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Anona Genus : Phytochemical, Anticancer and Activity Structure Relationship

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A B S T R A C T

The Annonagenus, consisting of 119 species, has been continuously researched and proven to have various pharmacological activities such as anticancer, antioxidant, anti-inflammatory, antibacterial and so on. Annona plants such as *Annona cherimolia Mill*, *Annona Reticulate*, *Annona Squamosa*, *Annona muricata L* have antioxidant, antimicrobial, anti-inflammatory, antihelmintic, antipyretic, antihyperglycemic, analgesic, wound healing, and cytotoxic effects caused by the presence of active compounds such as acetogenin, alkaloids. And terpenoids whose role as treatment or prevent anti-cancer. Active compounds in inhibiting or preventing cancer cells are mostly found in the leaves, seeds and fruit of the Annona plant. The anticancer or antitumor activity of bioactive compounds is related to the structure of these compounds. The large number of hydroxyl groups and supported by the hydroxyl position flanking the γ-lactone ring and the stereochemical arrangement of the THF ring determines the effectiveness of cytotoxic activity (the stereochemical arrangement of the THF ACG ring, threo/trans/erythro is more active than threo/trans/threo), the presence of hydroxyl groups at the tail of the ACG carbon chain and for alkaloids in the presence of 1,2-methylenedioxy and methylated nitrogen.

Introduction

The genus Annona consists of 119 plant species, most of which grow in the tropics; One of them is soursop (*Annona muricata*), *Annona cherimola*, *Annona reticula* and *Annona squamosal*. Annona species are moderately erect shrubs or small trees that grow to 5–11 m tall depending on the species and region they inhabit, and are iron to grayish, and tomentose when young, but then become bare (Badrie *et al.*, 2010, Quilez *et al.*, 2018). Ethnobotanically, plants of this genus play an important role as food and medicinal products (Tellez *et al.*, 2018). This Annona species has been used as medicine by the community such as parasite disorders, infections, inflammation, diabetes and cancer (Mishra *et al.*, 2013). This is related to the content of bioactive compounds contained in these plants, namely the presence of acetogenins, alkaloids, essential oils,

flavonoids, terpenoids, and (oliveira *et al.*, 2002; Barbalho *et al.*, 2012). Acetogenins (ACGs) are the major constituents of the genus Annona and have been found to possess various pharmacological properties including antitumor, immunosuppressive, pesticide, antiprotozoal, antimicrobial, antimalarial, anthelmintic, and antiviral properties. (Barbalho *et al.*, 2012; Asar *et al.*, 2015) (nugraha)The number of studies that have been carried out on Annona plants is needed to make a summary of the research results. So with this review, it is intended to provide knowledge about the active compounds in *Annona cherimola, Annona muricata, Annona reticula* and *Annona squamosa*. Where there are active compounds that are anticancer or antitomur and considering the high price of cancer drugs. The relationship of anticancer properties or tumors to the structure of these compounds. Therefore, it is necessary to collect and review the research that has been conducted done before. Journals collected from 2000-2020, have a minimum of H-Index 17, and has a quartile score of 1 to 3.

Phytochemical Study of Secondary Metabolites of Annona Genus

Annona contains a variety of phytochemicals in roots, leaves, twigs, bark, seeds, and fruit flesh. The main bioactive compounds include acetogenins (ACGs), alkaloids (ALKs), phenolic compounds, essential oils (EO), cyclopeptides (CPs), carotenoids, and amino acids. Flavonoids isolated from aqueous extract of *Annona squamosa* have shown antimicrobial activity (Kotkar *et al.*, 2002) Podophyllptoxin (a non-alkaloid toxin lignan compound) and its demethyl derivatives 4‟‟-demethylpodophyllotoxin, liriodenine and (-)-kaur-16-en-19 -oic acid was also isolated from the (Hatano *et al.*, 2002). GC analysis of fatty acid methyl esters (FAMEs) of the seed oil revealed the presence of saturated fatty acids such as hexadecanoic acid (palmitic acid), octadecanoic acid (stearic acid), and unsaturated fatty acids such as octadecenoic acid (oleic acid), eicosanoic acid (gondoic acid).) (Alassane *et al.*, 2004). Extraction of various parts of *Annona squamosa* in different solvents revealed the presence of alkaloids, flavonoids, phenols, carbohydrates, saponins, sterols and tannins (Agrawal *et al.*, 2012; Ashok *et al.*, 2010). *Annona Squamosa*, a drought-resistant multipurpose evergreen tree commonly known as “Custard Apple” to the Annonaceae family, is gaining increasing importance due to its therapeutic potential (Vyas *et al.*, 2012). The fruit of this plant is edible. Usually, the leaves are used as a vermicide, to treat cancerous tumors and applied to abscesses, insect bites and other skin complaints, then root bark scrapings are used for toothaches (Saha, 2011). Custard apples are reported to have various beneficial chemical compounds such as alkaloids, isomeric hydroxyl ketones from leaves, acetogenin, samaquasine, annonacin and annonastatin from seeds, acetogenin, and squamone from bark. Various Research shows that custard apples have antibacterial activity. antidiabetic, antitumor, antimalarial, anthelmintic, antigenotoxic, and hepatoprotective (Singh *et al.*, 2019).

Annona cherimola Mill seed extract, known to have strong toxic activity, induces apoptosis in AML cell lines by activation of both extrinsic and intrinsic pathways (Haykal *et al.*, 2019). *Annona cherimola* Mill. (Custad apple) is widely used in traditional and folkloric medicine systems, because it contains many bioactive compounds such as acetogenins annonaceous, annocherine A, cherianoine, annocherine B, cherimoline, annomolin, romucosine H, anonaine and others (Jamkhand *et al.*, 2017). Cherianoine, annocherine B, *Annona muricata L* is a tropical fruit tree of the genus Annonaceae. *Annona muricata L* is also known as soursop plant. Soursop seeds are rich in oil, vitamins, and low in toxins

(tannins, phytates, and cyanides) (Badire *et al.*, 2010).

