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REVIEW

Annona muricata: A comprehensive review on its traditional medicinal uses, phytochemicals, pharmacological activities, mechanisms of action and toxicity

Ana V. Coria-Téllez [a,d], Efigenia Montalvo-Gónzalez [b], Elhadi M. Yahia [c], Eva N. Obledo-Vázquez [d,*]

[a] *Laboratorio de Análisis y Diagnóstico del Patrimonio, El Colegio de Michoacán A.C., Cerro de Nahuatzen No. 85, Fracc. Jardines del Cerro Grande, La Piedad, C.P. 59370 Michoacán, Mexico*
[b] *Laboratorio Integral de Investigación en Alimentos, Instituto Tecnológico de Tepic, Av. Tecnológico 2595, C.P. 63175 Tepic, Nayarit, Mexico*
[c] *Facultad de Ciencias Naturales, Universidad Autonoma de Queretaro, Avenida de las Ciencias S/N, Juriquilla, 76230 Queretaro, Qro., Mexico*
[d] *Unidad de Biotecnología Vegetal, Centro de Investigación y Asistencia en Tecnología y Diseño del Estado de Jalisco, A.C., Av. Normalistas No. 800, Col. Colinas de la Normal, Guadalajara, C.P. 44270 Jalisco, Mexico*

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Abstract *Annona muricata* L. (Magnoliales: Annonaceae) is a tropical plant species known for its edible fruit which has some medicinal merits, but also some toxicological effects. This review focuses on the phytochemicals contents, bioactivity, biological actions and toxicological aspects of extracts and isolated compounds, as well as medicinal uses of *A. muricata*, with the objective of stimulating further studies on extracts and fruit pulp used for human consumption. Traditional medicinal uses of *A. muricata* have been identified in tropical regions to treat diverse ailments such as fever, pain, respiratory and skin illness, internal and external parasites, bacterial infections, hypertension, inflammation, diabetes and cancer. More than 200 chemical compounds have been identified and isolated from this plant; the most important being alkaloids, phenols and acetogenins. Using *in vitro* studies, extracts and phytochemicals of *A. muricata* have been characterized as an antimicrobial, anti-inflammatory, anti-protozoan, antioxidant, insecticide,

* Corresponding author. Tel.: +52 (33) 33 45 52 00.
E-mail addresses: anac@colmich.edu.mx (A.V. Coria-Téllez), efimontalvo@gmail.com (E. Montalvo-Gónzalez), yahia@uaq.mx (E.M. Yahia), nobledo@ciatej.mx (E.N. Obledo-Vázquez).

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larvicide, and cytotoxic to tumor cells. *In vivo* studies of the crude extracts and isolated compounds of *A. muricata* were shown to possess anxiolytic, anti-stress, anti-inflammatory, contraceptive, anti-tumoral, antiulceric, wound healing, hepato-protective, anti-icteric and hypoglycemic activities. In addition, clinical studies support the hypoglycemic activity of the ethanolic extracts of *A. muricata* leaves. Mechanisms of action of some pharmacological activities have been elucidated, such as cytotoxic, antioxidant, antimicrobial, antinociception and hypotensive activities. However, some phytochemical compounds isolated from *A. muricata* have shown a neurotoxic effect *in vitro* and *in vivo*, and therefore, these crude extracts and isolated compounds need to be further investigated to define the magnitude of the effects, optimal dosage, mechanisms of action, long-term safety, and potential side effects. Additionally, clinical studies are necessary to support the therapeutic potential of this plant.

Contents

1. Introduction

Medicinal plants are considered as the basis for health preservation and care worldwide. Chronic degenerative diseases (diabetes, cardiovascular and cancer) have reached epidemic proportions and are considered as a serious health problem; therefore, the treatments of these diseases are of clinical importance (WHO, 2005). *Annona muricata* L. is a species of the Annonaceae family that has been widely studied in the last decades due to its therapeutic potential. The medicinal uses of the Annonaceae family were reported long time ago (Billón, 1869), and since then, this species has attracted the attention due to its bioactivity and toxicity.

Ethnobotanical studies have indicated that *A. muricata* has been used as insecticide (Leatemia and Isman, 2004) and parasiticide (Langenberger et al., 2009). Fruit juice and infusions of leaves or branches have been used to treat fever (Betancur-Galvis et al., 1999; Dagar and Dagar, 1991; Magaña et al., 2010), sedative (Defilippis et al., 2004; Joyeux et al., 1995), respiratory illness (Beyra et al., 2004; Kossouoh et al., 2007; Vandebroek et al., 2010; Waizel and Waizel, 2009), malaria (Boyom et al., 2011; Nguyen-Pouplin et al.,

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2007), gastrointestinal problems (Atawodi, 2011; Magaña et al., 2010; Samuel et al., 2010), liver, heart and kidney affections (Badrie and Schauss, 2009; Coe, 2008). In recent years it has become widely used for hypoglycemic (De Souza et al., 2011; Rodríguez, 2011), hypotensive (De Souza et al., 2011; Hajdu and Hohmann, 2012; Samuel et al., 2010) and cancer treatments (Monigatti et al., 2013; Tisott et al., 2013).

Some publications and reviews about *A. muricata* have been conducted to integrate the available scientific studies on this plant with special interest on acetogenins as principal bioactive compounds (Badrie and Schauss, 2009; Moghadamtousi et al., 2015a; Pinto et al., 2005) Other bioactive compounds have been identified, more bioactivities have been evaluated, and medicinal uses have been extended. The aim of this review was to integrate the scientific studies reported until 2015 that describe the traditional medicinal uses and phytochemical contents of *A. muricata,* and relate them with the pharmacological and its mechanisms of action and toxicological evaluation. The bioactivity tested can be the base for therapeutic utilization, but the toxicological research results are important to consider the therapeutical uses of this plant versus its toxicity, and the potential harmful effects of products prepared from this plant.

2. Botany and traditional uses

2.1. Botany

A. muricata is known as soursop (English), graviola (Portuguese), guanábana (Latin American Spanish) and other local indigenous names listed in Table 1. This plant is species of the genus *Annona*, of the Annonaceae family, order Magnoliales and Division Magnoliophyta (Pinto et al., 2005). The genus *Annona* comprises over 70 species among which *A. muricata* is the most widely grown. Its synonyms are *A. bonplandiana* Kunth; *A. cearensis* Barb. Rodr., *A. macrocarpa* Wercklé; *A. muricata* var. *borinquensis* Morales and *Guanabanus muricatus* M. Gómez (Pinto et al., 2005).

