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Phytochemistry and pharmacological activities of *Annona* genus: A review

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ABSTRACT

Plants have been significantly used in traditional medicine by a variety of societies since antiquity, and knowledge of their safety, efficacy, and quality value can be developed through further research. The genus *Annona*, consisting of 119 species, has been extensively researched and proven to have a diverse range of pharmacological activities such as antioxidant, antiulcer, antidiarrheal, and antiparasitic. This is because the *Annona* plants possess a great number of phytochemicals found in almost every part of the plant, which can be isolated to be developed into herbal medicine. Phytochemicals are classified into several classes, such as Annonaceous acetogenin, alkaloids, flavonoids, and essential oils. This article was created by collecting 124 research articles which discuss phytochemical compounds from 20 species and the pharmacological activity from 13 species.

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1. Introduction

Natural products, specifically those derived from plants, have helped mankind in many aspects of life, particularly medicine. Plants possess extremely high potential to be developed as medicine. Nevertheless, usage of natural medicines should also consider safety, efficacy, and quality. Therefore, research on medicinal plants from compound isolation to pharmacological activity testing is carried out to improve treatment standards.

The genus of *Annona* is part of the Annonaceae family and includes approximately 119 species. Most species of *Annona* grow in tropical America, except for *Annona senegalensis,* which grows in tropical Africa. Members of the genus grow as deciduous shrubs or small trees, whose height ranges from 5 to 11 meters. The stem is hairy when young, with color ranging from rusty to grayish (Bhardwaj et al., 2019). The *Annona* plant's uses in traditional medicine have been widely known, such as the antidiarrheal effect of plants *Annona muricata, Annona reticula*, and *Annona salzmannii*; plants *Annona cherimola*, *Annona squamosa*, and *A. reticula* for antiparasitic uses; the anti-inflammatory effect from using *A. salzmannii* and *Annona vepretorum*; along with other uses (Egydio-Brandão et al., 2017).

Based on the great potential of these plants as drug candidates and the large body of available research on the *Annona* plant, a literature review is necessary in order to summarize part of the results. This review is intended to provide the public with knowledge of the potential and benefits of *Annona* plants. Therefore, a review of the phytochemical compounds and pharmacological activities of the *Annona* genus was created by collecting and analyzing of past research articles. The inclusion criteria are the sources come from the last 25 years, has a minimum H-Index of 17, and has quartile score 1 until 3. The exclusion criteria are the sources come from over the last 25 years, H-Index is less than 17, and has quartile score of 4.

2. Phytochemistry of *Annona*

A wide range of phytochemical compounds from nearly every part of the *Annona* plants have been successfully discovered, isolated, and characterized by variety of methods. Each compound is classified into several classes according its' characteristics such as Annonaceous acetogenins, alkaloids, flavonoids, megastigmanes, steroids, and essential oils (Table 1).

Table 1. Phytochemicals isolated from plants of the *Annona* genus.

Species	Part	Compound	Class	Reference
A. atemoya	Fruit	α-pinene, β-pinene, limonene, bornyl acetate and germacrene D.	ESO	Pino and Rosado (1999)
	Seed	Atemoine Cleistopholine Mixture of *N*-tricosanoyl-4,5-dihydroxytryptamine	ALK	Wu et al. (2005)

Species	Part	Compound	Class	Reference
		N-behenoyltryptamine *N*-cerotoyltryptamine *N*-heptacosanoyl-4,5-dihydroxytryptamine *N*-lignoceroyl-4,5-dihydroxytryptamine *N*-lignoceroyltryptamine *N*-nonadecanoyltryptamine *N*-octacosanoyl tryptamine *N*-pentacosanoyl-4,5-dihydroxytryptamine		
A. cherimola	Fruit	Germacrene D, Terpinen-4-ol, α-pinene, α-thujene	ESO	Pino (2011)
	Root	Corytenchine, Isocoreximine	ALK	Martinez-Vazquez et al. (2005)
	Seed	2,4-*cis*-annocherinones 2,4-*trans*-annocherinones Annocherin 2,4-*cis*-isoannonacins 2,4-*trans*-isoannonacins *cis*-Annonacin	ACT	Woo et al. (1999)
		Annocherimolin, Annomolin	ACT	Kim et al. (2001)
		Annogalene, Annosenegalin	ACT	Sahpaz et al. (1996)
		Annomocherin, Annomontacin, Annonacin	ACT	Kim et al. (2001)
		Annomolon A, Annomolon B	ACT	Son et al. (2003)
		Asimicin, Tucumanin	ACT	Barrachina et al. (2004)
		Cherimolacyclopeptide C	CYP	Wele et al. (2004)
	Stem	Aromin-A	ACT	Chen et al. (1999)
		Annocherine A Annocherine B Artabonatine B Cherianoine Romucosine H	ALK	Chen et al. (2001)
A. coriacea	Root	Coriadienepoxyne-A	ACT	Gleye et al. (2001)
A. crassiflora	Leaves	Kaempferol 3-*O*-β-diglucoside Kaempferol 3-*O*-β-glucoside	FLA	Rocha et al. (2016)
A. foetida	Bark	Annomontine Liriodenine *N*-hydroxyannomontine *O*-methylmoschatoline	ALK	Costa et al. (2006)
	Branch	Atherospermidine	ALK	Costa et al. (2011b)
	Leaves	(E)-caryophyllene, Bicyclogermacrene, α-copaene	ESO	Costa et al. (2009)
A. glabra	Fruit	16α-17-dihydroxy-*ent*-kauran-19-oic acid 16α-hydro-19-al-*ent*-kauran-17-oic acid 16α-hydro-*ent*-kauran-17-oic acid 16β-hydro-*ent*-kauran-17-oic acid 16β-hydroxy-17-acetoxy-*ent*-kauran-19-oic acid 16β-hydroxyl-17-acetoxy-*ent*-kauran-19-al 19-nor-*ent*-kauran-4α-ol-17-oic acid Annoglabasin A Annoglabasin B *ent*-kaur-15-ene-17,19-diol *ent*-kaur-16-en-19-oic acid *ent*-kaur-16-en-19-ol Methyl-16α-hydro-19-al-*ent*-kauran-17-oate	ALK	Chang et al. (1998)
		Annoglabayin	ALK	Chen et al. (2004)
	Fruit and Stem	Annoglabasin A Annoglabasin B Annoglabasin C Annoglabasin D Annoglabasin E Annoglabasin F	ALK	Chen et al. (2004)
		(-)-anonaine (-)-asimilobine	ALK	Chang et al. (2000)

Species	Part	Compound	Class	Reference
		(-)-kikemanine (-)-*N*-formylanonaine (-)-nornuciferine (+)-nordomesticine (+)-stepharine Annobraine Blumenol A Dehydrocorydalmine Liriodenine Lysicamine *N*-*p*-coumaroyltyramine *N*-*trans*-feruloyltyramine		
	Fruit and Stem	6-*O*-palmitoyl-ß-sitosteryl-D-glucoside ß-sitosterol ß-sitosteryl--glucoside Stigmasterol Stigmasteryl-D-glucoside	STD	Chang et al. (2000)
	Leaves	Bullatanocin Glabracins A Glabracins B Javoricin Glacins A, Glacins B	ACT	Liu et al. (1998)
		(–)-(6a*S*,7*R*)-7-hydroxyactinodaphnine (–)-actinodaphnine (−)-anolobine (−)-asimilobine (−)-*N*-methylactinodaphnine (−)-pallidine (−)-roemeroline (+)-1*S*,2*S*-reticuline *N*-oxide (+)-boldine (+)-magnoflorine (+)-norisodomesticine (+)-reticuline (+)-stepharine 3-*O*-α-L-arabinopyranoside 3-*O*-β-D-glucopyranoside Liriodenine	ALK	Lee et al. (2015)
		Quercetin, Quercetin−3-*O*-β-D-galactopyranoside	FLA	Lee et al. (2015)
	Seed	Isodesacetyluvaricin	ACT	Wu et al. (2012)
A. jahnii	Twig	Annojahnin	ACT	Colman-saizarbitoria et al. (1998)
A. montana	Leaves	Annolatine, Annoretine, Argentinine, Liriodenine	ALK	Wu et al. (1995)
		β-sitosterol, β-sitosterol-β-D-glucoside	STD	Wu et al. (1995)
A. mucosa	Leaves	Atherospermidine, Liriodenine	ALK	Lima et al. (2012)
A. muricata	Fruit	*cis*-annoreticuin	ACT	Ragasa et al. (2012)
		Epomuricenins-A Epomuricenins-B Epomurinins-A Epomurinins-B Epomusenins-A Epomusenins-B	ACT	Melot et al. (2009)
		Muricin J, Muricin K, Muricin L	ACT	Sun et al. (2014)
		Annonaine, Asimilobine, Nomuciferine	ALK	Hasrat et al. (1997)
	Fruit, Root	Sabadelin	ACT	Ragasa et al. (2012); Gleye et al. (1999)
	Leaves	(2,4-*cis*)-10*R*-annonacin-A-one (2,4-*trans*)-10*R*-annonacin-A-one Annomutacin	ACT	Fenge (1995)
		Annohexocin	ACT	Zeng et al.1995)
		Annomuricin C, Muricatocin C	ACT	Wu et al. (1995b)