Annonacin is the most abundant acetogenin isolated from the leaves of *A. muricata* (Champy *et al.*, 2009). *Annona muricata* leaves produce crude extract with a concentration of 0.125% of the total alkaloids from chloroform extraction. These alkaloids were identified as anonaine, isolaureline, xylopine, colaurine, benzyltetrahydroiso-quinoline alkaloids (Fofana *et al.*, 2011). In further research, Fofana produced N-methylcoclaurine, asimilobin, remerine, isoboldin, and liriodenine. The leaves contain alkaloids with the highest concentration compared to roots, stems and fruit (Fofana *et al.*, 2011, 2012). Isoquinoline, aporphine, and protoberberine are types of alkaloids often isolated from *Annona muricata* (Mohanty *et al.*, 2008).

Phytochemical studies on different parts of *Annona muricata* have isolated and identified secondary metabolites, such as: acetogenins, alkaloids, phenolic compounds, and megastigman (Yang *et al.*, 2015; Coria-Téllez *et al.*, 2016). The *Annonaceous acetogenins* are most abundant in leaves, a unique group of long-chain fatty acid derivatives derived from the polyketide pathway (Sun *et al.*, 2016) Using in vitro studies, extracts and phytochemicals of *A. muricata* have been characterized as antimicrobial, anti-inflammatory, anti-inflammatory and anti-inflammatory. protozoa, antioxidants, and insecticides (Cario-Tellez *et al.*, 2016). The results obtained in this study indicate that the consumption of soursop fruit can do a good alternative to prevent diseases such as prostate and cervical cancer (Raybaudi-Massilia *et al.*, 2015).

Annona reticulate is a fruit native to Central America which has become an important crop because of its delicious taste, high flesh content, nutritional value and antioxidant properties (Julián-Loaeza *et al.*, 2011). *Annona reticulate* is a plant that is very clearly seen in the Ayurvedic system of medicine for the treatment of various diseases (A. Jayaprakash, 2017).

Anti Cancer Activity

Annona muricata leaf extract is an effective therapeutic agent for human liver cancer cells Huh-7 (Adewole and Ojewole, 2008). HeriSusilo *et al.*, 2012 stated that this extract could inhibit the population of MCF-7 cells with an IC50 value of 97µg/ml and showed a cytotoxic level of 2.5 g/ml for Leukemia cancer cells, K-562, a chronic myelogenous cell line. (Ezirim *et al.*, 2013). In addition, *Annona muricata* leaves can cause higher cell death (2000 g/ml has 91.86%; 15.625 g/ml has 2.68%) (Parma AO *et al.*, 2013). In 2014, the distribution of Annona leaf extract muricata showed increased levels of ROS (Reactive Oxygen Species) thereby inhibiting A549 cells (human basal alveolar epithelial cell adenocarcinoma). Intracellular ROS play an important role in cancer cell death. (Zorofchian *et al.*, 2014a). In another report, this extract strongly inhibited colon cancer cells with IC50 values of 11.43 ± 1.87 g/ml and 8.98 ± 1.24 g/ml against HT-29 and HCT-116 cells, respectively (Zorofchian *et al.*, 2014b). On the other hand, it can help stabilize metastatic breast cancer for 5 years and inhibit the action of breast cancer cell lines, MCF-7, MDA-MB-231 and 4T1 (Hansra, 2014, Syed N *et al.*, 2016). The ethanol extract of *Annona muricata* leaves with IC50 values = 335.85, 248.77, 202.33µg/mL for EACC, MDA and SKBR3 cell lines, respectively, and did not show anticancer effect on normal spleen cells, while aqueous extract did not (Gavamukulya *et al.*, 2014). Anti-proliferative and apoptotic effects against hyperplastic benign prostate tumor cells (BPH-1) shown by Annona leaf extract. Muricata in vivo (Asare *et al.*, 2015).

In rats, *A. muricata* leaves also showed chemopreventive potential against azoxymethane-induced colonic aberrant crypt foci. (Moghadamtousi *et al.*, 2015c). Another investigation reported that in liver cancer HepG2 cells, ethanol extract of *A. muricata* leaves induced apoptosis through the endoplasmic reticulum stress pathway (Liu *et al.*, 2016). Proteomic analysis found 14 proteins associated with the extract in triggering apoptosis; including upregulation in HSP70-associated protein, GRP94, and DPI 5 expression levels, which further confirmed the work of the endoplasmic reticulum stress pathway by the extract. This investigation proved the potential of *A. muricata* leaf extract as an effective anticancer agent. Then, *A. muricata* extract was found to suppress HL-60 cell proliferation by inducing morphological changes, G0/G1 cell phase arrest, impaired cell viability and mitochondrial membrane potential loss (Pieme *et al.*, 2014). These findings prove that *A. muricata* has a promising potential as a chemotherapeutic agent to cure cancer. From all these findings, not only the leaves, the whole *A. muricata* plant part proved to be a versatile anticancer agent. Referring to the main results of prospective in vitro and in vivo oncogenic investigations on various extracts of *A. muricata* leaves (Abdulwahab *et al.*, 2018).

The growth of ovarian cancer both in vivo and in vitro can also be inhibited (Cletus *et al.*, 2016). Annonacin, found in the leaves of *Annona muricata*, showed the effect of inducing PaCa-2 cancer cell death in vivo (Yiallouris *et al.*, 2018). Besides acetogenin, alkaloid compounds, (−)-coclaurine, (+)-reticuline, argentinine, atherosperminine, and (+)-xylopine were isolated from the roots of *Annona muricata* Indonesia. (−)-coclaurine, (+)-reticuline was non-toxic to the human suspension cancer cell line (HL-60 leukemia cell) and two fibroblastic cell lines (A549 lung cancer cell and HepG2 liver cancer cell line). (+)-Xylopine shows an IC50 of 20-80 M (Nugraha *et al.*, 2019).