The soursop tree is about 5–10 m tall and 15–83 cm in diameter with low branches (Benavides, 2003; Evangelista-Lozano et al., 2003; Orwa et al., 2009). It tends to bloom and fruit most of the year, but there are more defined seasons depending on the altitude (Pinto et al., 2005). It is distributed in the tropical regions of Central and South America, Western Africa and Southeast Asia (Pinto et al., 2005), at altitudes below 1200 m above sea level, with temperatures between 25 and 28 °C, relative humidity between 60 and 80%, and annual rainfall above 1500 mm. The soursop fruit is an edible collective ovoid berry, dark green in color. Its average weight is 4 kg in some countries (Pinto et al., 2005), but in México (Evangelista-Lozano et al., 2003), Venezuela (Ojeda et al., 2007) and Nicaragua (Benavides, 2003), it ranges between 0.4 and 1.0 kg. Each fruit may contain 55–170 black seeds (Awan et al., 1980) when fresh and they turn light brown when dry. The flesh is white and creamy with a characteristic aroma and flavor (Pinto et al., 2005).

2.2. Traditional medicinal uses

The leaves, bark, fruit and seed of *A. muricata* have been subject of countless medicinal uses (Badrie and Schauss, 2009; Billón, 1869). Table 1 enlists the traditional medicinal uses that have been reported for this species, as well as the places in which they are used. The most widely used preparation in traditional medicine is the decoction of bark, root, seed or leaf and applications are varied. In Indonesia, the Caribbean islands (Boulogne et al., 2011) and South Pacific countries, the leaves are used in bath (Longuefosse and Nossin, 1996) to treat skin ailments, while in Mauritius (Sreekeesoon and Mahomoodally, 2014), New Guinea (WHO, 2009) and Ecuador (Tene et al., 2007), the application of leaves is local on the pain site. The ingestion of leaves decoction is used as analgesic in Brazil (Ross, 2010), Martinique (Longuefosse and Nossin, 1996), Mexico and Nicaragua (Ross, 2010), while in several countries such as Benin (Kossouoh et al., 2007), the Caribbean (Joyeux et al., 1995), Cuba (Beyra et al., 2004) and México (Waizel and Waizel, 2009), it is used to treat discomfort associated with colds, flu and asthma. Natives of Malaysia used *A. muricata* leaves to treat cutaneous (external) and internal parasites (Badrie and Schauss, 2009). The use of leaves to treat malaria is very important in tropical countries as Cameroon, Togo, and Vietnam (Boyom et al., 2011; Nguyen-Pouplin et al., 2007; Ross, 2010). In Ghana, *A. muricata* and some other plants are decocted into a mixture and used in bath where females sit in (Asase et al., 2012).

The fruit is not only appreciated as food, but the juice is used as galactogogue to treat diarrhea, heart and liver diseases (Badrie and Schauss, 2009; Hajdu and Hohmann, 2012), and against intestinal parasites in South America (Badrie and Schauss, 2009). Lately, the medicinal uses of *A. muricata* leaves included treatments for hypertension (Badrie and Schauss, 2009; Ezuruike and Prieto, 2014; Hajdu and Hohmann, 2012; Mootoosamy and Fawzi, 2014; TDRG, 2002), diabetes (Badrie and Schauss, 2009; De Souza et al., 2011; Ezuruike and Prieto, 2014) and cancer (Alonso-Castro et al., 2011; Atawodi, 2011; Bussmann et al., 2010; Monigatti et al., 2013). Some patients used decoctions or capsules of *A. muricata* for cancer and pharmacological treatments (Tisott et al., 2013).

Unripe fruit, seeds, leaves and roots are also used as biopesticides, bioinsecticides and topical insect repellents (Brechelt, 2004; Isman and Akhtar, 2007; Leatemia and Isman, 2004). The importance of this species in pest control was indicated in the edition of "Pesticide action and alternatives for Latin America", which recommended the use of aqueous extract of *A. muricata* to control lepidopteran larvae, aphids and thrips, among others (Brechelt, 2004).

3. Phytochemicals

Two hundred and twelve bioactive compounds have been reported to be found in *A. muricata*. The predominant compounds are acetogenins followed by alkaloids, phenols and other compounds. Leaves and seeds are the main plant organs studied, probably because they are the most traditionally used. Table 2 lists the bioactive compounds, and their structures are shown in Figs. 1–4. The majority of phytochemicals have been identified from organic extract, but recently focus has also been directed toward aqueous extracts. Several other compounds such as carbohydrates and essential oils have also been reported, but these are not considered in this review.

3.1. Alkaloids

Alkaloids are naturally occurring compounds containing basic nitrogen atoms. The most abundant in *A. muricata* (Table 2)

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Table 1 *A. muricata*: local names, medicinal uses, plant part used, and type of preparations.

Country or region	Local name	Medicinal uses	Plant part	Preparation/application	References
Benin	Araticum, araticum-do-grande condessa; graviola; jaca-do-para; jaca-de-pobre; fruta-do conde, cameroon, soursop	Insomnia, catarrh, febrifuge	Leaf Bark Root Seed	Decoction/oral	Kossouoh et al. (2007)
Bolivia	Sinini	Kidney disorders, hypertension	Fruit Leaf	Juice/oral Decoction/oral	Hajdu and Hohmann (2012)
Brazil	Araticum, araticum-do-grande, coração-da-rainha, condessa; graviola; jaca-do-pará; jaca-de-pobre; fruta-do conde, cameroon, Soursop	Snake bite Analgesic Lactagogue, astringent, diarrhea, dysentery Arthritis pain, rheumatism, neuralgia, weight loss	Leaf Fruit Leaf	Macerate/topical Decoction/oral Juice/oral Decoction/oral	Ritter et al. (2012) and Ross (2010) Badrie and Schauss (2009) and Cercato et al. (2015)
Cameroon	Soursop, Sabasaba Ebom beti	Malaria, anthelmintic, parasites, antimicrobial, anticonvulsant, digestive Typhoid fever	Leaf	Decoction/oral	Boyom et al. (2011), Tsabang et al. (2012) Roger et al. (2015)
Caribbean	Graviola, Jamaica soursop, prickly custard apple, soursop	Chills, febrifuge, flu, indigestion, nervousness, palpitations, rash, spasms, skin disease, sedative	Leaf Bark	NR	Joyeux et al. (1995), TDRG (2002), and Boulogne et al. (2011)
Colombia	Guanábana	Febrifuge, inflammation Diarrhea, abortifacient, lactagogue	Fruit, Leaf NR	Juice/oral Decoction/oral NR	Betancur-Galvis et al. (1999) Gómez-Estrada et al. (2011)
Cuba	Guanábana	Catarrh	Leaf	Decoction in milk or water/oral	Beyra et al. (2004)
Dominican Republic	Guanábana	Respiratory conditions, women in labor Galactogogue Plague	Leaf Fruit Seed	NR Infusion/oral NR	Vandebroek et al. (2010) and Ross (2010) Brechelt (2004)
Ecuador	Guanábana	Rheumatism	Leaf	Heated/topical	Tene et al. (2007)
Ghana	Apre	Malaria	Root	Decoction/bath	Asase et al. (2012)
Guyana	Cachiman, corossol, Money Apple, soursop, sorasaka, kaiedi, zuurzak, soensaka, sroesaka, soeng sakka, sun-saka, corossolier	Sedative, cardiotonic Convulsion	Stem Leaf Seed	Infusion/oral Infusion/oral NR	Defilippis et al. (2004) and TDRG (2002)
Haiti	Guanábana, korosol	Flu, heart affectation parasite, pellagra, anxiety, febrifuge, diarrhea, lactagogue	Leaf Fruit	NR	Badrie and Schauss (2009)
India	Mamphal, Fófí,	Suppurative, febrifuge Pain and pus from ulcers Tonic Spasms, parasites Bechic Insecticidal, astringent, fish-poison	Leaf Bark Root Flower Seed	Decoction/oral Smeared in coconut oil/topical NR	Dagar and Dagar (1991) Badrie and Schauss (2009)