Species	Part	Compound	Class	Reference
		Annomuricine, Muricapentocin	ACT	Kim et al. (1998b)
		Annomuricins A, Annomuricins B	ACT	Wu et al. (1995)
		Annopentocins A Annopentocins B Annopentocins C *cis*-annomuricin-D-ones *trans*-annomuricin-D-ones	ACT	Zeng et al. (1996)
		Muricatocins A, Muricatocins B	ACT	Wu et al. (1995a)
		Muricoreacin, Murihexocin C	ACT	Kim et al. (1998a)
		Murihexocin A, Murihexocin B	ACT	Zeng et al. (1995)
		(R)-4-*O*-methylcoclaurine (R)-anonaine (R)-*O,O*-dimethylcoclaurine (S)-Norcorydine Annonamine	ALK	Matsushige et al. (2012)
		Anonaine Benzyltetrahydroisoquinoline alkaloid coclaurine Isolaureline Xylopine	ALK	Fofana et al. (2011)
		Argentinine (1-N,N-dimethylethanyl-4,6-dimethoxy-3,8-dihydroxy phenanthrene) 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)
		Annoionols A Annoionols B Annoionoside	MGS	Matsushige et al. (2012)
	Leaves, Pericarp, Root, Seed	Annonacin	ACT	Luna Jde et al. (2006); Jaramillo et al. (2000); Champy et al. 2004); Yu et al. (1998)
	Leaves, Seed	Annocatacin A, Annocatacin B	ACT	Chang et al. (2003)
		Annocatalin, *cis*-corossolone	ACT	Liaw et al. (2002)
		Annonacinone	ACT	Liaw et al. (2002); Vila-Nova et al. (2011)
		Corossolone	ACT	Vila-Nova et al. (2011)
		Goniothalamicin, Isoannonacin	ACT	Luna Jde et al. (2006)
	Pericarp	Annomuricin A	ACT	Jaramillo et al. (2000)
	Pericarp, Seed	Annonacin A	ACT	Jaramillo et al. (2000); Yu et al. (1998)
	Root	Chatenaytrienins-1 Chatenaytrienins-2 Chatenaytrienins-3 Muricadienin Muridienins-1 Muridienins-2 Muridienins-3 Muridienins-4	ACT	Gleye et al. (1998)
		cis-panatellin *cis*-reticulatacin *cis*-reticulatacin-10-one *cis*-solamin *cis*-uvariamicin IV Cohibins A, Cohibins B Coronin Montecristin	ACT	Gleye et al. (1998)

Species	Part	Compound	Class	Reference
	Seed	2,4-*cis*-Gigantetrocinone 2,4-*trans*-gigantetrocinone 2,4-*trans*-isoaiinonacin 2,4-*trans*-Isoannonacin- 10-one Annomontacin Gigantetrocin-A Gigantetronenin Muricatenol	ACT	Li et al. (2001)
		Annoreticum-9-one	ACT	Ragasa et al. (2012)
		cis-annomontacin Muricin H Muricin I Murisolin Xylomaticin	ACT	Liaw et al. (2002)
		Arianacin *cis*-annonacin *cis*-annonacin-10-one *cis*-goniothalamicin Javoricin	ACT	Rieser et al. (1996)
		Cohibins C, Cohibins D	ACT	Gleye et al. (2000)
		Donhexocin, Murihexol	ACT	Yu et al. (1998)
		Gigantetrocin-B	ACT	Li et al. (2001)
		Longifolicin Muricin A Muricin B Muricin C Muricin D Muricin E Muricin F Muricin G	ACT	Chang and Wu (2001)
		Annomuricatin B	CYP	Chao-ming et al. (1998)
		Annomuricatin C	CYP	Wélé et al. (2004)
	Stem Bark	Muricatin A, Muricatin B,Muricatin C	ACT	Chang and Wu (2001)
A. nutans	Bark Root	Chatenaytrienin-1 Chatenaytrienin-2 Chatenaytrienin-3 Chatenaytrienin-4	ACT	Gleye et al. (1998)
	Root	Cohibins C, Cohibins D	ACT	Gleye et al. (2000)
Annona pickelii	Leaves	Bicyclogermacrene, (E)-caryophyllene, δ-cadinene, α-copaene, and allo-aromadendrene	ESO	Costa et al. (2011a)
Annona purpurea	Leaves	7-formyl-dehydrothalicsimidine 7-hydroxy-dehydrothalicsimidine Lirinidine *N*-methylasimilobine *N*-methyllaurotetanine Norpurpureine Thalicsimidine	ALK	Chang et al. (1998)
	Root	Annomontine	ALK	Rejon-Orantes Jdel et al. (2011)
A. reticula	Fruit	α-pinene, β-pinene, Germacrene D, Limonene, Myrcene, Terpinen-4-ol	ESO	Pino et al. (2003)
	Leaves	(E,E)-farnesyl acetate, ar-turmerone, benzyl benzoate and γ-terpinene	ESO	Ogunwande et al. (2006)
	Seed	Annonacin	ACT	Yuan et al. (2003)
		Annoreticuin Annoreticuin-9-one Bullatacin *cis*-bullatacinone *cis*-isomurisolenin *cis*-murisolinone Squamocin	ACT	Chang et al. (1998)

Species	Part	Compound	Class	Reference
		trans-bullatacinone *trans*-isomurisolenin *trans*-murisolinone		
A. salzmannii	Bark	Anonaine Asimilobine Cleistopholine Liriodenine Reticuline	ALK	Costa et al. (2013)
	Leaves	Bicyclogermacrene, (E)-caryophyllene, and α-copaene	ESO	Costa et al. (2011a)
A. senegalensis	Aerial parts	(−)-anonaine (−)-asimilobine (+)-catechin (+)-nornantenine	ALK	Lall et al. (2017)
	Leaves	(-)-roemerine	ALK	You et al. (1995)
		Germacrene D α-humulene β-caryophyllene γ-cadinene	ESO	Ch. Nébié et al. (2005)
	Seed	Annogalene, Annosenegalin	ACT	Sahpaz et al. (1996)
Annona sericea	Leaves	Aporphines Benzyltetrahydroisoquinolines Oxoaporphines	ALK	Campos et al. (2008)
A. squamosa	Bark	2,4-*cis*-Mosinone A 2,4-*trans*-Mosinone A Annoreticum-9-one Mosin B Mosin C	ACT	Hopp et al. (1997)
	Leaves	(-) Anonaine	ALK	Porwal and Kumar (2015)
		O-methylarmepavine	ALK	Vila-Nova et al. (2011)
		β-Caryophyllene, β-Cedrene	ESO	Joy and Rao (1997)
		Bicyclogermacrene, (E)-Caryophyllene, Germacrene D	ESO	Meira et al. (2014)
		Quercetin-3-*O*-glucoside	FLA	Panda and Kar (2007)
	Pulp Fruit	α-pinene, Limonene, Sabinene	ESO	Andrade et al. (2001)
	Seed	Annosquamins A, Annosquamins B, Annosquamins C	ACT	Chen et al. (2012)
		Neoannonin-B	ACT	Gleye et al. (2001)
	Stem	11 *ent*-kauranes	ALK	Yeh et al. (2005)
		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)
Annona sylvatica	Leaves	Hinesol; z-Caryophyllene; β-Maaliene; γ-Gurjunene; Silphiperfol-5-en-3-ol; Ledol; Cubecol-1-epi; Muurola-3,5-diene.	ESO	Formagio et al. (2013)
A. vepretorum	Leaves	α-phellandrene, Bicyclogermacrene, Spathulenol	ESO	Meira et al. (2014)

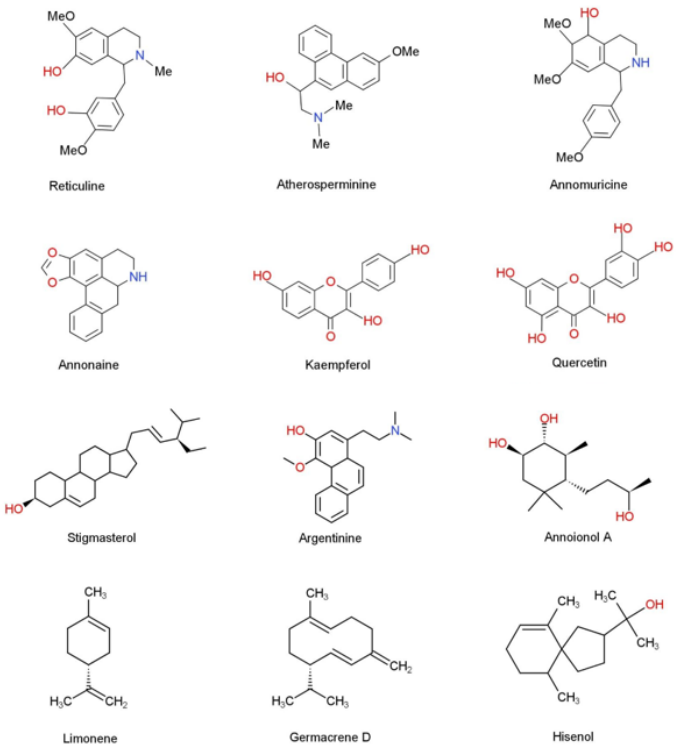

Fig. 1. Several phytochemicals of the *Annona* genus.