In addition to leaf extract, there are other parts of *Annona Muricata* can be used as an anticancer such as parts of the fruit, seeds, twigs and roots. Ethanol extracts from leaves, roots and twigs of *Annona muricata* have shown anti-proliferative effects on HL-60 cells with IC50 varying from 6-49 g/mL (Pieme *et al.*, 2014). In vivo acetogenin, Annomuricin E from *Annona muricata* leaves, was found to inhibit the growth of HT-29 cells. with an IC50 value of 1.62 ± 0.24 g/mL (Zorofchian, *et al.*, 2015a). Leaf, seed and peel extract of *Annona muricata* was cytotoxic against CCRF–CEM leukemia cells with a value of 0.57 ± 0.02 ; 0.36 ± 0.03 and 4.58 ± 0.2 g/mL (Kuete *et al.*, 2016). *Annona muricata* fruit extract showed its toxic activity against breast cancer cells (MDA-MB-468) but did not show its toxicity against normal breast cells (MCF-10A) (Dai *et al.*, 2011). Acetogenins, Muricin M, Muricin N and Muricenin, isolated from the fruit of *Annona muricata*, have been reported to be potent anti-prostate cancer agents (Sun *et al.*, 2016). The same thing also happened to HeLa cervical cancer cells given Methanol:dichloroethane extract (1:1) from *Annona muricata* fruit with an IC50 of 25µg/ml (Jepkorir *et al.*, 2018).

Annonaceous acetogenin was isolated from the seeds of *Annona muricata*: muricins AG, and known compounds: a mixture of muricatetrocin A and muricatetrocin B, longifolicin, corossolin, and corossolone. These acetogenins exhibit significant selective in vitro cytotoxicity against the human hepatoma cell lines Hep G2 and 2,2,15 (Chang *et al.*, 2001). Two years later, Annocatacin A and B, isolated from methanol extracts of the seeds and leaves of *Annona muricata*, respectively, showed significant anti-proliferative effects in vitro in human hepatoma cell lines, Hep G2 and Hep 2.2.15.

Compounds 1 and 2 showed significant in vitro anti-proliferative effects in human hepatoma cell lines Hep G2 and Hep 2,2,15, but 2 were more selective against Hep G2 (Chang *et al.,* 2003).

Annona squamosal

Squamocin-O1 and squamocin-O2 were reported from the methanol extract of *Annona squamosa* seeds. Cytotoxic activity of squamocin-O1 (1) and squamocin-O2 (2) against human K562 leukemia and HLE hepatoma cells. n (1: K562, IC50=4.0 x 10-4 g/ml; HLE, IC50=3.7 x 10-3 g/ml, 2: K562, IC50=4.3 x 10-4 g/ml; HLE, IC50=3.5 x 10-3 g/ml (Araya *et al.,* 2002) Squadiolins A and B showed high potency against human Hep G2 hepatoma cells and significant cytotoxic activity against human MDA-MB 231 breast cancer cells extracted from *Annona squamosa* seeds (Liaw *et al.,* 2008). Further investigation, the bark extract protects the cell surface glycoconjugate for 7,12-dimethyl benz(a) anthracene (DMBA) induced hamster buccal sac carcinogenesis. Aqueous and ethanol extract can reduce the total number of tumors and normalize glycoconjugate levels in tumor carrier animals at doses of 500 mg/kg bw and 300 mg/kg bw (Suresh *et al.,* 2010) *Annona squamosa* has shown significantly higher antitumor activity against MCF-7, HCT-116, KB-3- cells. 1, and HepG2.

This antitumor activity was further confirmed by in vivo studies conducted on mice with H22 d hepatoma cells. An also against AD-5 tumors (Chen *et al.,* 2011 and 2012, Yang *et al.,* 2015). The mechanism that may be involved is the induction of apoptosis in tumor cells through the involvement of stress (De Pedro *et al.,* 2013, Pandey, 2011, Pardhasaradhi *et al.,* 2004 and 2005). Activity against lung and ovarian cancer cells of diterpene compounds isolated from bark (Sun *et al.,* 2012).

Annosquacin-I, annosquatin-I, annosquatin-II, uvarigrandin A, bullatacin, squamostatin-A, and squamostatin-D were produced from the ethanol extract of *Annona squamosal* seeds. The five bioactive compounds had significant cytotoxic values for 5 types of human cancer cells, namely 1.2 × 10 2 - 6.8 × 10 1 for A-549 (human lung cancer); 2.5 × 10 2 – 1.5 for HeLa (human cervical cancer); 4.3 × 10 2 - 7.5 × 10 1 for MCF-7 (human breast cancer); 8.2 × 10 3 -8.3 × 10 1 for HepG2 ; 4.8 × 10 3 - 4.9 × 10 1 g/ml for SMMC-7721 (human hepatoma cancer) (chen2011), *Annona squamosal* leaf chloroform extract showed the strongest cytotoxic activity against MT-1 and MT-2 cells with values (EC 50) was > 100 g/Ml. Alkaloids were isolated as active compounds from Annona leaves. squamosa is and lanugiosine. (Nakano *et al.,* 2013)