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Table 1 (*continued*)

Country or region	Local name	Medicinal uses	Plant part	Preparation/application	References
Indonesia	Sirsak; nangka belanda; nangka seberang; Zuurzak Wulanda	Insecticidal	Leaf and other tree parts	NR Pounding	Leatemia and Isman (2004), Badrie and Schauss (2009) Roosita et al. (2008)
		Dermatitis	Leaf		Abdillah et al. (2015)
		Malaria			
Jamaica	Jamaica soursop	Spasms, anxiety, asthenia, asthma, heart affections, febrifuge, parasites, diarrhea, lactagogue, dewormer, dysentery, pain, diuretic	Branch Leaf Fruit	Decoction/oral	Asprey and Thornton (1955) and Badrie and Schauss (2009)
Madagascar	Corossol	Heart palpitation, malaria, liver maladies	Leaf	Decoction	Novy (1997)
Malaysia	Durian belanda, durian blanda, durian, benggala, durian maki, durian makkah, seri kaya belanda	Lice	Leaf	Crushed/topical	Badrie and Schauss (2009)
		Stomach pain, hypertension	Fruit	Juice/oral	Samuel et al. (2010)
Martinique	Kowosol	Skin rashes, sedative Thoracic pain, inflammation, flatulence, liver disease	Leaf	Crushed/Bath Decoction/oral	Longuefosse and Nossin (1996)
Mauritius	Corossol	Hypertension	Leaf	Infusion/oral	Mootoosamy and Fawzi (2014) and Sreekeesoon and Mahomoodally (2014)
	Corossol	Headache		Crushed/topical	
Mexico	Takole, pobox, ajpox Cabeza de negro; catuch, chincua, guanábana; guanábano;	Dysentery, diabetes	Fruit	Juice/oral	Alonso-Castro et al. (2011)
	polvox; takʹob; takʹop caduts-at; xunʹapill; llama de tehuantepec; zopote de viejas,	Gastric cancer, gastrointestinal disorders, stomach pain	Leaf	Decoction/oral	
	zapote agrio. Anona, tzon te chkia nion	Febrifuge, diarrhea, dysentery, stomach pain	Young leaf	Infusion/oral	Magaña et al. (2010) and Yasunaka et al. (2005)
		Bronchitis, asthma, leprae	Leaf, stem	Infusion/oral	Waizel and Waizel (2009)
Nicaragua	Guanábana, pumo, puntar waithia, saput, sarifa, seremaia, soursap	Ringworm	Leaf	Plaster/topical	Benavides (2003) and Ross (2010), Coe (2008)
		Abdominal and back pain, menstrual hemorrhage, abortions, fever, vaginal infection		Infusion/oral	
		Renal and skin disorders, diarrhea		Decoction/oral	
		Insecticidal	Seed		
Nigeria	Soursop, graviola, pawpaw brasileña, Abo, Chop-chop, Sapi sapi	Gastric disorders, Prostate cancer, diabetes, neuralgia, rheumatism, arthritic pain	Leaf Unripe fruit	Decoction/oral Juice/oral	Pinto et al. (2005), Atawodi (2011), and Ezuruike and Prieto (2014)
Panama	Guanábana	Dyspepsia, allergy, helminthiasis	Leaf	NR	Gupta et al. (1979) and Ross (2010)
		Diarrhea			
		Stomach ulcer	Bark Pulp	Decoction/oral	

(*continued on next page*)

Table 1 (*continued*)

Country or region	Local name	Medicinal uses	Plant part	Preparation/application	References
Philippines	Babana Babaná, guyabano, gwabana	Lice, dandruff	Leaf	NR	Badrie and Schauss (2009) and Langenberger et al. (2009) Ong and Kim (2014)
		Cancer, ascariasis, high blood pressure, stomach acidity, urination difficulty, cough Headache Diabetes	Leaf	Decoction/oral	
				Poultice/topical	
			Fruit	Pulp/oral	
New Guinea	Saua sap Sow sop Kahiloko	Stomach pain	Leaf	Heated/compression	Badrie and Schauss (2009) and WHO (2009)
Peru	Guanábano, guanábana, cashacushma	Obesity, gastritis, dyspepsia, diabetes, inflammation, cancer, spasms, sedative, flu, febrifuge, anxiety, kidneys, prostate, urinary tract, infection, inflammation, panacea	Fruit, Leaf	Pulp, juice/oral Infusion/oral	Badrie and Schauss (2009), Bussmann et al. (2010), Rodríguez (2011), Poma et al. (2011), and Monigatti et al. (2013)
South pacific countries	Durian belanda, soursop, seremaia, sarifa, apele, katara ara tara	Stomach ailments, indigestión Skin diseases	Leaf	Infusion/oral	WHO (1998)
		Dizziness, fainting spells	Leaf	Bath Inhaled	Ross (2010)
Thailand	Thu-rian-khack, thurian-thet, thurian khaek	Insecticidal	Seed	NR	Badrie and Schauss (2009)
Trinidad y Tobago	Soursop	Hypertension	Leaf	NR	Badrie and Schauss (2009), Lans (2006)
Togo	Anyigli, apele	Hypertension, diabetes Malaria	Leaf	Decoction/oral	De Souza et al. (2011) Ross (2010)
Uganda	Ekitafeli	Diabetes	Leaf Fruit	Infusion/oral Pulp/oral	Ssenyange et al. (2015)
Vanuatu	Soursop Karasol, korosol, saosop	Scabies	Leaf	Infusion/Bath	Bradacs et al. (2011)
Venezuela	Catoche, catuche	Liver affectation, stomach pain, insecticidal	Leaf Seed	Decoction/oral Crushed/topical	TDRG (2002) and Badrie and Schauss (2009)
West Africa	Dukumé porto, niom, pinha, sawa sap, alukuntum,	Sedative, nasopharyngeal affectation Diarrhea, dysentery, vermifuge, antidote	Leaf Seed, bark root	Decoction/oral	Burkill (1985)
West Indies	Apple leaf, kowoso, soursopl	Asthmas, diarrhea, hypertension, parasites, lactagogue, sedative Skin ailments Galactogogue	Leaf	Decoction/oral Decoction/bath	Feng et al. (1962), TDRG (2002), Ross (2010), and Boulogne et al. (2011)
			Fruit	Poultice/oral	
Vietnam South	Măng câu xiêm	Malaria	Leaf	Infusion/oral	Nguyen-Pouplin et al. (2007)

NR, Not reported.

