was reported with $IC_{50}$ values lower than 15 µg/mL (Meira *et al.*, 2015). The lower antiprotozoal effect of *A. squamosa* pericarp was reported against *Haemaphysalis bispinosa*, *Hippobosca maculate*, and *R. microplus* (Madhumitha *et al.*, 2012). A bioassay-guided research on the *A. squamosa* seeds against *Meloidogyne incognita* and *Bursaphelenchus xylophilus* led to the isolation of eight ACGs as bioactive compounds. Three of these displayed significant activity (Dang *et al.*, 2011). An ALK and an ACG, isolated from leaves, were tested against two forms of *Leishmania chagasi*. Against promastigotes, the ALK showed an $IC_{50}$ value of 23.3 µg/mL. In the promastigotes and amastigote assay, the ACG showed the $IC_{50}$

**Table 3. Antiparasitic Studies on *A. squamosa***

| Plant Part | Subject of Studies | Result | Reference |
|---|---|---|---|
| Essential oils from *A. squamosa* leaves | Trypomastigote and epimastigote forms of *T. cruzi* | $IC_{50}$ values were 12.7 µg/mL and 14.9 µg/mL respectively | (Meira *et al.*, 2015) |
| Aqueous extract of the pericarp | Adults of *H. bispinosa*, *Hippobosca maculate*, and larvaes of *R. microplus* | $LC_{50}$ values were 404.51, 600.75 and 548.28 µg/mL respectively. | (Madhumitha *et al.*, 2012) |
| Methanol extract of *A. squamosa* seeds | *M. incognita* and *B. xylophilus* (nematode) | Bioassay-guided isolation of squamocin G, squamocin H and squamocin | (Dang *et al.*, 2011) |
| *A. squamosa* leaves | Promastigotes and amastigote forms of *Leishmania chagasi* | Bioassay-guided isolation of O-me-thylarmepavine and an ACG | (Vila-Nova *et al.*, 2011) |

values ranging from 25.9 µg/mL to 37.6 µg/mL and 13.5 µg/mL to 28.7 µg/mL, respectively (Vila-Nova *et al.*, 2011).

### *Antimalarial Activity*

Malaria, as one of the most enervating diseases, afflicts a large proportion of population, especially in Africa (Murray *et al.*, 2012). The available antimalarial drugs demonstrate varying degrees of failure due to the rapid spread of malaria. Meanwhile, there is a limited armory of drugs in widespread use for falciparum malaria (Winstanley, 2000). An affordable new drug is definitely warranted. The methanolic extract of leaves was assayed against two strains of *Plasmodium falciparum*: chloroquine (CQ) sensitive strain 3D7 and resistant strain Dd2; a promising antimalarial activity was obtained with $IC_{50}$ values of 2 µg/mL and 30 µg/mL, respectively. While the stem bark showed lower activity with $IC_{50}$ values of 8.5 µg/mL and 120 µg/mL, respectively (Tahir *et al.*, 1999). Other studies on bark methanol of *A. squamosa* also confirmed the reported toxicity against CQ sensitive strain (3D7 and D10) and a CQ resistant strain (Dd2) of *P. falciparum* (Johns *et al.*, 2011; Kamaraj *et al.*, 2012). A bioassay-guided investigation on the barks of *A. squamosa* against CQ sensitive and resistant strain of *P. falciparum* led to the isolation of three ALKs, N-nitrosoxylopine, roemerolidine and duguevalline. Isolated aporphine ALKs displayed *in vitro* antiplasmodial activity with $IC_{50}$ values ranging from 7.8 µM to 34.2 µM (Johns *et al.*, 2011). These findings supported the folk use of *A. squamosa* as an antimalarial.