Squamocin-I (1), II (2) and III (3) and squamoxinone-D (4) were isolated from the seeds of *Annona squamosa*. Compounds 1-4 were tested for cytotoxicity against Hep G2, SMMC 7721, BEL 7402, BGC 803 and H460 human cancer cells. Compound 1 showed better cytotoxic activity and compound 3 showed selective cytotoxic activity against H460 with an IC50 value of 0.0492 g/ml. A year later Squamocin-IV (1), squamocin-V (2) and squamoxinone-E (3), along with seven other *Annonaceous acetogenins* were isolated. The new *Annonaceous acetogenins* 1–3 were tested for cytotoxicity against the human cancer cell lines Hep-G2, SMMC-7721, BEL-7402, BGC-803 and H460. Compound 3 showed the best cytotoxic activity, with IC50 values of 0.103, 0.687, 4.19, 0.43 and 6.56 g/mL, for the tested cell lines. Meanwhile, Compound 1 showed selective cytotoxic activity against H460, with an IC50 value of 0.049 g/mL. The first mono-ACG (2) consisting of 38 carbons was discovered (Miao *et al.,* 2015, Miao *et al.,* 2016). In vivo, Squamocin and squamostatin (A, B, C, D and E) have important antitumor activity against

AD-5 tumors (Bhattacharya and Chakraverty. 2016). Dieporeticenin B (1), squamocin P (2) and annosquatin III (3) were isolated from the seeds of *Annona squamosa*. This compound exhibited an inhibitory effect against three drug-resistant cancer cell lines. Compounds 2 and 3 showed selective cytotoxicity to SMMC 7721/T (IC50 0.435 and 1.79 M) and MCF-7/ADR (IC50 values 3.34 and 4.04 M) (Ma *et al.*, 2017)

Annona reticulate

The important antiproliferative activity of the ethanolic extract of *Annona reticulata* root in vitro against human cancer cell lines A-549, K-562, HeLa and MDA-MB could be attributed to the presence of acetogenins and alkaloids. Annona reticulate can be used as a chemopreventive agent in cancer therapy (Suresh *et al.*, 2011).

The ethanolic extract of *Annona reticulata* root produces liriodenine (1) norushinsunine (2), reticuline (3) and neoannonine (4). Found an inhibitory effect against human lung carcinoma (A-549), chronic myelogenous leukemia in human bone marrow (K-562), cervical carcinoma (HeLa) and human mammary gland adenocarcinoma tumors (MDA-MB). Neoannoninacetogenin gave the strongest cytotoxicity in each cell tested IC50 = 5.8 – 6.9 g/ml. (Suresh *et al.*, 2012).

Strongest activity against MT-1 and M.cells

T-2 was shown from the chloroform extract of *Annona reticulata* leaves while the bark showed moderate activity. The cytotoxicity activity of *Annona reticulata* extract has a value (EC 50) is > 100 g/mL. Two alkaloids isolated as active compounds from the leaves of *Annona reticulata* are liriodenine (1), lysicamina (2), and lanugiosine (3) (Nakano *et al.*, 2013).

Long ago Annonacin from *Annona reticulata* seeds caused cell death of ovarian cancer (SKOV3 and PA-1), cervical cancer (HeLa and HeLa S3), breast cancer (MCF7), bladder cancer (T-24) and skin cancer (BCC-1).) with each IC50 value = 0.452; 0.411; 0.219; 4.26; 4.33; 0.324 and 0.427 g/mL (yuan SSF *et al.*, 2002). This effect may be attributed to the presence of acetogenins and alkaloids

Annonacin, a monotetrahydrofuranacetogenin was isolated from the seeds of *Annona reticulata* and showed it causes significant cell death in various cancer cells and this compound has the potential to be a promising compound.

Annona cherimola

Annona ceousacetogenins isolated from the extract of *Annona cherimolia* seeds were filtered to obtain annomolin (1) and annocherimolin (2). Annomolin showed strong cytotoxicity against breast (MCF-7), colon (HT-29) and prostate (PC-3) cell lines. demonstrated cytotoxic selectivity for human prostate tumor cell line (PC-3), with a potency more than 10,000 times that of adriamycin. annocherimolin (2) showed an approximately 10,000-fold cytotoxic potential of adriamycin in breast (MCF-7) and colon (HT-29) cancer cell lines. Blockage of mitochondrial complex I (NADH-ubiquinone oxidoreductase) and inhibition of NADH oxidase may be the mechanisms responsible for the cytotoxic activity of this acetogenin (Kim *et al.*, 2001)

Table.1 Secondary metabolites in *Annona cherimola, Annona muricata, Annona reticulata and Annona Squamosa*