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Table 2 Bioactive compounds isolated from *A. muricata*.

No	Chemical name	Part of plant	Type	Bioactivity	References
Alkaloids					
1	Anonaine	Fruit Leaf	Aporphine	Antidepressive Anti-plasmodium, Dopamine inhibitor Cytotoxic	Hasrat et al. (1997a, 1997b), Fofana et al. (2011), Ocampo and Ocampo (2006), and Matsushige et al. (2012)
2	Annonamine	Leaf	Aporphine	Cytotoxic	Matsushige et al. (2012)
3	Anomuricine	Root Bark	Isoquinoline	NR	Leboeuf et al. (1981)
4	Anomurine	Root Bark	Isoquinoline	NR	Leboeuf et al. (1981)
5	Asimilobine	Fruit Leaf	Aporphine	Antidepressive Cytotoxic	Hasrat et al. (1997a, 1997b) and Fofana et al. (2012)
6	Atherospermine	Stem	Aporphine	NR	Leboeuf et al. (1981)
7	Atherosperminine	Root Bark	Aporphine	NR	Leboeuf et al. (1981)
9	Casuarine	Leaf/stem	Imino sugar	NR	Mohanty et al. (2008)
10	Coclaurine	Root Bark Leaf	Isoquinoline	NR	Leboeuf et al. (1981) and Fofana et al. (2012)
11	Coreximine	Root Bark Leaf	Protoberberine	Neurotoxic	Leboeuf et al. (1981) and Lannuzel et al. (2002)
12	DMDP (2,5-Dihydroxymethyl-3,4, dihydroxypyrrolidine)	Leaf/stem	Imino sugar	NR	Mohanty et al. (2008)
13	DMJ (Deoxymannojirimycin)	Leaf/stem	Imino sugar	NR	Mohanty et al. (2008)
14	DNJ (Deoxynojirmycin)	Leaf/stem	Imino sugar	NR	Mohanty et al. (2008)
15	(R)-O,O-dimethylcoclaurine	Leaf	Isoquinoline	Cytotoxic	Matsushige et al. (2012)
16	Isoboldine	Leaf	Aporphine	Antimalarial	Fofana et al. (2012)
17	Isolaureline	Leaf	Aporphine	Cytotoxic	Fofana et al. (2011)
18	Liriodenine	Leaf	Aporphine	NR	Fofana et al. (2012)
19	(R)-4′O-methylcocaurine	Leaf	Isoquinoline	Cytotoxic	Matsushige et al. (2012)
20	N-methylcoclaurine	Leaf	Isoquinoline	NR	Fofana et al. (2012)
21	N-methylcoculaurine	Leaf Pulp	Isoquinoline	NR	Kotake et al. (2004)
22	Muricine	Bark	Isoquinoline	NR	TDRG (2002)
23	Muricinine	Bark	Isoquinoline	NR	TDRG, 2002
24	(S)-Narcorydine	Leaf	Aporphine	Cytotoxic	Matsushige et al. (2012)
25	Nornuciferine	Fruit	Isoquinoline	Antidepressive/ *in vitro* NIH-3T3	Hasrat et al. (1997a, 1997b)
26	Remerine	Leaf	Isoquinoline	NR	Fofana et al. (2012)
27	Reticuline	Stem Leaf Pulp	Isoquinoline	Neurotoxic	TDRG (2002) Leboeuf et al. (1981), Lannuzel et al. (2002), and Kotake et al. (2004)
28	Stepharine	Leaf	Isoquinoline	NR	Leboeuf et al. (1981)
29	Swainsonine	Leaf/stem	Imino sugar	Stimulate immune response	Mohanty et al. (2008)
30	Xylopine	Leaf	Isoquinoline	NR	Fofana et al. (2011)
Acetogenins					
31, 32	Cohibin A, B	Root Seed	Linear, unsaturated, 2OH	NR	Alali et al. (1999) and Gleye et al. (2000b)
33, 34	Cohibin C, D	Seed	Linear, unsaturated, 2OH	NR	Gleye et al. (2000b)
35	Donhexocin	Seed	Linear, 6OH	NR	Yu et al. (1997)
36	Montecristin	Root Pulp Nectar	Linear, unsaturated, 2OH	NR	Alali et al. (1999) and Champy et al. (2009)
37	Muricatenol	Seed	Linear, unsaturated, 4OH	NR	Li et al. (2000)
38	Murihexol	Seed	Linear, 6OH	NR	Yu et al. (1997)
39	Coronin	Root		NR	TDRG (2002)

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Table 2 (*continued*)