3. Pharmacological activities of *Annona*

The *Annona* genus is known to contain a large number of phytochemicals compounds in nearly every part of the plant. Various researches revealed pharmacological activity from its phytochemical compounds: antinociceptive (Carballo et al., 2010), anti-acetylcholinesterase (Lee et al., 2015), anticonvulsant (Eva Gonzalez-Trujano et al., 2013), antidepressant (Martinez-Vazquez et al., 2012), antibacterial (Takahashi et al., 2006), antifungal (Navarro García et al., 2003), anticancer (Ajaiyeoba et al., 2005), antidiabetic (Panda and Kar, 2007), antidiarrhea (Afroz et al., 2020), antiulcer (Castillo-Juarez et al., 2009), anti-inflammatory (Rocha et al., 2016), antimalarial (Ajaiyeoba et al., 2005), dengue vector control activity (de Omena et al., 2007), antioxidant (Essama et al., 2015), and antileishmanial(Lima et al., 2012) (Table 2).

3.1. Antinociceptive, anti-acetylcholinesterase, anticonsulvant, and antidepressant activities

Antinociceptive compounds have analgesic effect resulting in reduction of pain. Ethanol crude extract from *Annona diversifolia* leaves had a comparable antinociceptive response (ED_{50} = 15.35 mg/kg) to tramadol, the reference drug, (ED_{50} = 12.42 mg/kg) when evaluated with the writhing test in mice (Carballo et al., 2010). Fifteen alkaloids derived from *A. glabra* leaves through fractionation using centrifugal partition chromatography (CPC) possess anti-acetylcholinesterase activity. The compounds (−)-anolobine and (−)-roemeroline indicated moderate inhibitory activity against cell acetylcholinesterase with IC_{50} values of 22.4 μM and 26.3 μM (Lee et al., 2015).

A. senegalensis crystals obtained from *A. senegalensis* root bark fraction indicated anticonvulsant activity. *A. senegalensis* crystals were characterized as kaur-16-*ent*-19-oic acid then orally administrated to mice with (PTZ)-induced seizures, providing LD_{50} value of 3800 mg/kg (Okoye et al., 2013). Supporting its use in traditional medicine, the aerial parts of *A. cherimola* had therapeutic potency as an antidepressant (Martinez-Vazquez et al., 2012).

Table 2. Pharmacological activities of plants from the *Annona* genus.

Pharmacological Activity	Species	Part	Reference
Analgesic	*A. diversifolia*	Leaves	Carballo et al. (2010)
Anti-Acetylcholinesterase	*A. glabra*	Leaves	Lee et al. (2015)
Anticonvulsant	*A. diversifolia*	Leaves	Eva Gonzalez-Trujano et al. (2006); Cano-Europa et al. (2010)
Anticonvulsant	*A. senegalensis*	Root Bark	Okoye et al. (2013)
Antidepressant	*A. muricata*	Fruit	Hasrat et al. (1997)
Antidepressant	*A. cherimola*	Aerial parts	Martinez-Vazquez et al. (2012)
Antibacterial	*A. ambotay*	Stem	Takahashi et al. (2006)
Antibacterial	*A. cherimola*	Leaves	Takahashi et al. (2006)
Antibacterial	*A. crassiflora*	Leaves, seed, fruit	de Lima et al. (2006)
Antibacterial	*A. muricata*	Bark, Leaves, Stem, Fruit	Afroz et al. (2020); Essama et al. (2015)
Antibacterial	*A. pickelii*	Leaves	Costa et al. (2011a)
Antibacterial	*A. salzmannii*	Bark, Leaves, fruit	Costa et al. (2011a); Costa et al. (2013); de Lima et al. (2006)
Antibacterial	*A. senegalensis*	Twigs, leaves, bark, root	More et al. (2008)
Antibacterial	*A. squamosa*	Root, Seed, Leaves	Aher et al. (2012); Mohamad et al. (2017); Shanker et al. (2007)
Antifungal	*A. cherimola*	Seed	Navarro García et al. (2003)
Antifungal	*A. crassiflora*	Leaves	Silva et al. (2008)
Antifungal	*A. pickelii*	Leaves	Costa et al. (2011a)
Antifungal	*A. salzmannii*	Bark, Leaves	Costa et al. (2011a); Costa et al. (2013)
Anticancer	*A. cherimola*	Seed	Woo et al. (1999); Kim et al. (2001); Son et al. (2003); Barrachina et al. (2004)
Anticancer	*A. muricata*	Leaves	Asare et al. (2015); Yang et al. (2015)
Anticancer	*A. pickelii*	Leaves	Costa et al. (2013)
Anticancer	*A. salzmannii*	Leaves	Costa et al. (2013)
Anticancer	*A. senegalensis*	Leaves	You et al. (1995); Ajaiyeoba et al. (2005)
Anticancer	*A. squamosa*	Leaves, Seed, Stem	Chen et al. (2012); Mohamad et al. (2017); Wang et al. (2014)
Anticancer	*A. sylvatica*	Leaves	Formagio et al. (2013)
Antidiabetic	*A. squamosa*	Leaves	Panda and Kar (2007)
Antidiabetic	*A. cherimola*	Leaves	Calzada et al. (2017)
Antidiabetic	*A. muricata*	Leaves	Adeyemi et al. (2009)

Pharmacological Activity	Species	Part	Reference
Antidiarrhea	*A. muricata*	Fruit, Seed	Afroz et al. (2020); Doe et al. (2019)
Antidiarrhea	*A. senegalensis*	Stem Bark	Suleiman et al. (2008)
Antiulcer	*A. cherimola*	Stem, Leaves	Castillo-Juarez et al. (2009)
Antiulcer	*A. squamosa*	Twigs	Yadav et al. (2011)
Antiinflamatory	*A. crassiflora*	Leaves	Rocha et al. (2016)
Antiinflamatory	*A. glabra*	Seed	Wu et al. (2012)
Antiinflamatory	*A. squamosa*	Stem	Yeh et al. (2005)
Antiinflamatory	*A. sylvatica*	Leaves	Formagio et al. (2013)
Antimalaria	*A. senegalensis*	Leaves	Ajaiyeoba et al. (2005)
Antimalaria	*A. squamosa*	Bark, Leaves	Kamaraj et al. (2012); Singh et al. (2015)
Dengue Vector Control Activity	*A. crassiflora*	Root Bark, Root Wood	de Omena et al. (2007); Rodrigues et al. (2006)
Dengue Vector Control Activity	*A. glabra*	Stem	de Mendonca et al. (2005)
Dengue Vector Control Activity	*A. muricata*	Seed	Grzybowski et al. (2013)
Antioxidant	*A. muricata*	Bark, Leaves, Stem	Essama et al. (2015)
Antioxidant	*A. pickelii*	Leaves	Costa et al. (2011a)
Antioxidant	*A. salzmannii*	Bark, Leaves	Costa et al. (2011a); Costa et al. (2013)
Antioxidant	*A. senegalensis*	Leaves	Ajboye et al. (2010)
Antioxidant	*A. squamosa*	Leaves, Pulp, Seed, Stem	Panda and Kar (2007); Yang et al. (2004); Mohamad et al. (2017); Nandhakumar and Indumathi (2013)
Antileishmanial	*A. mucosa*	Leaves, Seed	Lima et al. (2012)
Antileishmanial	*A. muricata*	Leaves	Vila-Nova et al. (2011); Osorio et al. (2007)
Antileishmanial	*A. purpurea*	Bark, Seed	Camacho et al. (2003)
Antileishmanial	*A. squamosa*	Leaves	Vila-Nova et al. (2011)

3.2. Antibacterial and antifungal activity

Acetogenins in *A. cherimola* leaves had antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus* with inhibitory diameter of 14 mm and 11 mm, respectively. *A. ambotay* also had antibacterial activity with diameter of 10 mm and 9 mm, respectively (Takahashi et al., 2006). Another *Annona* plant, *A. squamosa*, has high potency antibacterial activity, especially its seed compounds. The methanol extract, chloroform extract, and petroleum ether extract of *A. squamosa* could inhibit *Escherichia coli*, *Pseudomonas aeruginosa*, *S. aureus*, *Klebsiella pneumonia*, and *B. subtilis* (Aher et al., 2012). The water-methanol extract worked against *S. aureus* with Minimum Inhibitory Concentrations (MIC) of 50 mg/mL and Minimum Bactericidal Concentrations (MBC) of 100 mg/mL (Mohamad et al., 2017).

Besides antibacterial activity, *Annona* plants also have antifungal activity. Ethanol extract from the leaves of *A. crassiflora* was active against all microorganisms and indicated antifungal activity based on the MIC values of 57 inhibited strains of *Candida albicans* (Silva et al., 2008). The sesquiterpenes of essential oils from the leaves of *A. salzmannii* show MIC values of 1 mg/mL for *C. albicans* and 0.5 mg/mL for *Candida tropicalis* (Costa et al., 2011a).