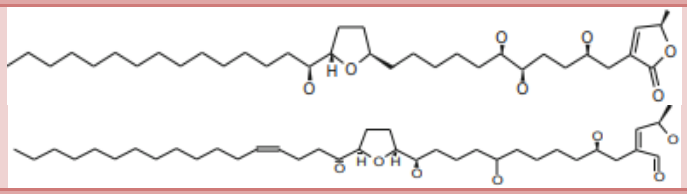
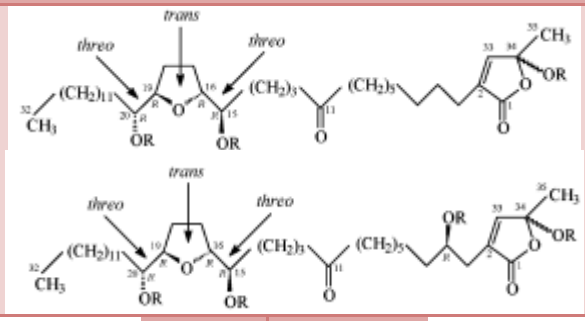
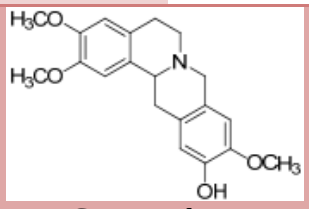
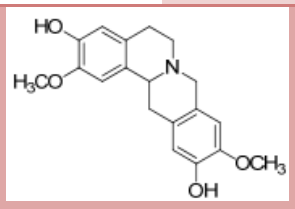
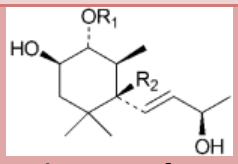
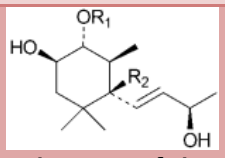
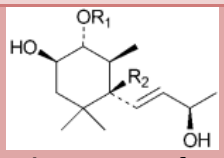
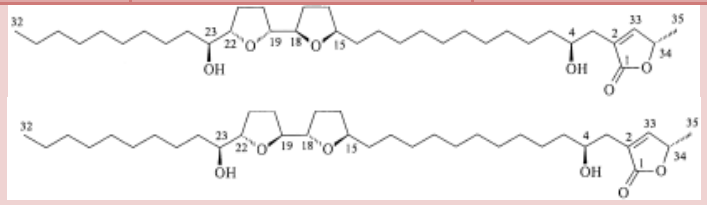
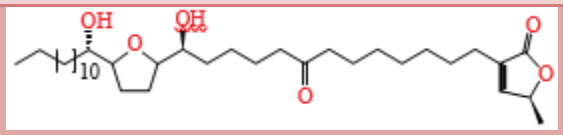
Species	Active Compound	Compound Group	Tested cancer cells	Reference
Annona cherimola	Leaves :annocherine C (1), liriodenine (2), oxoxylopine (3), oxonantenine (4), (-)-asimilobine (5), (-)-xylopine (6) and (-)-anolobine (7)	ALK	-	Chen & Wu, 2001
	Leaves : anonaine, liriodenine, dannornuciferine		-	Martínez-Vázquez *et al*., 2012
	Stem : Annocherine A dan B, Artabonatine B, Cherianoine, romucosine H	ALK	-	Chen *et al* 2001
	Fruit : α-pinene, β-pinene, limonene, bornyl acetate and germacrene D.		-	Pino *et al.* 2001
	Seed : annomolin (1) danannocherimolin (2)	ACT	Annomolin was more cytotoxic to PC-3 cells and Annocherimolin was more cytotoxic to MCF-7 and HT29 cells.	Kim *et al*. 2001
	Seed : annomocherin (1), annonacin (2) danannomontacin (3)	ACT	Compound 1 showed strong and selective cytotoxicity against MCF-7 and A-498 cells.	Kim *et al*. 2001
	Seed : annomolon A dan B	ACT	Both compounds are more toxic to MIA PaCa-2 cells	Son *et al* 2003
	Seed: asimicin, tucumanin	ACT	-	Barrachina *et al*. 2004
	Seed : cherimolacyclopeptide C	CYP	-	Wele *et al* 2004
	Root : corytenchine (1) and isocoreximine (2)		isocoreximine showed more cytotoxic activity against K-562, U-251, PC-3, HCT-15, and MCF-7 thanncorytenchine	Martinez-Vazquez, M dkk.2005
Annona muricata	Leaves : Anonaine, Benzyltetrahydroisoquinoline, coclaurine, isolaureline, xylopine	ALK	-	Fofana *et al* 2011
	Leaves : (R)-4'-O-	ALK	Neurotoxic to SH-SY5Y	Matsushige