No	Chemical name	Part of plant	Type	Bioactivity	References
40, 41	Epomuricenins A, B or epoxymurin	Seed Root Pulp	Mono epoxy unsaturated	NR	Zafra-Polo et al. (1996) and Melot et al. (2009)
42, 43	Epomurinins A, B	Pulp	Mono epoxy	NR	Melot et al. (2009)
44, 45	Epomusenins A B	Pulp	Mono epoxy unsaturated	NR	Melot et al. (2009)
46	Epoxyrollin-A = Dieporeticanin-1		Mono epoxy	NR	Zafra-Polo et al. (1996)
47	Murin A	Stem	Mono epoxy	NR	TDRG (2002)
48	Rolin B	Seed	Mono epoxy	NR	TDRG (2002)
49	Sabadelin	Root Pulp	Mono epoxy, 1 carbonyl	Cytotoxic	Gleye et al. (1999) Ragasa et al. (2012)
50	Corepoxylone	Seed	Diepoxy, 1 carbonyl	NR	Gromek et al. (1993)
51, 52	Diepomuricanin A, B = Epoxyrollin B	Seed	Diepoxy	NR	Zafra-Polo et al. (1996)
53	Annocatalin	Leaf	Mono THF, 4OH	Cytotoxic	Liaw et al. (2002)
54	Annoglaxin	Seed	Mono THF 4OH, 1 carbonyl	NR	Yang et al. (2010)
55	Annohexocin	Leaf	Mono THF, 6OH	Cytotoxic	Zeng et al. (1996)
56	Annomontacin	Seed Leaf	Mono THF, 4OH	Cytotoxic Insecticidal	Liaw et al. (2002), Nakanishi et al. (2003), and Castillo-Sánchez et al. (2010)
57	Annomontacin, cis	Seed	Mono THF, 4OH	Cytotoxic	Liaw et al. (2002) and Nakanishi et al. (2003)
58	Annomuricin	Leaf	Mono THF, 5OH	Cytotoxic	Kim et al. (1998b)
59	Annomuricin A	Leaf Peric	Mono THF, 5OH	Cytotoxic	Wu et al. (1995a) and Jaramillo et al. (2000)
60	Annomuricin B	Leaf	Mono THF, 5OH	Cytotoxic	Wu et al. (1995a)
61, 62	Annomuricin C, E	Leaf	Mono THF, 5OH	Cytotoxic	Zeng et al. (1996) and Moghadamtousi et al. (2015c)
63, 64	Cis, trans, Annomuricin-D-one	Leaf	Mono THF, 4OH	Cytotoxic	Alali et al. (1999)
65	Annomutacin	Leaf	Mono THF, 4OH	Cytotoxic	Wu et al. (1995c)
66	Annonacin	Leaf Peric Seed Root Leaf Pulp Nectar	Mono THF, 4OH	Cytotoxic Insecticidal Antimicrobial Antitumor Neurotoxic Neurodegenerative	Wu et al. (1995c), Guadaño et al. (2000), Liaw et al. (2002), Jaramillo et al. (2000), Nakanishi et al. (2003), Champy et al. (2004, 2009), Castillo-Sánchez et al. (2010), and Ko et al. (2011)
67	Annonacin A	Peric Leaf Seed	Mono THF, 4OH	NR	Jaramillo et al. (2000) and Wu et al. (1995c)
68	Annonacin, cis-	Seed	Mono THF, 4OH	Cytotoxic	Rieser et al. (1996)
69	Annonacin-10-one, cis-	Seed	Mono THF, 3OH, 1 carbonyl	Cytotoxic	Rieser et al. (1996)
70	Annonacinone Annonacin 10-one	Leaf Seed Pulp Nectar	Mono THF, 3OH 1 carbonyl	Cytotoxic Antileishmaniasis	Liaw et al. (2002), Nakanishi et al. (2003), Champy et al. (2009), and Vila-Nova et al. (2013)
71	(2,4-trans)-1OR-annonacin A-one	Leaf	Mono THF, 3OH, ketolactone	Cytotoxic	Wu et al. (1995c)
72, 73, 74	Annopentocin A, B, C	Leaf	Mono THF, 5OH	Cytotoxic	Alali et al. (1999)
75	Annoreticuin-9-one	Seed	Mono THF, 3OH, 1 carbonyl	Cytotoxic	Ragasa et al. (2012)
76	Annoreticuin, cis	Pulp	Mono THF, 4OH	Cytotoxic	Ragasa et al. (2012)
77	Arianacin	Seed	Mono THF, 4OH	Cytotoxic	Alali et al. (1999)
78	Corossolin	Seed Leaf	Mono THF, 3OH	Cytotoxic	Chang and Wu (2001), Nakanishi et al. (2003), and Champy et al. (2009)

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Table 2 (*continued*)

No	Chemical name	Part of plant	Type	Bioactivity	References
79	Corossolone	Leaf Seed Pulp	Mono THF, 2OH, 1 carbonyl	Cytotoxic	Zafra-Polo et al. (1996), Liaw et al. (2002), Chang and Wu (2001), Nakanishi et al. (2003), and Champy et al. (2009)
80	Cis-corossolone	Leaf	Mono THF, 2OH, 1 carbonyl	Cytotoxic	Liaw et al. (2002) and Nakanishi et al. (2003)
81	Gigantetrocin A	Seed	Mono THF, 4OH	Cytotoxic Insecticidal	Alali et al. (1999)
82,	Gigantetrocin B	Seed	Mono THF, 4OH	Cytotoxic	Alali et al. (1999)
83, 84	2,4 Cis or trans Gigantetrocinone	Seed	Mono THF, 3OH, ketolactone	NR	Li et al. (2001)
85	Gigantetronenin	Leaf seed	Mono THF, 4OH, 1 double bond	Cytotoxic	Wu et al. (1995b)
86	Goniothalamicin	Seed Leaf	Mono THF 4OH	Cytotoxic	Rieser et al. (1996)
87	Cis-goniothalamicin	Seed	Mono-THF 4OH	Cytotoxic	Rieser et al. (1996)
88	Isoannonacin	Leaf	Mono THF, 3OH		Rieser et al. (1993),
89, 90	2,4-trans; cis-isoannonacin	Leaf seed	Mono THF	NR	Wu et al. (1995d) and Li et al. (2001)
91	2,4-trans-isoannonacin-10-one	Seed	Mono THF, 3OH, ketolactone	NR	Li et al. (2001)
92	Javoricin	Seed	Mono THF, 4OH	Cytotoxic	Rieser et al. (1996)
93	Longifolicin	Seed	Mono THF, 3OH	Cytotoxic	Chang and Wu (2001) and Nakanishi et al. (2003)
94	Montanacin	Leaf	Mono THF, 5OH	Cytotoxic	Champy et al. (2009)
95	Montanacin H	Leaf Nectar	MonoTHF, 4OH, 1 carbonyl	Cytotoxic	Champy et al. (2009)
96	Muricapentocin	Leaf	Mono THF, 5OH	Cytotoxic	Alali et al. (1999)
97	Muricatalicin	Leaf	Mono THF, 5OH	NR	Yu et al. (1997)
98	Muricatalin	Leaf	Mono THF, 5OH	NR	Yu et al. (1997)
99, 100	Muricatetrocin A,B	Seed	Mono THF, 4OH	Cytotoxic	Chang and Wu (2001) and Nakanishi et al. (2003)
101, 102	Muricatin A, B	Seed	Mono THF, 5OH	NR	Zafra-Polo et al. (1996)
103	Muricatin C	Bark Pulp Nectar	Mono THF, 4OH, 1 carbonyl	NR	Zafra-Polo et al. (1996) and Champy et al. (2009)
104	Muricatin D	Seed	Mono THF, 5OH	NR	TDRG (2002);
105	Muricatocin A	Leaf Pulp Nectar	Mono THF, 5OH	Cytotoxic	Wu et al. (1995d) and Champy et al. (2009)
106, 107	Muricatocin B, C	Leaf	Mono THF, 5OH	Cytotoxic	Wu et al. (1995d)
108	Muricenin	Pulp	Mono THF, 4OH	Cytotoxic	Sun et al. (2014)
109, 110, 111112,	Muricin A, B, C D,	Seed	Mono THF, 4OH	Cytotoxic	Chang and Wu (2001), Nakanishi et al. (2003)
114, 115	Muricin F, G	Seed	Mono THF, 4OH, unsaturated	Cytotoxic	Chang and Wu (2001)
116	Muricin H	Leaf seed	Mono THF, 3OH	Cytotoxic	Liaw et al. (2002) and Quispe et al. (2006)
117	Muricin I	Leaf Seed	Mono THF, 3OH, unsaturated	Cytotoxic	Liaw et al. (2002) and Lannuzel et al. (2006)
118, 119, 120	Muricin J, K, L	Fruit	Mono THF, 4OH	Cytotoxic	Sun et al. (2014)
121	Muricin M	Pulp	Mono THF, 4OH	Cytotoxic	Sun et al. (2014)
122	Muricin N	Pulp	Mono THF, 4OH	Cytotoxic	Sun et al. (2014)
123	Muricoreacin	Leaf	Mono THF, 6OH	Cytotoxic	Alali et al. (1999)
124, 125	Muricoreacin A, B	Leaf	Mono THF, 5OH	Cytotoxic	Alali et al. (1999)
126	Murihexocin	Leaf	Mono THF, 6OH	Cytotoxic	Alali et al. (1999)
127	Murihexocin A	Leaf Pulp	Mono THF, 6OH	Cytotoxic	Zeng et al. (1996) and Champy et al. (2009)
128	Murihexocin B	Leaf	Mono THF, 6OH	Cytotoxic	Zeng et al. (1996)
129	Murihexocin C	Leaf	Mono THF, 6OH	Cytotoxic	Kim et al. (1998a)