3.3. Anticancer activity

Cancer is a common cause of death worldwide. Nowadays, several methods performed to cure cancer are surgical treatment, radiotherapy, and chemotherapy. Therapy is the main method to cure this disease, but it is still not accessible for many people. Anticancer herbal drugs have been developed, especially from *Annona* plants (Wang et al., 2014).

An aporphine alkaloid from *A. senegalensis* leaf extract, (-)-roemerine, was found to increase the cytotoxic response mediated by vinblastine with multidrug-resistant KB-V1 cells. Evaluation of the cytotoxic potential was conducted with cultured P-388 cell and KB-V1 treated with vinblastine (1 μg/mL). The results indicated ED_{50} value of > 5 μg/mL of P-388 cell and ED_{50} value of 0.6 μg/mL of KB-V1 cell with vinblastine (1 μg/mL) (You et al., 1995). In other plants, anticancer activity was shown by cytotoxicity test with IC_{50} value of 27.2 μg/mL for *A. pickelii* leaf essential oil, 89.7 μg/mL for *A. salzmannii* leaf essential oil (Costa et al., 2013) and 1.36 mg/mL for *A. muricata* leaf (Asare et al., 2015).

3.4. Antidiabetic activity

Diabetes or hyperglycemia is a disease characterized by increasing in sugar blood levels due to certain factors. The development of herbal remedies from *Annona* plant has been conducted abundantly. In a preclinical study using hyperglycemia-induced rats, methanol extract of *A. muricata* leaf could decrease blood glucose concentration from 26.64 mmol/L until 4.22 mmol/L in the test group (Adeyemi et al., 2009). The leaves of *A. cherimola* also have high antidiabetic potential, could decrease blood glucose concentration from 331.5 mg/dL to 149.2 mg/dL. Routine administration as α-glucosidase inhibitor could increase antidiabetic activity (Calzada et al., 2017).

3.5. Antidiarrhea and antiulcer activity

A. muricata has been traditionally used for a long period of time. Testing of the *A. muricata* fruit methanol fraction showed 58.38% inhibition of diarrhea at a dose of 400 mg/kg body weight in Swiss albino mice (Afroz et al., 2020). As another example, the stem-bark extract of *A. senegalensis* was tested using the intestinal transit time of mice method. The extract at the dose of 10 mg/kg significantly decreased intestinal transit time at concentrations of 0.2 – 3.2 mg/mL (Suleiman et al., 2008). Therefore, antidiarrhea activity in *A. muricata* and *A. senegalensis* has been scientifically proven.

Helicobacter pylori is the major etiological agent of chronic active gastritis and peptic ulcer disease. The traditional use of water-based *A. cherimola* as antiulcer had a long history. A study showed that the methanol leaf/stem extract of *A. cherimola* is better than the water extract with the indicated MIC value of methanol extract amounting to < 15.6 μg/ml and MIC value of 250 μg/ml for

water extract (Castillo-Juarez et al., 2009). Administration of *A. squamosa* twig extract using doses of 25, 50, 100 mg/kg body weight on rats with cold-restraint induced ulcer indicated percentage protection of 50%, 87.50%, and 81.20%, respectively, whereas omeprazole (10 mg/kg) as reference drug showed 77.4% (Yadav et al., 2011).

3.6. Anti-inflammatory activity

Inflammation can occur due to development of tissue lesions, which cause pain from edema exerting pressure on nerve endings. The kaempferol 3-*O*-β-glucoside and kaempferol 3-*O*-β-diglucoside from *A. crassiflora* leaves might inhibit the occurrence of edema. Doses of 100 mg/kg and 300 mg/kg can inhibit the formation of carrageenan-induced edema to about 53% and 47% (Rocha et al., 2016). The essential oil from the leaves of *A. sylvatica* at doses of 20 mg/kg and 200 mg/kg showed 19% and 27% inhibition (Formagio et al., 2013). These results can be used in the development of herbal anti-inflammatory medicine.

3.7. Antimalarials and dengue vector control activity

Malaria is a disease caused by *Plasmodium* sp. with *Anopheles* female mosquito as the vector. Plants are rich in compounds with antimalarial effect, such as quinine and artemisinin. The development of antimalarial drugs continues to be conducted, including compounds from *Annona* plants. The leaves of *A. senegalensis* were tested on *Plasmodium berghei* and 91.1% chemosuppression was obtained at dose of 800 mg/kg/day (Ajaiyeoba et al., 2005). Another study tested the bark and leaves of *A. squamosa* on 3D7 and INDO strains of *Plasmodium falciparum*. *A. squamosa* leaves indicated IC_{50} value of 2.1 µg/mL and 3.3 µg/mL on *P. falciparum* 3D7 and *P. falciparum* INDO, respectively. Bark of *A. squamosa* showed IC_{50} value of 30 µg/mL on *P. falciparum* 3D7 (Kamaraj et al., 2012; Singh et al., 2015).

Besides antimalarial, *Annona* plants also have Dengue Vector Control Activity. It is evidenced in the two species tested on *Aedes aegypti* larvae. Stem extracts of *A. glabra* possess LC_{50} value of 26.9 µg/L against the fourth-instar larvae of *A. aegypti* (de Mendonca et al., 2005), while seeds of ripe fruits from *A. muricata* has LC_{50} value of 93.48 µg/ml against the third-instar larvae of *A. aegypti* (Grzybowski *et al.*, 2013). The potential of Dengue Vector Control of *Annona* plant is high enough to merit large-scale development as herbal medicine.

3.8. Antioxidant activity

Antioxidants are compounds that prevent or inhibit free radicals. Adverse effects caused by free radicals included decreasing in activity of immune system, cancer, and diabetes. Certain plants have high antioxidant activity, one of them being the *Annona* plant. Antioxidant activity assay using DPPH method on some parts of *A. muricata* is indicated by the EC_{50} value of barks amounting to 90 mg/g DPPH, 290 mg/g DPPH for leaves, 116 mg/g DPPH for stems, compared to 157.5 mg/g DPPH for ascorbic acid as reference drug (Essama et al., 2015). On the ORAC method testing of several alkaloid isolated from the bark of *A. salzmannii*, asimilobine was found to be the most active with ORAC value of 2.09 relative Trolox equivalents (Costa et al., 2013).

3.9. Antileishmanial activity

Visceral leishmaniasis is an endemic in 88 countries infecting 12 million people. Many phytochemicals from the *Annona* group were tested against Leishmania. Alkaloids and acetogenins isolated from *A. muricata* seeds and *A. squamosa* leaves were tested against promastigote and amastigote forms of *Leishmania chagasi*. The alkaloids in *A. squamosa* showed EC_{50} of 23.3 µg/mL against promastigotes and 25.4 µg/mL against amastigotes, while acetogenin show EC_{50} of 25.9-37.6 µg/mL against promastigotes and 13.5-28.7 µg/mL against amastigotes (Vila-Nova et al., 2011). Methanol leaf and seed extracts of *A. mucosa* presented activity against *L. amazonensis* with IC_{50} of 28.32 µg/mL and 46.54 µg/mL, respectively. The results of the study displayed that *Annona* plants possess high antileishmanial potential and deserve further development (Lima et al., 2012).

4. Conclusion

The *Annona* Genus has several classes of chemical compounds that are found in almost every part of certain *Annona* plants, such as *Annona*ceous acetogenins, alkaloids, cyclic peptides, essential oils, flavonoids, megastigmanes, and steroids. Additionally, the *Annona* plants have many pharmacological effects that have been scientifically proven, such as antinociceptive, anti-acetylcholinesterase, anticonvulsant, antidepressant, antibacterial, antifungal, anticancer, antidiabetic, antidiarrhea, antiulcer, anti-inflammatory, antimalarial, Dengue vector control activity, antioxidant, and antileishmanial. This article was created by collecting 124 research articles discussing phytochemicals from 20 species and the pharmacological activity from 13 species, which can be utilized by the public for knowledge of herbal treatments from *Annona* plants.

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Conflict of Interest

The authors declare no conflict of interest.

References

Adeyemi DO, Komolafe OA, Adewole OS, Martins OE, and Kehinde AT. 2009. Antihyperglycemic activities of *Annona muricata* (Linn). *Afr J Trad CAM* 6**:** 62-9.

Afroz N, Ahsanul Hoq M, Jahan S, Mainul Islam M, Ahmed F, Shahid-Ud-Daula AFM. 2020. Methanol soluble fraction of fruits of *Annona muricata* possesses significant antidiarrheal activities. *Heliyon* 6**:** e03112. doi: 10.1016/j.heliyon.2019.e03112

Aher PS, Shinde YS, P.Chavan P. 2012. In vitro evaluation of antibacterial potential of *Annona squamosa* L. against pathogenic bacteria. *IJPSR* 3**:** 1457-60. doi: 10.13040/IJPSR.0975-8232.3(5).1457-60

Ajaiyeoba E, Falade M, Ogbole O, Okpako L, Akinboye D. 2005. In vivo antimalarial and cytotoxic properties of *Annona senegalensis* extract. *Afr J Tradit Complem* 3 (1): 137-41.