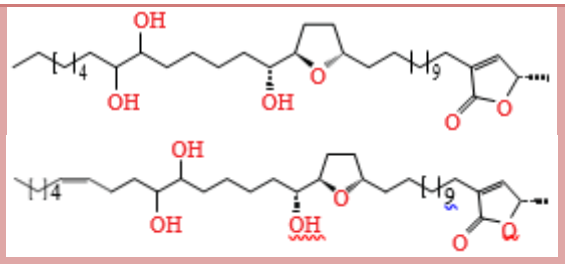
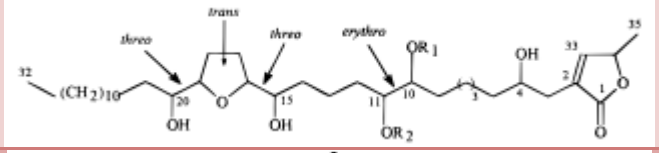
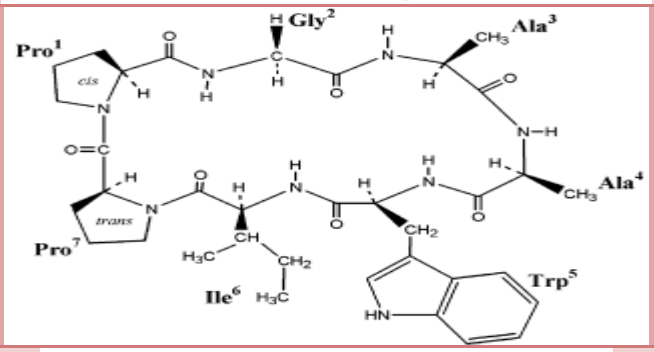
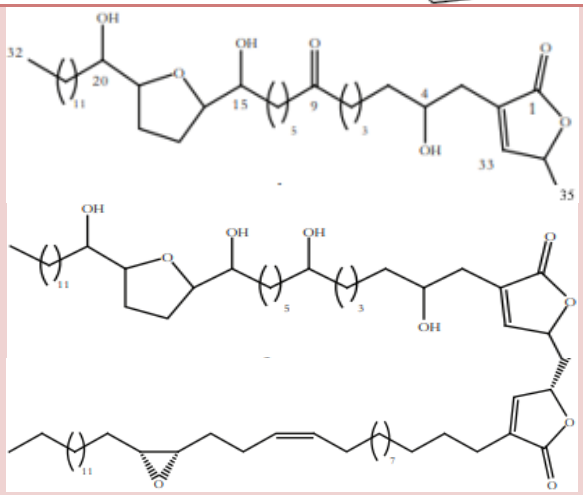
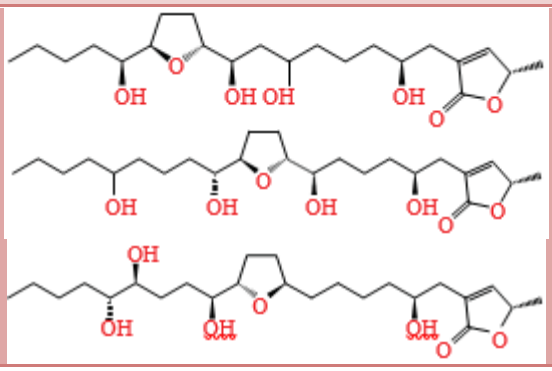
	methylcoclaurine, (R)-anonaine, : (R)-O-O-dimethylcoclaurine, (S)-norcorydine, annonamine		cells	*et al*. 2012
	Leaves : Argentinine, Catechine, Chlorogenic acid, Epicatechine Gallic acid, Kaempferol, Kaempferol 3-O-rutinoside, Quercetin 3-O-glucoside, Quercetin 3-O-neohispredoside, Quercetin 3-O-robinoside, Quercetin 3-O-rutinoside	FLA	-	Nawwar et.al. 2012
	Leaves : Annoionol A dan B, annoionosidedanannoionol C	MSG	inhibition of tumor cell growth towards A549 and SBC-3	Matsushige *et al*. 2012
	Leaves, pericarp, Root, dan Seed : annonacin	ACT	-	Luna *et al*. 2006, Jaramilo *et al*. 2000, Champy *et al*. 2004
	Leaves And Seed: annocatacin A dan B	ACT	Showed significant cytotoxic activity against Hep G2 and Hep 2.2.15 cells	Chang *et al*. 2003
	Leaves and Seed : muricin H, muricin I, cisannomontacin, annocatalin, cis-corossolone	ACT	Showed significant cytotoxic activity against Hep G2 and Hep 2.2.15 cells	Liaw *et al*. 2002
	Leaves And Seed : annonacinone	ACT	-	Liaw *et al*. 2002, Vila-Nova *et al*. 2011
	Leaves and Seed: corossolone	ACT	-	Vila-Nova *et al*. 2011
	Leaves : Annomuricin E		The cytotoxic effect of annomuricin E inhibited the growth of HT-29 cells with an IC50 value of 1.62 ± 0.24 g/ml	Zorofchian *et al*. 2015
	Leaves And Seed: goniothalamicin, isoannonacin	ACT	-	Luna *et al*. 2006
	Stem Bark : Muricins A-G (1-7) muricatetrocin A (8) danmuricatetrocin B (9),	ACT	Showed significant cytotoxic activity against Hep G2 and Hep 2.2.15	Chang and Wu. 2001

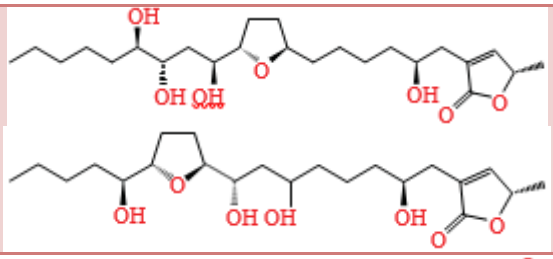
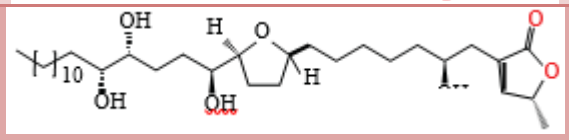
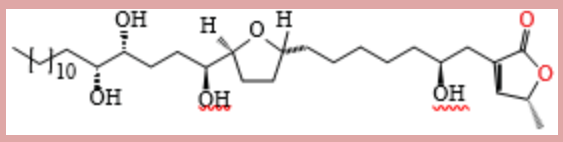
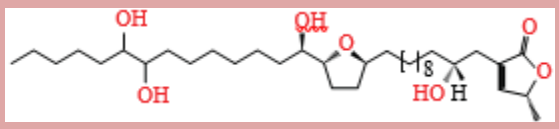
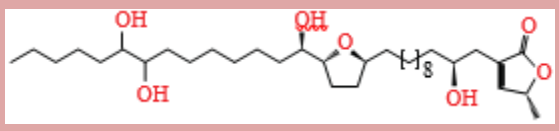
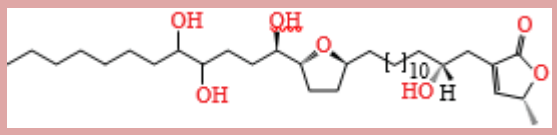
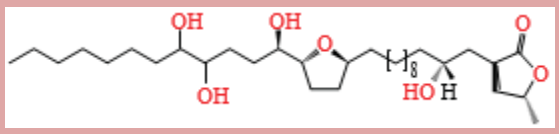
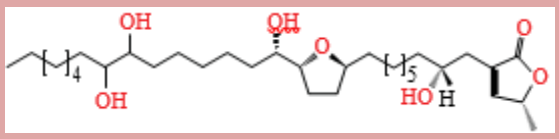
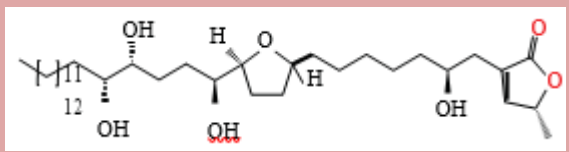
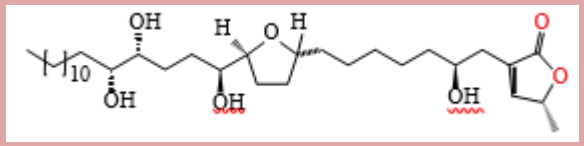
	longifolicin (10), corossolin (11), dancorossolone (12)		cells	
	Fruit : annoreticuin-9-one (1) cis-annoreticuin (2) and sabadelin (3)	ACT	Compound 1 shows its cytotoxic activity against cells PACA-2), PC-3 and A-549, while 2 cells Hep G2	Ragasa *et al* 2012
	Fruit : Epomuricenins-A dan B; Epomurinins-A dan B; Epomusenins A dan B	ACT	-	Molet *et al* 2009
	Fruit : Muricin J, K dan L	ACT	Antiproliferative properties against PC-3 cells	Sun *et al*. 2014
	Fruit: muricin M dan N, muricenin	ACT	showed stronger anti-proliferative activity against human prostate cancer cells PC-3	Sun *et al*. 2016
	Fruit dan Root : Sabadelin	ACT	-	Ragasa *et al* 2012
	Pericarp : Annomuricin A	ACT	-	Jaramilo *et al*. 2000
	Pericarp danbiji : Annonacin A	ACT	-	Jaramilo *et al*. 2000
	Seed : Cohibins C dan D	ACT	-	Gleye *et al*. 2000
	Seed : muricins A-G (1-7), muricatetrocin A (8) danmuricatetrocin B (9), longifolicin (10), corossolin (11), dancorossolone (12)	ACT	These acetogenins exhibit significant cytotoxicity that are selective against Hep G2 and Hep 2,2,15 cells in vitro.	Chang & Wu. 2001
	Seed : 2,4-cis-Gigantetrocinone, 2,4-trans-gigantetrocinone, 2,4-trans-isoaiinonacin, 2,4-trans-Isoannonacin- 10-one, Annomontacin, Gigantetrocin-A dan B Gigantetronenin, Muricatenol	ACT	-	Li *et al*. 2001
	Seed : Annomuricatin C			Wele *et al*. 2004
	Seed : cherimolacyclopeptide C		showed significant in vitro cytotoxic activity against KB cell	Wele *et al*. 2004
	Root : Neoannonin-B	ACT	-	Gleye *et*