(*continued on next page*)

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Table 2 (*continued*)

No	Chemical name	Part of plant	Type	Bioactivity	References
130	Murisolin	Seed	Mono THF, 3OH	Cytotoxic	Nakanishi et al. (2003), and Yang et al. (2010)
131	Cis-panatellin	Root	Mono THF, 2OH	NR	Alali et al. (1999)
132	Cis-reticulatacin	Root	Mono THF, 2OH	NR	Alali et al. (1999)
133	Cis-reticulatacin-10-one	Root	Mono THF, 2OH, carbonyl	NR	Alali et al. (1999)
134	Solamin	Seed Stem Root Leaf	Mono THF, 2OH	Cytotoxic	Zafra-Polo et al. (1996), Liaw et al. (2002), and Nakanishi et al. (2003)
135	Cis-solamin	Root Leaf	Mono THF, 2OH	NR	Alali et al. (1999)
136	Cis-solamin A	Leaf Root Seed	Mono THF, 2OH	NR	Konno et al. (2008)
137, 138	Cis-uvariamicin I, IV	Root	Mono THF, 2OH	NR	Alali et al. (1999)
139	Xylomatenin	Pulp	Mono THF, 4OH, unsaturated		Champy et al. (2009)
140	Xylomaticin	Seed	Mono THF, 4OH	Cytotoxic	Liaw et al. (2002) and Nakanishi et al. (2003)
141	Bullatalicin	Seed	Bis THF nonadjacent, 4OH	Cytotoxic	Alali et al. (1999)
142	Gigantecin	Seed Leaf	Bis THF nonadjacent, 4OH	Cytotoxic, Antitumor *in vitro*	Champy et al. (2009)
143, 144	Cis-squamostatin A, D	Seed	Bis THF nonadjacent, 4OH, 3OH	Cytotoxic	Yang et al. (2010)
145	Annocatacin A	Seed	Bis THF adjacent, 2OH	Cytotoxic	Chang et al. (2003) and Nakanishi et al. (2003)
146	Annocatacin B	Leaf	Bis THF adjacent, 2OH	Cytotoxic	Chang et al. (2003)
147	Asimicinone-9-oxo	Leaf	Bis THF adjacent, 2OH, 1 carbonyl, keto lactone	Cytotoxic	Champy et al. (2009)
148	Asiminecin	Seed	Bis THF adjacent, 3OH	Cytotoxic	Yang et al. (2010)
149	Bullatacin	Seed	Bis TFH adjacent, 3OH	Cytotoxic Antitumor Neurotoxic	Landolt et al. (1995), Wang et al. (2002), Nakanishi et al. (2003), and Yang et al. (2010)
150	Desacetyluvaricin	Seed	Bis THF adjacent, 2OH	NR	Yang et al. (2010)
151	Isodesacetyluvaricin	Seed	Bis THF adjacent, 2OH	NR	Yang et al. (2010)
152	Robustocin	Seed	Bis THF adjacent, 1OH	NR	Gleye et al. (2000a)
153	Rolliniastatin 1, 2	Seed	Bis THF adjacent, 3OH	Cytotoxic	Gromek et al. (1994)
154	Squamocin	Seed	Bis THF adjacent, 3OH	Cytotoxic Insecticide	Guadaño et al. (2000) and Nakanishi et al. (2003)
155, 156	Montanacin D, E	Leaf Pulp	Mono THF, Mono THP, 2OH, 1 carbonyl	NR	Champy et al. (2009)
Phenols					
157	Emodin	Leaf	Anthraquinone	NR	George et al. (2014)
158	Caffeoylquinic acid	Leaf Pulp	Chlorogenic acid	NR	Marques and Farah (2009) Jiménez et al. (2014)
159	Chlorogenic acid	Leaf	Chlorogenic acid	NR	Nawwar et al. (2012)
160	Dicaffeoylquinic acid	Leaf Pulp	Chlorogenic acid	NR	Marques and Farah (2009) Jiménez et al. (2014)
161	Feruloylquinic acid	Leaf	Chlorogenic acid	NR	Marques and Farah (2009)
162	Cinnamic acid	Leaf Pulp	Cinnamic acid	NR	George et al. (2014) Jiménez et al. (2014)
163	Apigenin-6-C-glucoside	Leaf	Flavonoid	Antioxidant	George et al. (2012)
164	Argentinine	Leaf	Flavonoid	Antioxidant	Nawwar et al. (2012)
165	Catechin	Leaf	Flavonoid	Antioxidant	Nawwar et al. (2012)
166	Coumarid acid	Leaf Pulp	Flavonoid Flavonoid	NR	George et al. (2014) Jiménez et al. (2014)
167	Daidzein	Leaf	Flavonoid	NR	George et al. (2014)
168	Dihydrokaempferol-hexoside	Pulp	Flavonoid	NR	Jiménez et al. (2014)
169	Epicatechin	Leaf	Flavonoid	Antioxidant	Nawwar et al. (2012)

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Table 2 (*continued*)