Ajboye TO, Yakubu MT, Salau AK, Oladiji AT, Akanji MA, Okogun JI. 2010. Antioxidant and drug detoxification potential of aqueous extract of *Annona senegalensis* leaves in carbon tetrachloride-induced hepatocellular damage. *Pharm Biol* 48**:** 1361-70. doi: 10.3109/13880209.2010.483247

Andrade EHA, Zoghbi MdGB, Maia JGS, Fabricius H, Marx F. 2001. Chemical characterization of the fruit of *Annona squamosa* L. occurring in the amazon. *J Food Compost Anal* 14**:** 227-32. doi: 10.1006/jfca.2000.0968

Asare GA, Afriyie D, Ngala RA, Abutiate H, Doku D, Mahmood SA. 2015. Antiproliferative activity of aqueous leaf extract of *Annona muricata* L. on the prostate, BPH-1 cells, and some target genes. *Integr Cancer Ther* 14**:** 65-74. doi: 10.1177/1534735414550198

Barrachina I, Neske A, Granell S, Bermejo A, Chahboune N, El Aouad N. 2004. Tucumanin, a beta-hydroxy-gamma-lactone bistetrahydrofuranic acetogenin from *Annona* cherimolia, is a potent inhibitor of mitochondrial complex I. *Planta Med* 70**:** 866-8. doi: 10.1055/s-2004-827237

Bhardwaj R, Pareek S, Sagar NA, Vyas N. 2019. Bioactive compounds of *Annona*. In bioactive compounds in underutilized fruits and nuts. pp 1-26. Reference Series in Phytochemistry. Springer, Cham. Doi: 10.1007/978-3-030-06120-3_5-1

Calzada F, Solares-Pascasio JI, Ordonez-Razo RM, Velazquez C, Barbosa E, Garcia-Hernandez N. 2017. Antihyperglycemic activity of the leaves from *Annona cherimola* miller and rutin on alloxan-induced diabetic rats. *Pharmacog Res* 9(1)**:** 1-6. doi: 10.4103/0974-8490.199781

Camacho MdR, Phillipson JD, Croft SL, Solis PN, Marshall SJ, Ghazanfar SA. 2003. Screening of plant extracts for antiprotozoal and cytotoxic

activities. *J Ethnopharmacol* 89(2-3)**:** 185-91. doi: 10.1016/s0378-8741(03)00269-1

Campos FR, Batista RL, Batista CL, Costa EV, Barison A, dos Santos AG. 2008. Isoquinoline alkaloids from leaves of *Annona sericea* (*Annona*ceae). *Biochem Syst Ecol* 36**:** 804-6. doi: 10.1016/j.bse.2008.07.005

Cano-Europa E, Gonzalez-Trujano ME, Reyes-Ramirez A, Hernandez-Garcia A, Blas-Valdivia V, Ortiz-Butron R. 2010. Palmitone prevents pentylenetetrazole-caused neuronal damage in the CA3 hippocampal region of prepubertal rats. *Neurosci Lett* 470(2)**:** 111-114. Doi: 10.1016/j.neulet.2009.12.066

Carballo AI, Martinez AL, Gonzalez-Trujano ME, Pellicer F, Ventura-Martinez R, Diaz-Reval MI. 2010. Antinociceptive activity of *Annona diversifolia* Saff. leaf extracts and palmitone as a bioactive compound. *Pharmacol Biochem Behav* 95(1)**:** 6-12. doi: 10.1016/j.pbb.2009.11.017

Castillo-Juarez I, Gonzalez V, Jaime-Aguilar H, Martinez G, Linares E, Bye R. 2009. Anti-Helicobacter pylori activity of plants used in mexican traditional medicine for gastrointestinal disorders. *J Ethnopharmacol* 122(2)**:** 402-5. doi: 10.1016/j.jep.2008.12.021

Ch. Nébié RH, Yaméogo RT, Bélanger A, Sib FS. 2005. Chemical composition of leaf essential oil of *Annona senegalensis* Pers. from burkina faso. *J Essent Oil Res* 17(3)**:** 331-2. doi: 10.1080/10412905. 2005.9698922

Champy P, Hoglinger GU, Feger J, Gleye C, Hocquemiller R, Laurens A. 2004. *Annona*cin, a lipophilic inhibitor of mitochondrial complex I, induces nigral and striatal neurodegeneration in rats: possible relevance for atypical parkinsonism in Guadeloupe. *J Neurochem* 88(1)**:** 63-9. doi: 10.1046/j.1471-4159.2003.02138.x

Chang FR, Chen CY, Hsieh TJ, Cho CP, Wu YC. 2000. Chemical constituents from *Annona glabra* III. *J Chin Chem Soc-taip* 47(4B)**:** 913-20. Doi: 10.1002/jccs.200000124

Chang FR, Chen JL, Chiu HF, Wu MJ, Wu YC. 1998. Acetogenins from seeds of *Annona reticulata*. *Phytochem Anal* 47(6)**:** 1057-61. Doi: 10.1016/S0031-9422(98)80072-1

Chang FR, Liaw CC, Lin CY, Chou CJ, Chiu HF, Wu YC. 2003. New adjacent bis-tetrahydrofuran *Annona*ceous acetogenins from *Annona muricata*. *Planta Med* 69(3)**:** 241-46. doi: 10.1055/s-2003-38485

Chang FR, Wei JL, Teng CM, Wu YC. 1998. Two new 7-dehydroaporphine alkaloids and antiplatelet action aporphines from the leaves of *Annona purpurea*. *Phytochem* 49(7)**:** 2015-18. doi: 10.1016/S0031-9422(98)00376-8

Chang FR and Wu YC. 2001. Novel cytotoxic *Annona*ceous acetogenins from *Annona muricata*. *J Nat Prod* 64(7)**:** 925-31. doi: 10.1021/np010035s

Chang FR, Yang PY, Lin JY, Lee KH, Wu YC. 1998. Bioactive kaurane diterpenoids from *Annona glabra*. *J Nat Prod* 61(4)**:** 437-39. doi: 10.1021/np970497z

Chao-Ming L, Ning-Hua T, Hui-Lan Z, Qing M, Xiao-Jiang H, Yi-Neng H. 1998. Cyclopeptide from the seeds of *Annona muricata*. *Phytochemistry* 48(3)**:** 555-6. Doi: 10.1016/S0031-9422(98)00002-8

Chen CH, Hsieh TJ, Liu TZ, Chern CL, Hsieh PY, Chen CY. 2004. Annoglabayin, a novel dimeric kaurane diterpenoid, and apoptosis in hep G2 cells of annomontacin from the fruits of *Annona glabra*. *J Nat Prod* 67**:** 1942-6. doi: 10.1021/np040078j

Chen CY, Chang FR, Chiu HF, Wu MJ, Wu YC. 1999. Aromin-A, an *Annona*ceous acetogenin from *Annona cherimola*. *Phytochem* 51(3)**:** 429-33. doi: 10.1016/S0031-9422(99)00002-3

Chen CY, Chang FR, Pan WB, Wu YC. 2001. Four alkaloids from *Annona cherimola*. *Phytochem* 56(7)**:** 753-7. doi: 10.1016/s0031-9422(00)00486-6

Chen Y, Chen JW, Li X. 2012. Monotetrahydrofuran *Annona*ceous acetogenins from the seeds of *Annona squamosa*. *Phytochem Lett* 5(1)**:** 33-6. doi: 10.1016/j.phytol.2011.08.015

Colman-Saizarbitoria T, Johnson H, Alali FQ, Hopp DC, Rogers LL, Mclaughlin JL. 1998. Annojahnin from *Annona jahnii*: a possible precursor of mono-tetrahydrofuran acetogenins. *Phytochem* 49(6)**:** 1609-16. doi: 10.1016/S0031-9422(98)00316-1

Costa EV, da Cruz PE, de Lourenco CC, de Souza Moraes VR, de Lima Nogueira PC, Salvador MJ. 2013. Antioxidant and antimicrobial activities of aporphinoids and other alkaloids from the bark of *Annona salzmannii* A. DC. (*Annona*ceae). *Nat Prod Res* 27(11)**:** 1002-6. doi: 10.1080/14786419.2012.688044

Costa EV, Dutra LM, de Jesus HCR, de Lima Nogueira PC, de Souza Moraes VR, Salvador MJ. 2011. Chemical composition and antioxidant, antimicrobial, and larvicidal activities of the essential oils of *Annona salzmannii* and *A. pickelii* (*Annona*ceae). *Nat Prod Commun* 6(6): 907-12. doi: 10.1177/1934578X1100600636

Costa EV, Dutra LM, Salvador MJ, Ribeiro LH, Gadelha FR, de Carvalho JE. 2013. Chemical composition of the essential oils of *Annona pickelii* and *Annona salzmannii* (*Annona*ceae), and their antitumour and trypanocidal activities. *Nat Prod Res* 27(11)**:** 997-1001. doi: 10.1080/14786419.2012.686913

Costa EV, Pinheiro ML, de Souza AD, Barison A, Campos FR, Valdez RH. 2011b. Trypanocidal activity of oxoaporphine and pyrimidine-beta-carboline alkaloids from the branches of *Annona foetida* Mart. (*Annona*ceae). *Mol* 16(11)**:** 9714-20. doi: 10.3390/molecules16119714