### *Insecticidal Activity*

Natural pesticides, also called botanicals, have a high potential as an alternative to synthetic pesticides and their associated negative effects (Wezel *et al.*, 2014). Due to the existence of ACGs, *Annona* plants such as *A. squamosa* have been shown to be promising biological

pesticides among tropical plants. A study on *Annona* species showed the strong growth inhibition effects of *A. squamosa* against *chrysanthemum aphis* (Tattersfield and Potter, 1940). In another investigation, different extracts of the seeds were examined against Raj, CR 1, FSS II and CTC-12 strains of *Tribolium castaneum*. The promising activity was obtained from the food medium treatment of the petroleum ether extracts, and this activity was attributed to the presence of ACGs in the less polar fractions (Khalequzzaman and Sultana, 2006). The similar promising insecticidal activity was reported against *Trichoplusia ni* in the laboratory and the greenhouse (de Cássia Seffrin *et al.*, 2010). In addition, the toxicities of aqueous and aqueous emulsion of ethanolic seed extracts were evaluated against *Plutella xylostella* and *Trichoplusia ni*. The results showed $LC_{50}$ values of aqueous extracts ranging from 0.2% to 35.2%, $LC_{50}$ values of aqueous emulsions of ethanolic extracts ranging from 0.02% to 0.67% for neonate to fourth-instar DBM (Leatemia and Isman, 2004). A bioassay-guidance investigation on *A. squamosa* seed against *D. melanogaster* led to the isolation of two ACGs (squamocin and neoannonin) as bioactive compounds (Kawazu *et al.*, 1989). The partly purified flavonoids from aqueous leaf extract of *A. squamosa* showed 80% insecticidal activity against *Callosobruchus chinensis* at a concentration of 0.07 mg/mL (Kotkar *et al.*, 2002).

Mosquito-controlling activity of the methanolic extract of *A. squamosa* leaves against *Culex quinquefasciatus* Say revealed mosquito mortality of 61.6% and 93.6% at 3% (v/v) and 5% (v/v) concentrations after 24 h, respectively (Jaswanth *et al.*, 2002). In addition, the total ALKs of *A. squamosa* leaves showed larvicidal growth-regulating and chemosterilant activities against *Anopheles stephensi* at concentrations of 50–200 ppm (Saxena *et al.*, 1993). A comprehensive investigation reported the insecticidal activity of *A. squamosa* against Anopheles mosquito larvae under laboratory and semi-field conditions. The dose response result showed that the $LC_{50}$ values of different extracts were obtained at the concentrations lower than 50 ppm after 24 h and 5 h exposures, respectively. The $LC_{50}$ and $LC_{90}$ values for *A. squamosa* oil were 41.5 and 79.2 ppm, respectively against 3rd-4th instar *An. arabiensis* larvae after 24 h exposure (Assefa, 2011).

### *Antimicrobial and Antifungal Activity*

In recent decades, of the one-quarter to one-half of all pharmaceuticals dispensed in USA having higher-plant origins, very few are intended to use as antimicrobials, since we have relied on bacterial and fungal sources for these activities (Marjorie Murphy, 1999). Due to the worsening situation of clinical drug resistance in fungi and bacteria (Adcock, 2002; Araya, 2004), new antimicrobial and anifungidal drugs are urgently needed.

Different extracts of *A. squamosa* leaves were assayed the antibacterial activities against two Gram-positive and two Gram-negative bacteria. The screening results showed that the highest inhibition was observed in methanolic extract against *Pseudomonas aeruginosa* ($IC_{50}$: 130 µg/mL) and *Escherichia coli* ($IC_{50}$: 180 µg/mL) (Patel and Kumar, 2008). Different extracts of fruits showed positive effect in all tested bacteria strains. These extracts had stronger activity against Gram-negative bacteria than Gram-positive bacteria (Vijayalakshmi and Nithiya, 2015).

To evaluate the antifungal capacity of *A. squamosa* leaves, methanol, chloroform and aqueous extracts were evaluated against five strains of fungi (*Alternaria alternate*, *Candida albicans*, *Fusarium solani*, *Microsporum canis* and *Aspergillus niger*) by the agar well diffusion method. Meanwhile, the minimum inhibitory concentrations of different extracts were determined. The methanolic extracts showed the highest inhibitory activity (Kalidindi *et al.*, 2015). The promising antifungal properties of fresh fruit extracts were also reported (Vijayalakshmi and Nithiya, 2015). A bio-assayed guidance study on seeds led to separation of three ACGs. All of isolated constituents showed dose-dependent activities against the germination of sporangium and zoospore of *P. infestans* (Dang *et al.*, 2011).