No	Chemical name	Part of plant	Type	Bioactivity	References
170	Fisetin	Pulp	Flavonoid	NR	Correa-Gordillo et al. (2012)
171	Gallocatechin	Leaf	Flavonoid	NR	George et al. (2014)
172	Genistein	Leaf	Flavonoid	NR	George et al. (2014)
173	Glycitein	Leaf	Flavonoid	NR	George et al. (2014)
174	Homoorientin	Leaf	Flavonoid	Antioxidant	George et al. (2014)
175	Isoferulic acid	Leaf	Flavonoid	NR	George et al. (2014)
176	Kaempferol	Leaf Pulp	Flavonoid	Antioxidant	Nawwar et al. (2012) Sandoval et al. (2014)
177	Kaempferol 3-O-rutinoside	Leaf Pulp	Flavonoid	Antioxidant	Nawwar et al. (2012) Sandoval et al. (2014)
178	Luteolin 3′7-di-O-glucoside	Leaf Pulp	Flavonoid	Antioxidant	George et al. (2012) Sandoval et al. (2014)
179	Morin	Pulp	Flavonoid	Antioxidant	Correa-Gordillo et al. (2012)
180	Myricetin	Pulp	Flavonoid	Antioxidant	Correa-Gordillo et al. (2012)
181	Quercetin	Leaf	Flavonoid	Antioxidant	George et al. (2012), Nawwar et al. (2012)
182	Quercetin 3-O-glucoside	Leaf	Flavonoid	Antioxidant	Nawwar et al. (2012)
183	Quercetin 3-O-neohesperidoside	Leaf	Flavonoid	Antioxidant	Nawwar et al. (2012)
184	Quercetin 3-O-robinoside	Leaf	Flavonoid	Antioxidant	Nawwar et al. (2012)
185	Quercetin –O-rutinoside	Leaf	Flavonoid	Antioxidant	Nawwar et al. (2012)
186	Quercetin 3-O-α-rhamnosyl	Leaf	Flavonoid	Antioxidant	Nawwar et al. (2012)
187	Robinetin	Leaf	Flavonoid	Antioxidant	George et al. (2012)
188	Tangeretin	Leaf	Flavonoid	NR	George et al. (2014)
189	Taxifolin (+)	Leaf	Flavonoid	NR	
190	Vitexin	Leaf	Flavonoid		George et al. (2012)
191	Caffeic acid	Leaf	Hydroxycinnamic acid	Antioxidant	Jiménez et al. (2014)
192	Gentisic acid	Leaf	Hydroquinone	Antimicrobial Inhibitor	TDRG (2002)
193	Gallic acid	Leaf	Tannin		George et al. (2012) and Nawwar et al. (2012);
Other compounds					
194, 195, 196	Annoionol A, B, C	Leaf	Megastigmane	NR	Matsushige et al. (2011)
197	Annoionoside	Leaf	Megastigmane	NR	Matsushige et al. (2011)
198 199	Annomuricatin A, B	Seed	Cyclopeptides	Insecticide	Li et al. (1995) and Li et al. (1998)
200	Annomuricatin C	Seed	Cyclopeptides	Cytotoxic	Wélé et al. (2004)
201	Vitamin A	Leaf	Vitamin	Antioxidant	Non published
202	Vitamin C	Pulp leaf	Vitamin, organic acid	Antioxidant	Vijayameena et al. (2013); non published
203	Vitamin E (tocopherols)	Leaf Seed Pulp	Vitamin	Antioxidant	Vijayameena et al. (2013) and Correa-Gordillo et al. (2012)
204 205	Carotenes α, β	Pulp	Carotenoid	Antioxidant	Correa-Gordillo et al. (2012)
206	Cryptoxanthin β	Pulp	Carotenoid	Antioxidant	Correa-Gordillo et al. (2012)
207	Lycopene	Pulp	Carotenoid	Antioxidant	Correa-Gordillo et al. (2012);
208	Lutein	Pulp	Carotenoid	Antioxidant	Correa-Gordillo et al. (2012)
209	Tocopherol α	Pulp	Carotenoid	Antioxidant	Correa-Gordillo et al. (2012)
210 211	Tocotrienol α, γ	Pulp	Carotenoid	Antioxidant	Correa-Gordillo et al. (2012)
212	N-p-coumaroyl tyramine	Leaf	Amide	Antitumoral	Wu et al. (1995c)

NR, Not reported.

are reticuline and coreximine (Leboeuf et al., 1981), and leaves contain the higher alkaloid concentration (Fofana et al., 2011, 2012; Matsushige et al., 2011), although they have also been found in roots, stems (Leboeuf et al., 1981) and fruit (Hasrat et al., 1997a, 1997b). The alkaloids reported in *A. muricata* are mainly of the isoquinoline, aporphine and protoberberine type (Mohanty et al., 2008). Their chemical structures and representative compounds are shown in Fig. 1. Previous studies

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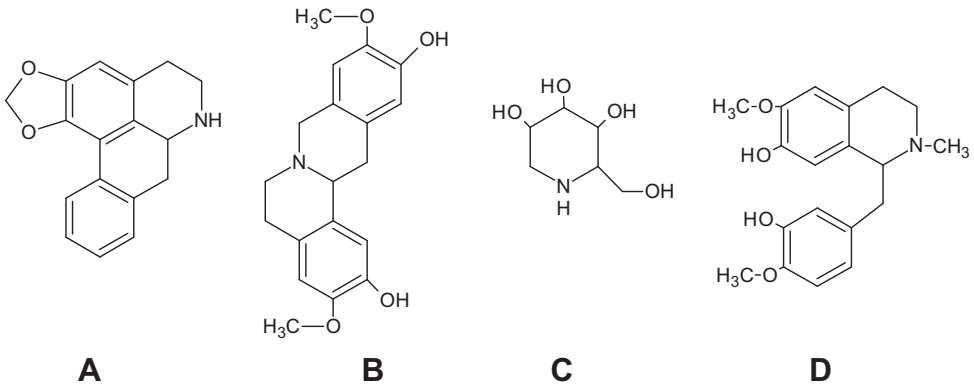

Figure 1 Chemical structure of alkaloids present in *A. muricata*. (A) Aporphine type. (B) Protoberberine type. (C). Iminosugar type. (D) Isoquinoline type. Representative compounds of alkaloids are found in Table 2 at numbers 2, 11, 12 and 27 respectively.