Costa EV, Pinheiro MLcB, Xavier CM, Silva JRA, Amaral ACuF, Souza ADL. 2006. A pyrimidine-carboline and other alkaloids from *Annona foetida* with antileishmanial activity. *J Nat Prod* 69(2)**:** 292-4. doi: 10.1021/np050422s

Costa EV, Silva mlbPeJrdA, Maia BHLDNS, Duarte MCT, Amaral ACF, Leon Gmdcmell. 2009. Antimicrobial and antileishmanial activity of essential oil from the leaves of *Annona foetida* (*Annona*ceae). *Quim Nova* 32**:** 78-81. doi: 10.1590/S0100-40422009000100015

de Lima MR, de Souza Luna J, dos Santos AF, de Andrade MC, Sant'Ana AE, Genet JP. 2006. Anti-bacterial activity of some brazilian medicinal plants. *J Ethnopharmacol* 105(1-2)**:** 137-47. doi: 10.1016/j.jep.2005.10.026

de Mendonca FA, da Silva KF, dos Santos KK, Ribeiro Junior KA, Sant'Ana AE. 2005. Activities of some brazilian plants against larvae of the mosquito *Aedes aegypti*. *Fitoterapia* 76(7-8)**:** 629-36. doi: 10.1016/j.fitote.2005.06.013

de Omena MC, Navarro DM, de Paula JE, Luna JS, Ferreira de Lima MR, Sant'Ana AE. 2007. Larvicidal activities against *Aedes aegypti* of some brazilian medicinal plants. *Bioresour Technol* 98(13)**:** 2549-56. doi: 10.1016/j.biortech.2006.09.040

Doe P, Iddrisu A, Lartey P, Elijah K, Issaka S, Enock DA. 2019. Evaluation of the anti-diarrheal activity of the ethanolic seed extract of *Annona muricata*. *J Phytopharmacol* 8(4)**:** 199-202. doi: 10.31254/phyto.2019.8409

Egydio-Brandão, Monteiro AP, Novaes, Santos Pa, dos DYAC. 2017. Alkaloids from *Annona*: review from 2005 to 2016. *JSM Biochem Mol Biol* 4**:** 1-12.

Essama SHR, Nyegue MA, Foe CN, Silihe KK, Tamo SPB, Etoa FX. 2015. Antibacterial and antioxidant activities of hydro-ehanol extracts of barks, leaves and stems of *Annona muricata*. *Am J Pharmacol Sc* 3**:** 126-31. doi: 10.12691/ajps-3-6-1

Eva Gonzalez-Trujano M, Tapia E, Lopez-Meraz L, Navarrete A, Reyes-Ramirez A, Martinez A. 2006. Anticonvulsant effect of *Annona diversifolia* Saff. and palmitone on penicillin-induced convulsive activity. a behavioral and EEG study in rats. *Epilepsia* 47(11)**:** 1810-17. doi: 10.1111/j.1528-1167.2006.00827.x

Fenge WGS, Lu Z, Yan Z, Jon TS, Jerry LM. 1995. Additional bioactive acetogenins, annomutacin from the leaves of *Annona muricata* and (2,4-trans and cis)-10r-*Annona*cin-a-ones, from the leaves of *Annona muricata*. *J Nat Prod* 58(9): 1430-37. doi: 10.1021/np50123a015

Fofana S, Ziyaev R, Abdusamatov A, Zakirov SK. 2011. Alkaloids from *Annona muricata* leaves. *Chem Nat Compd* 47**:** 321. doi: 10.1007/s10600-011-9921-5

Formagio AS, Vieira Mdo C, Dos Santos LA, Cardoso CA, Foglio MA, de Carvalho JE. 2013. Composition and evaluation of the anti-inflammatory and anticancer activities of the essential oil from *Annona sylvatica* A. St.-Hil. *J Med Food* 16(1)**:** 20-25. doi: 10.1089/jmf.2011.0303

Gleye C, Akendengue B, Laurens A, Hocquemiller R. 2001. Coronin from roots of *Annona muricata*, a putative intermediate in acetogenin biosynthesis (1). *Planta Med* 67(6)**:** 570-2. doi: 10.1055/s-2001-16481

Gleye C, Duret P, Laurens A, Hocquemiller R, Cave´ A. 1998. cis-monotetrahydrofuran acetogenins from the roots of *Annona muricata*. *J Nat Prod* 61(5)**:** 576-9. doi: 10.1021/np970494m

Gleye C, Laurens A, Hocquemiller R, Cave A. 1997. Isolation of montecristin, a key metabolite in biogenesis of acetogenins from *Annona muricata* and its structure elucidation by using tandem mass spectrometry. *J Org Chem* 62(3)**:** 510-13. doi: 10.1021/jo960901j

Gleye C, Laurens A, Hocquemiller R, Laprevote O, Serani L, Cave A. 1997. Cohibins A and B, acetogenins from roots of *Annona muricata*. *Phytochemistry* 44(8)**:** 1541-5. doi: 10.1016/S0031-9422(96)00769-8

Gleye C, Laurens A, Laprevote O, Serani L, Hocquemiller R. 1999. Isolation and structure elucidation of sabadelin, an acetogenin from roots of *Annona muricata*. *Phytochemistry* 52(8)**:** 1403-8. doi: 10.1016/S0031-9422(99)00423-9

Gleye C, Raynaud S, Fourneau C, Laurens A, Lapre´vote O, Serani L. 2000. Cohibins C and D, two important metabolites in the biogenesis of acetogenins from *Annona muricata* and *Annona nutans*. *J Nat Prod* 63(9)**:** 1192-6. doi: 10.1021/np000061a

Gleye C, Raynaud S, Hocquemiller R, Laurens A, Fourneau C, Serani L. 1998. Muricadienin, muridienins and chatenaytrienins, the early precursors of *Annona*ceous acetogenins. *Phytochemistry* 47(5)**:** 749-54. doi: 10.1016/S0031-9422(97)00908-4

Grzybowski A, Tiboni M, Silva MA, Chitolina RF, Passos M, Fontana JD. 2013. Synergistic larvicidal effect and morphological alterations induced by ethanolic extracts of *Annona muricata* and *Piper nigrum* against the dengue fever vector *Aedes aegypti*. *Pest Manag Sci* 69(5)**:** 589-601. doi: 10.1002/ps.3409

Hasrat JA, Bruyne TD, Backer JPD, Vauquelin G, Vlietinck AJ. 1997. Isoquinoline derivatives isolated from the fruit of *Annona muricata* as 5-HTergic 5-HT1A receptor agonists in rats: unexploited antidepressive (lead) products. *J Pharm Pharmacol* 49(11)**:** 1145-9. doi: 10.1111/j.2042-7158.1997.tb06058.x

Hopp DC, Zeng L, Gu ZM, Kozlowski JF, McLaughlin JL. 1997. Novel mono-tetrahydrofuran ring acetogenins, from the bark of *Annona squamosa,* showing cytotoxic selectivities for the human pancreatic carcinoma cell line, PACA-2. *J Nat Prod* 60(6)**:** 581-6. DOI: 10.1021/np9701283

Jaramillo MC, Arango GJ, Gonzalez MC, Robledo SM, Velez ID. 2000. Cytotoxicity and antileishmanial activity of *Annona muricata* pericarp. *Fitoterapia* 71(2): 183-6. doi: 10.1016/s0367-326x(99)00138-0

Joy B and Rao JM. 1997. Essential oil of the leaves of *Annona squamosa* L. *J Essent Oil Res* 9(3): 349-50. doi: 10.1080/10412905.1997.10554258

Kamaraj C, Kaushik NK, Mohanakrishnan D, Elango G, Bagavan A, Zahir AA. 2012. Antiplasmodial potential of medicinal plant extracts from malaiyur and javadhu hills of south india. *Parasitol Res* 111(2): 703-15. doi: 10.1007/s00436-011-2457-6

Kim DH, Ma ES, Suk KD, Son JK, Lee JS, Woo MH. 2001. Annomolin and annocherimolin, new cytotoxic *Annona*ceous acetogenins from *Annona cherimolia* seeds. *J Nat Prod* 64(4): 502-6. doi: 10.1021/np000335u

Kim DH, Son JK, Woo MH. 2001. Annomocherin, *Annona*cin and annomontacin: a novel and two known bioactive mono-tetrahydrofuran *Annona*ceous acetogenins from *Annona cherimolia* seeds. *Arch Pharm Res* 24(4): 300-6. doi: 10.1007/BF02975096

Kim GS, Zeng L, Alali F, Rogers LL, Wu FE. 1998a. Muricoreacin and murihexocin C monotetrahydrofuran acetogenins from the leaves of *Annona muricata*. *Phytochemistry* 49(2): 565-71. doi: 10.1016/s0031-9422(98)00172-1

Kim GS, Zeng L, Alali F, Rogers LL, Wu FE, McLaughlin JL. 1998b. Two new mono-tetrahydrofuran ring acetogenins, annomuricin E and muricapentocin, from the leaves of *Annona muricata*. *J Nat Prod* 61(4): 432-6. doi: 10.1021/np970534m