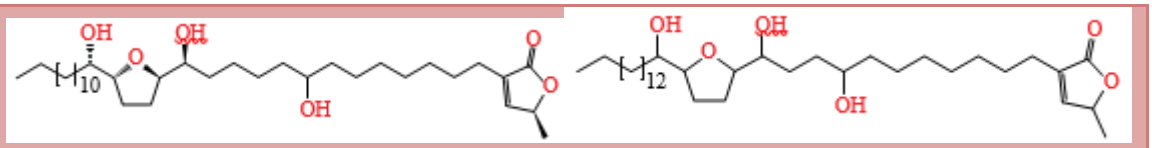
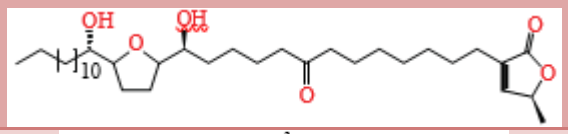
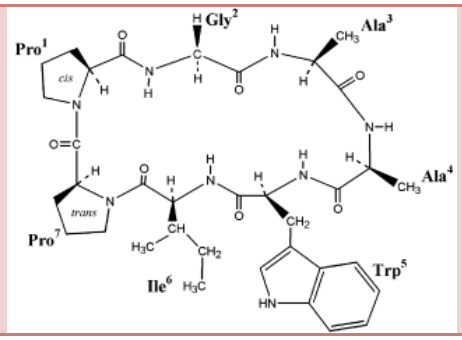
				al., 2001
Annona reticula	Leaves : (E,E)-farnesyl acetate, ar-turmerone, benzyl benzoate and γ-terpinene	ESO	-	Ogunwande *et al*. 2006
	Stem Bark : Kaur-16-en-19-oic acid, kopaena			Chavan *et al*., 2012
	Seed : Annonacin	ACT	annonacin causes significant cell death	Yuan *et al*. 2003
	Seed : cycloreticulin A dancycloreticulin B		-	. Wele *et al*., 2008
	Seed : squamocin		Cytotoxic against KB 3-1 cells in vitro	Duval *et al*. 2005
Annona squamosa	Leaves : Quercetin-3-O-glucoside	FLA	-	Panda &Kar, 2007
	Leaves : O-methylarmepavine	ALK	-	Vila-Nova *et al*. 2011
	Leaves : Bicyclogermacrene, (E)-Caryophyllene, Germacrene D	ESO	-	Meira *et al*. 2014
	Leaves : (-)- Anonaine	ALK	-	Porwal& Kumar, 2015
	Fruit : α-pinene, Limonene, Sabinene	ESO	-	Andrade *et al*.,2001
	Seed : Annosquamins A, Annosquamins B, Annosquamins C	ACT		Chen *et al*., 2012
	Stem : 10-nor-ent-kaurane-4α,16β,17-triol, 16α,17-dihydroxy-ent-kauran-19-al, 16α,17-dihydroxy-ent-kauran-19-oic acid, 16α-hydro-19-al-ent-kauran-17-oic acid, 16β,17-dihydroxy-ent-kauran-19-al, 16β,17-dihydroxy-ent-kauran-19-oic acid, 16β-hydro-ent-kauran-17,19-dioic acid, 16β-hydroxy-17-acetoxy-ent-kauran-19-oic acid, 17-hydroxy-16β-ent-kauran-19 oic acid, 4α-hydroxy-19-nor-ent-kauran-17-oic acid, ent-kaur-16-en-19-oic acid	ALK		Yang *et al*. (2004)