### *Molluscicidal Activity*

To evaluate planted-derived molluscicides of the vector control of schistosomiasis, different parts of *Annona* species were tested against *Biomphalaria glabrata*, both in egg masses and in adult worms. In 2001, Dos Santos and Sant'Ana (2001) demonstrated that the root of *A. squamosa* possesses significant toxicity against adult forms with an $LD_{90}$ value of 8.55 ppm. Additional toxicity of the *A. squamosa* seeds and leaves against snail eggs masses was notable among *Annona* species. In the same year, a study was performed on different parts of *A. squamosa* against adult *lymnaea acuminate*. The result showed the highest molluscicidal activities of seed extracts. In addition, combinations of equal parts, seed power with oil from plants, was more toxic than the individual components (Singh and Singh, 2001).

## Toxicology

An investigation published in 1999 revealed that the incidence of atypical parkinsonism in Guadeloupe has a possible association among the consumption of fruits from Annonaceae family (Caparros-Lefebvre and Elbaz, 1999). Furthermore, the neurodegenerative tauopathy endemic in Guadeloupe Island exhibited a strong link with the consumption of fruits containing ACGs (Escobar-Khondiker *et al.*, 2007). Therefore, ACGs, natural lipophilic inhibitor of mitochondrial complex I, are considered as environmental neurotoxins led to neurological disorders, such as atypical Parkinsonism in Guadeloupe (Höllerhage *et al.*, 2009). A recent research proposed the fruits of *A. squamosa* may be environmental neurotoxins as a source of exposure to ACGs (Bonneau *et al.*, 2012). In striatal neurons of rats, annonacin (ACG) induced ATP depletion and retrograded the transport of mitochondria to the cell soma, which induced changes in the intracellular distribution of tau and resulted in characteristics with some neurodegenerative diseases (Escobar-Khondiker *et al.*, 2007).

Hence, the consumption of Annonaceae production should be below than a certain value. Toxicity testing of extracts from *A. squamosa* leaves and seeds was performed on eyes and on ear skin of rabbits. The results revealed that diethyl ether extracts produce highest toxicity in eyes and petroleum ether extracts show the most poisonous on ear skin (Sookvanichsilp *et al.*, 1994). The toxicological evaluation of *A. squamosa* root was tested on mice by oral administration. The results of the acute toxicity study revealed that treated

animal group did not show any toxic symptoms in behavior and mortality up to dose level of 2000 mg/kg (Darwin *et al.*, 2011). Annotemoyin-1 (an ACG isolated from the seeds of *A. squamosa*) showed no toxic effects on Long Evan's rats, administered at 200 µg daily for 14 days (Parvin *et al.*, 2003).

## Conclusion

*A. squamosa* is a tropical fruit tree on which extensive phytochemical and bioactive investigations have been implemented. Except for being an important part of the food industry, *A. squamosa* has been proven to possess a series of bioactivities. From the detailed literature survey above, the most promising are considered as anticancer, antiparasitic, and pesticidal activities. Because most previous investigations only focused on the bioactivities of different extracts of plant, further studies on the bioactive compounds and their exhaustive underlying mechanism are a crucial pivot for exploiting it in pharmaceutical and agricultural productions. In addition, the current clinical tests investigate the huge pharmacological potential of *A. squamosa* and neglect its neurodegenerative effects. Further investigations are necessary to distinguish all the constituents that contributed to the neurodegenerative effect and to ascertain the threshold of these constituents at which the mentioned effect is caused. This review is aimed to be the source and motivation for researchers to further conduct *in vivo*, *in vitro* and clinical experiments on the bioactivities of *A. squamosal*, applying it to pharmaceutical and agricultural domains.



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