Lall N, Kishore N, Bodiba D, More G, Tshikalange E, Kikuchi H. 2017. Alkaloids from aerial parts of *Annona senegalensis* against *Streptococcus* mutans. *Nat Prod Res* 31(16): 1944-7. doi: 10.1080/14786419.2016.1263847

Lee SS, Wu DY, Tsai SF, Chen CK. 2015. Anti-acetylcholinesterase alkaloids from *Annona glabra* leaf. *Nat Prod Commun* 10: 891-3. doi: 10.1177/1934578X1501000625

Li DY, Yu JG, Zhu JX, Yu DL, Luo XZ, Sun L. 2001. *Annona*ceous acetogenins of the seeds from *Annona muricata*. *J Asian Nat Prod Res* 3(4): 267-76. doi: 10.1080/10286020108040366

Liaw CC, Chang FR, Lin CY, Chou CJ, Chiu HF, Wu MJ. 2002. New cytotoxic monotetrahydrofuran *Annona*ceous acetogenins from *Annona muricata*. *J Nat Prod* 65(4): 470-5. doi: 10.1021/np0105578

Lima JPSd, Pinheiro MLB, Santos AMG, Pereira JLdS, Santos DMF, Barison A. 2012. In vitro atileishmanial and cytotoxic activities of *Annona mucosa* (*Annona*ceae). Rev Virtual de Química 4(6): 692. doi: 10.5935/1984-6835.20120052

Liu XX, Alali FQ, Hopp DC, Rogers LL, Pilarinou E, McLaughlin JL. 1998. Glabracins A and B, two new acetogenins from *Annona glabra*. *Bioorg Med Chem* 6: 959-65. doi: 10.1016/s0968-0896(98)00059-5.

Liu X-X, Alali FQ, Pilarinou E, McLaughlin JL. 1998. Glacins A and B: two novel bioactive mono-tetrahydrofuran acetogenins from *Annona glabra*. *J Nat Prod* 61(7): 620-4. doi: 10.1021/np970563x

Luna Jde S, De Carvalho JM, De Lima MR, Bieber LW, Bento Ede S, Franck X. 2006. Acetogenins in *Annona muricata* L. (*Annona*ceae) leaves are potent molluscicides. *Nat Prod Res* 20(3): 253-7. doi: 10.1080/14786410500161445.

Martinez-Vazquez M, De la Cueva Lozano DG, Estrada-Reyes R, Gonzalez-Lugo NM, Ramirez Apan T, Heinze G. 2005. Bio-guided isolation of the cytotoxic corytenchine and isocoreximine from roots of *Annona cherimolia*. *Fitoterapia* 76(7-8): 733-6. doi: 10.1016/j.fitote.2005.08.004

Martinez-Vazquez M, Estrada-Reyes R, Araujo Escalona AG, Ledesma Velazquez I, Martinez-Mota L, Moreno J. 2012. Antidepressant-like effects of an alkaloid extract of the aerial parts of *Annona cherimolia* in mice. *J Ethnopharmacol* 139(1): 164-70. doi: 10.1016/j.jep.2011.10.033

Matsushige A, Kotake Y, Matsunami K, Otsuka H, Ohta S, Takeda Y. 2012. *Annona*mine, a new aporphine alkaloid from the leaves of *Annona muricata*. *Chem Pharm Bull* 60(2): 257-9. doi: 10.1248/cpb.60.257

Matsushige A, Matsunami K, Kotake Y, Otsuka H, Ohta S. 2012. Three new megastigmanes from the leaves of *Annona muricata*. *J Nat Med* 66(2): 284-91. doi: 10.1007/s11418-011-0583-1

Meira CS, Guimarães ET, Macedo TS, da Silva TB, Menezes LRA, Costa EV. 2014. Chemical composition of essential oils from *Annona vepretorum* Mart. and *Annona squamosa* L. (*Annona*ceae) leaves and their antimalarial and trypanocidal activities. *J Essent Oil Res* 27: 160-8. doi: 10.1080/10412905.2014.982876

Melot A, Fall D, Gleye C, Champy P. 2009. Apolar *Annona*ceous acetogenins from the fruit pulp of *Annona muricata*. *Molecules* 14(11): 4387-95. doi: 10.3390/molecules14114387

Mohamad N, Majid EM, Falah As, Layla C, Akram H, Ali C. 2017. Antibacterial, antioxidant and antiproliferative activities of the hydroalcoholic extract of the lebanese *Annona squamosa* L. seeds. *Int Res J Pharm* 8: 1-7. doi: 10.7897/2230-8407.08011

More G, Tshikalange TE, Lall N, Botha F, Meyer JJ. 2008. Antimicrobial activity of medicinal plants against oral microorganisms. *J Ethnopharmacol* 119(3): 473-7. doi: 10.1016/j.jep.2008.07.001

Nandhakumar E and Indumathi P. 2013. In vitro antioxidant activities of methanol and aqueous extract of *Annona squamosa* (L.) fruit pulp. *J Acupunct Meridian Stud* 6(3): 142-8. doi: 10.1016/j.jams.2012.09.002

Navarro García VM, Gonzalez A, Fuentes M, Aviles M, Rios MY, Zepeda G. 2003. Antifungal activities of nine traditional Mexican medicinal plants. *J Ethnopharmacol* 87(1): 85-8. doi: 10.1016/s0378-8741(03)00114-4

Nawwar M, Ayoub N, Hussein S, Hashim A, El-Sharawy R, Wende K. 2012. A flavonol triglycoside and investigation of the antioxidant and cell stimulating activities of *Annona muricata* Linn. *Arch Pharm Res* 35(5): 761-7. doi: 10.1007/s12272-012-0501-4

Ogunwande IA, Ekundayo O, Olawore NO, Kasali AA. 2006. Essential oil of *Annona reticulata* L. leaves from nigeria. *J Essent Oil Res* 18(4): 374-6. doi: 10.1080/10412905.2006.9699117

Okoye TC, Akah PA, Omeje EO, Okoye FB, Nworu CS. 2013. Anticonvulsant effect of kaurenoic acid isolated from the root bark of *Annona senegalensis*. *Pharmacol Biochem Behav* 109: 38-43. doi: 10.1016/j.pbb.2013.05.001

Osorio E, Arango GJ, Jimenez N, Alzate F, Ruiz G, Gutierrez D. 2007. Antiprotozoal and cytotoxic activities in vitro of colombian *Annona*ceae. *J Ethnopharmacol* 111(3): 630-5. doi: 10.1016/j.jep.2007.01.015

Panda S and Kar A. 2007. Antidiabetic and antioxidative effects of *Annona squamosa* leaves are possibly mediated through quercetin-3-*O*-glucoside. *BioFactors* 31(3-4): 201-10. doi: 10.1002/biof.5520310307

Pino JA. 2011. Volatile components of cuban *Annona* fruits. *J Essent Oil Res*. 12(5): 613-6. doi: 10.1080/10412905.2000.9712170

Pino JA, Marbot R, Fuentes V. 2003. Characterization of volatiles in bullock's heart (*Annona reticulata* L.) fruit cultivars from cuba. *J Agric Food Chem* 51(13): 3836-9. doi: 10.1021/jf020733y

Pino JA and Rosado A. 1999. Volatile constituents of custard apple (*Annona atemoya*). *J Essent Oil Res* 11: 303-5. doi: 10.1080/10412905.1999.9701139

Porwal M and Kumar A. 2015. Neuroprotective effect of *Annona squamosa* and (-) anonaine in decreased GABA receptor of epileptic rats. *J Appl Pharm Sci* 5: 18-23. doi: 10.7324/JAPS.2015.54.S4

Ragasa CY, Soriano G, Torres OB, Don MJ, Shen CC. 2012. Acetogenins from *Annona muricata*. *Phcog J* 4: 32-7. doi: 10.5530/pj.2012.32.7

Rejon-Orantes Jdel C, Gonzalez-Esquinca AR, de la Mora MP, Roldan Roldan G, Cortes D. 2011. Annomontine, an alkaloid isolated from *Annona purpurea*, has anxiolytic-like effects in the elevated plus-maze. *Planta Med* 77(4): 322-7. doi: 10.1055/s-0030-1250406

Rieser MJ, Gu ZM, Fang XP, Zeng L, Wood KV, McLaughlin JL. 1996. Five novel mono-tetrahydrofuran ring acetogenins from the seeds of *Annona muricata*. *J Nat Prod* 59(2): 100-8. doi: 10.1021/np960037q

Rocha RS, Kassuya CA, Formagio AS, Mauro Mde O, Andrade-Silva M, Monreal AC. 2016. Analysis of the anti-inflammatory and chemopreventive potential and description of the antimutagenic mode of action of the *Annona crassiflora* methanolic extract. *Pharm Biol* 54(1): 35-47. doi: 10.3109/13880209.2015.1014567

Rodrigues AMS, De Paula JE, Degallier N, Molez JF, EspÍNdola LS. 2006. Larvicidal activity of some cerrado plant extracts against *Aedes aegypti*. *J m Am Mosquito Contr* 22(2): 314-7. doi: 10.2987/8756-971X(2006)22[314:LAOSCP]2.0.CO;2