Table.2 The structure of bioactive compounds that have anticancer activity

Annona Species	Compound structure
Annnona cherimola	
Seed : annomolin (1) danannocherimolin	
Seed : annomocherin (1), annonacin (2) danannomontacin	
Seed : annomolon A dan B	
Root : corytenchine (1) and isocoreximine	 Corytenchine  Isocoreximine
Annnonamuricata	
Leaves : Annoionol A dan B, annoionosidedanannoionol C	 Annoionol B R1 = H R2 = OH  Annoionol A R1 = Glc R2 = OH  Annoionoside R1 = R2 = H
Leaves And Seed : annocatacin A dan B	
Leaves and Seed : muricin H, muricin I, cisannomontacin, annocatalin, cis-corossolone	

	
Leaves : Annomuricin E	
Seed : cherimolacyclopeptide C	
Fruit : annoreticuin-9-one (1) **annoreticuin (2)** **sabadelin (3)**	
Fruit : Muricin J, **Muricin K** **Muricin L**	

Fruit : muricin M dan **muricin N, muricenin**	
Seed : muricins A	
Muricins B	
Muricins C	
Muricins D	
Muricins E	
Muricins F	
Muricins G **-G (1-7), muricatetrocin A (8)**	
danmuricatetrocin B (9), **longifolicin (10),**	 

corossolin (11), dan	
corossolone (12)	
Seed : cherimolacyclopeptide C	

Isocoreximine alkaloid isolated from *Annona cherimola*, at a concentration of 50 g/mL showed cytotoxicity to K-562, U-251, PC-3, HCT-15, and MCF-7 with % inhibition of cell viability 94.15%, 65, respectively..23%, 78.71%, 63.05%, and 85.76%. Isocoreximine showed cytotoxic activity in vitro against K-562, U-251, PC-3, HCT-15, and MCF-7 with % inhibition of cell viability 94.15%, 65.23%, 78.71%, respectively. 63.05%, and 85.76% (Martinez-Vazquez, *et al.*, 2005).

Annomolon A, annomolon B, and 34-epi annomolon A,B in *Annona cherimola* showed selective inhibition of mitochondrial complex I and specificity against different tumor lines of cells (De Pedro *et al.*, 2013). The essential oil and ethanolic extract obtained from *Annona cherimola* leaves were screened for antitumor activity against cancer (MCF-7), colon cancer (CACO-2) and liver cancer cell lines (HEPG-2). 0.03% essential oil was obtained which mainly contained sesquiterpenes and monoterpenes. Most included -elemene (25.02%), germacrene-D (17.71%), and -caryophyllene (9.50%). The ethanol extract showed significant cytotoxic activity on MCF-7, CACO-2 and HEPG-2 with IC50 of 3.43, 2.97 and 3.73 g/ml, respectively. The study concluded that the essential oil of the ethanolic extract had strong cytotoxic activity on all tested cell lines showing promising antitumor activity of *Annona cherimola* (Elhawary *et al.*, 2013).

Relationship of Structure with Anticancer Properties

The presence of part of the THF and/or THP ring in the compound chain, with the presence of a THF and/or THP ring in the compound chain so that it can have a V-type shape. The molecular length of the compound (33-38), the width of the three-dimensional structure of the compound, all of which are very important for the activity of inhibiting the growth of cancer cells. In addition, the position of the OH group in the compound affects the activity of inhibiting the growth of cancer cells. In this report, specifically mentions, compound 5 (pyranicin) showed the strongest inhibition of the acetogenins tested, affecting not only cell proliferation but also apoptosis induction.
Therefore, compound 5 is the main compound of cancer chemotherapeutic agents that have the potential to be developed (mitsui *et al.*, 2009).

The large number of hydroxyl groups supported by the hydroxyl position flanking the -lactone ring and the stereochemical arrangement of the THF ring determine the effectiveness of cytotoxic activity. (liaw *et al.*, 2008)

Bioactivity data showed that the annonaceousbistetrahydrofuranacetogenins adjacent to nosquacin-I, uvarigrandin A, and bullatacin were more cytotoxic than the nonaceousbistetrahydrofuranacetogeninssqua mostatin-A, squamostatin-D, annosquatin-I, and annosquatin-II.

The free OH at C-4 appears to increase the cytotoxicity of acetogenin. For example, roundacin and annosquatin-II are more active than uvarigrandin A and annosquatin-I. The nonadjacent tetrahydroxylatedbistetrahydrofuran*Annonaceous acetogenins*squamostatin-A is less cytotoxic than trihydroxylatedsquamostatin-D. (Chen Y. *et al.*, 2011)

The adjacent ACG bis-THF exhibited higher antitumor activity and toxicity than the nonadjacent mono-THF and ACG bis-THF in vivo. (Chen Y *et al.*, 2012) Acetogenins with hydroxyl located at C 16, 19 and 24 have strong cytotoxicity against A-549 cells. The number of hydroxyl can determine the cytotoxic properties supported by the presence of adjacent bis-non-ACG THF. The stereochemical arrangement of the THF ring is important for ACG bioactivity, threo/trans/erythro being more active than threo/trans/threo. (Yuan F *et al.*, 2015)

The high cytotoxic activity against H460 may be due to the presence of a hydroxyl group at the tail of the ACG carbon chain. (Mio *et al.*, 2015).

There are many metabolites found in Annona plants, especially *Annona cherimola, Annona muricata, Annona retukula* and *Annona squamosal* in every part of the plant. Most of the secondary metabolites that have anticancer activity are found in the leaves, seeds and fruit.

Acetogenen compounds (ACT), alkaloids (ALK) and flavonoids (FLA) contained in the Annona plant have many anticancer roles. Anticancer activity has been investigated is influenced by the structure of these bioactive compounds, for example for ACT due to the THF ring (tetrahydrofuran) as discussed in point 5

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