Sahpaz S, Gonzalez Mc, Hocquemiller R, Zafra-Polo Mc, Corte D. 1996. Annosenegalin and annogalene: two cytotoxic mono-tetrahydrofuran acetogenins from *Annona senegalensis* and *Annona* cherimolia. *Phytochemistry* 42(1): 103-7. doi: 10.1016/0031-9422(95)00891-8

Shanker KS, Kanjilal S, Rao BV, Kishore KH, Misra S, Prasad RB. 2007. Isolation and antimicrobial evaluation of isomeric hydroxy ketones in leaf cuticular waxes of *Annona squamosa*. *Phytochem Anal* 18(1): 7-12. doi: 10.1002/pca.942

Silva MV, Costa TR, Costa MR, Ferreira EC, Fernandes OFL, Santos SC. 2008. Growth inhibition effect of brazilian cerrado plant extracts on candida species. *Pharm Biol* 39(2): 138-41. doi: 10.1076/phbi.39.2.138.6248

Singh N, Kaushik NK, Mohanakrishnan D, Tiwari SK, Sahal D. 2015. Antiplasmodial activity of medicinal plants from chhotanagpur plateau, jharkhand, India. *J Ethnopharmacol* 165: 152-62. doi: 10.1016/j.jep.2015.02.038

Son JK, Kim DH, Woo MH. 2003. Two new epimeric pairs of acetogenins bearing a carbonyl group from *Annona cherimolia* seeds. *J Nat Prod* 66(10): 1369-72. doi: 10.1021/np0301487

Suleiman MM, Dzenda T, Sani CA. 2008. Antidiarrhoeal activity of the methanol stem-bark extract of *Annona senegalensis* Pers. (*Annona*ceae). *J Ethnopharmacol* 116(1): 125-30. doi: 10.1016/j.jep.2007.11.007

Sun S, Liu J, Kadouh H, Sun X, Zhou K. 2014. Three new anti-proliferative *Annona*ceous acetogenins with mono-tetrahydrofuran ring from graviola fruit (*Annona muricata*). *Bioorg Med Chem Lett* 24(12): 2773-6. doi: 10.1016/j.bmcl.2014.03.099

Takahashi JA, Pereira CR, Pimenta LP, Boaventura MA, Silva LG. 2006. Antibacterial activity of eight brazilian Annonaceae plants. *Nat Prod Res* 20(1): 21-6. doi: 10.1080/14786410412331280087

Vila-Nova NS, Morais SM, Falcao MJ, Machado LK, Bevilaqua CM, Costa IR. 2011. Leishmanicidal activity and cytotoxicity of compounds from two *Annona*cea species cultivated in northeastern brazil. *Rev Soc Bras Med Trop* 44(5): 567-71. doi: 10.1590/s0037-86822011000500007

Wang D-S, Rizwani GH, Guo H, Ahmed M, Ahmed M, Hassan SZ. 2014. *Annona squamosa* Linn: cytotoxic activity found in leaf extract against human tumor cell lines. *Pak J Pharm Sci* 27: 1559-63.

Wélé A, Zhang Y, Caux C, Brouard JP, Pousset JL, Bodo B. 2004. Annomuricatin C, a novel cyclohexapeptide from the seeds of *Annona*

muricata. *Comptes Rendus Chimie* 7(10-11)**:** 981-8. doi: 10.1016/j.crci.2003.12.022

Wele A, Zhang Y, Ndoye I, Brouard JP, Pousset JL, Bodo B. 2004. A cytotoxic cyclic heptapeptide from the seeds of *Annona cherimola. J Nat Prod* 67(9)**:** 1577-9. doi: 10.1021/np040068i

Woo MH, Chung SO, Kim DH. 1999. cis-*Annona*cin and (2,4)-cis-and trans-iso*Annona*cins: cytotoxic monotetrahydrofuran *Annona*ceous acetogenins from the seeds of *Annona cherimolia. Arch Pharm Res* 22(5)**:** 524-8. doi: 10.1007/BF02979164

Woo MH, Kim DH, Fotopoulos SS, McLaughlin JL. 1999. Annocherin and (2,4)-cis- and trans-Annocherinones, monotetrahydrofuran *Annona*ceous acetogenins with a C-7 carbonyl group from *Annona cherimolia* seeds. *J Nat Prod* 62**:** 1250-5. doi: 10.1021/np990135m

Wu FE, Gu ZM, Zheng L, Zhao GX, Zhang Y, Mclaughl JL. 1995. Two new cytotoxic monotetrahydrofuran *Annona*ceous acetogenins, annomuricins A and B, from the leaves of *Annona murzcata. J Nat Prod* 58(6)**:** 830-6. doi: 10.1021/np50120a002

Wu FE, Zeng L, Gu ZM, Zhao GX, Zhang Y, Schwedler JT. 1995a. Muricatocins A and B, two new bioactive monotetrahydrofuran *Annona*ceous acetogenins from the leaves of *Annona muricata. J Nat Prod* 58(6)**:** 902-8. doi: 10.1021/np50120a013

Wu FE, Zheng L, Gu ZM, Zhao GX, Zhang Y, Schwedler JT. 1995b. New bioactive monotetrahydrofuran *Annona*ceous acetogenins, annomuricin C and muricatocin C, from the leaves of *Annona Murzcata. J Nat Prod* 58(6)**:** 909-15. doi: 10.1021/np50120a014

Wu TY, Yang IH, Tsai YT, Wang JY, Shiurba R, Hsieh TJ. 2012. Isodesacetyluvaricin, an *Annona*ceous acetogenin, specifically inhibits gene expression of cyclooxygenase-2. *J Nat Prod* 75(4)**:** 572-6. doi: 10.1021/np200719r

Wu YC, Chang FR, Chen CY. 2005. Tryptamine-derived amides and alkaloids from the seeds of *Annona atemoya. J Nat Prod* 68(3)**:** 406-8. doi: 10.1021/np040177x

Wu YC, Chang GY, Feng-NienKo, Teng CM. 1995. Bioactive constitutents from the stems of *Annona montana. Planta Med* 61(2)**:** 146-9.

Yadav DK, Singh N, Dev K, Sharma R, Sahai M, Palit G. 2011. Anti-ulcer constituents of *Annona squamosa* twigs. *Fitoterapia* 82(4)**:** 666-75. doi: 10.1016/j.fitote.2011.02.005

Yang C, Gundala SR, Mukkavilli R, Vangala S, Reid MD, Aneja R. 2015. Synergistic interactions among flavonoids and acetogenins in graviola (Annona muricata) leaves confer protection against prostate cancer. *Carsinogenesis* 36(6): 656-65. doi: 10.1093/carcin/bgv046

Yang YL, Chang FR, Hwang TL, Chang WT, Wu YC. 2004. Inhibitory effects of ent-kauranes from the stems of *Annona squamosa* on superoxide anion generation by human neutrophils. *Planta Med* 70(3): 256-8. doi: 10.1055/s-2004-815544

Yeh SH, Chang FR, Wu YC, Yang YL, Zhuo SK, Hwang TL. 2005. An anti-inflammatory ent-kaurane from the stems of *Annona squamosa* that inhibits various human neutrophil functions. *Planta Med* 71(10)**:** 904-909. doi: 10.1055/s-2005-871234

You M, Wickramaratne DBM, Silva GL, Chai H, Chagwedera TE, Farnsworth NR.1995. (-)-roemerine, an aporphine alkaloid from *Annona Senegalensis* that reverses the multidrug-resistance phenotype with cultured cells. *J Nat Prod* 58(4): 598-604. doi: 10.1021/np50118a021.

Yu JG, Gui HQ, Luo XZ, Sun L. 1998. Murihexol, a linear acetogenin from *Annona muricata. Phytochemistry* 49(6)**:** 1689-92. doi: 10.1016/s0031-9422(98)00224-6

Yuan SSF, Chang HL, Chen HW, Yeh YT, Kao YH, Lin KH. 2003. *Annona*cin, a mono-tetrahydrofuran acetogenin, arrests cancer cells at the G1 phase and causes cytotoxicity in a Bax- and caspase-3-related pathway. *Life Sci* 72(25)**:** 2853-61. doi: 10.1016/s0024-3205(03)00190-5.

Zeng L, Wu FE, Gu ZM, McLaughlin JL. 1995. Murihexocins A and B, two novel mono-thf acetogenins with six hydroxyls, from *Annona muricata* (*Annona*ceae). *Tetrahedron Lett* 36(30)**:** 5291-4. doi: 10.1155/2018/1826170

Zeng L, Wu FE, McLaughlin JL. 1995. Annohexocin, a novel mono-thf acetogenin with six hydroxyls, from *Annona muricata* (*Annona*ceae). *Bioorg Med Chem Lett* 5(16)**:** 1865-8. doi: 10.2147/DDDT.S103216

Zeng L, Wu FE, Oberlies NH, McLaughlin JL. 1996. Five new monotetrahydrofuran ring acetogenins from the leaves of *Annona muricata. J Nat Prod* 59(11)**:** 1035-42. doi: 10.1021/np960447e