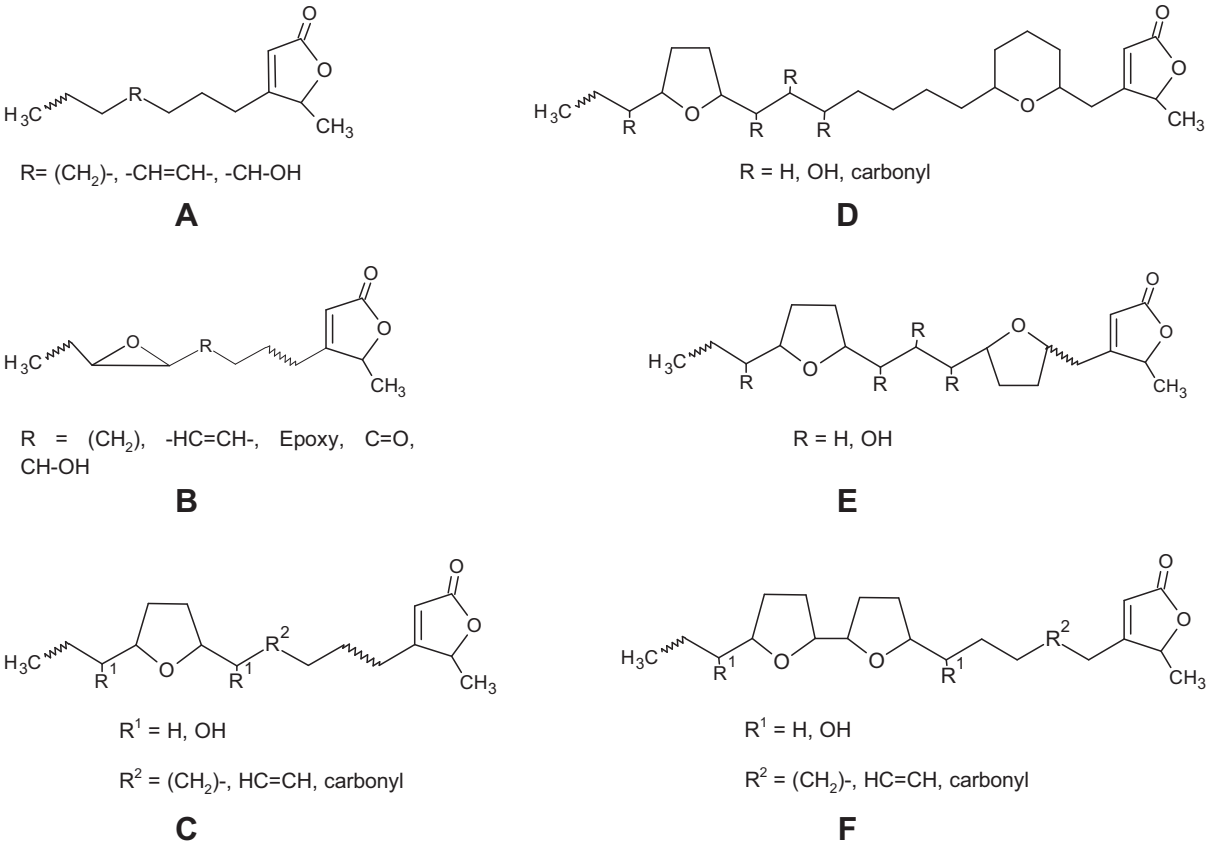

Figure 2 Chemical structures of six types of acetogenins present in *A. muricata*. (A) Chemical structure of linear derivatives corresponding to the acetogenins numbers 31–39 of Table 2. (B) Chemical structure of epoxy acetogenins corresponding to the acetogenins numbers 40–52 of Table 2. (C) Chemical structure of mono THF acetogenins corresponding to the acetogenins numbers 53–140 of Table 2. (D) Chemical structure of mono THF, mono THP acetogenins corresponding to the acetogenins numbers 155–156 of Table 2. (E) Chemical structure of Bis-THF nonadjacent acetogenins corresponding to the acetogenins numbers 141–144 of Table 2. (F) Chemical structure of Bis-THF adjacent acetogenins corresponding to the acetogenins numbers 145–154 of Table 2.

have shown that alkaloids isolated from *Annona* species possess an affinity for the 5-HT1A receptors *in vitro* and participate in dopamine biosynthesis (Hasrat et al., 1997a, 1997b). Thus, it has been proposed that alkaloids derived from the *Annona* could induce antidepressant-like effects (Hasrat et al., 1997a, 1997b), and cytotoxic activity (Matsushige et al., 2012). Neurotoxic effects have also been reported for some alkaloids, and suggested that neuronal death occurred by apoptosis (Lannuzel et al., 2002).

3.2. Acetogenins

More than 120 acetogenins have been identified in ethanolic, methanolic or another organic extracts of different organs

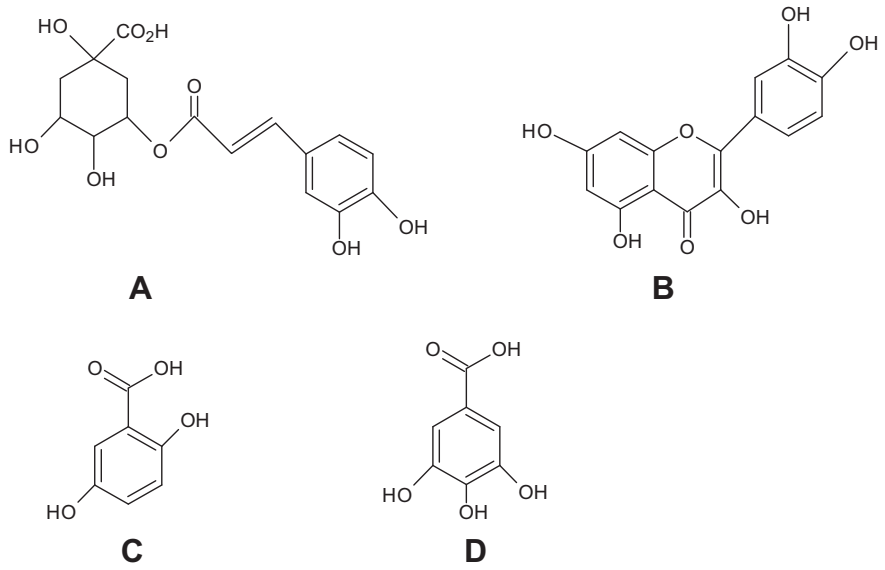

Figure 3 Chemical structures of types of phenols present in *A. muricata*. (A) Chlorogenic acid type. (B) Flavonoid type. (C) Hydroquinone type, (D) Tannin type. Representative compounds of these flavonoids are found in Table 2 for numbers 158, 181, 192 and 193, respectively.

and tissues of *A. muricata* such as leaves, stems, bark, seeds (Alali et al., 1999; Chang et al., 2003; Li et al., 2001; Liaw et al., 2002), pulp (Ragasa et al., 2012), and fruit peel (Jaramillo et al., 2000) (Table 2). Acetogenins are characterized by a long aliphatic chain of 35 to 38 carbons bonded to a γ-lactone α ring, terminally substituted by β-unsaturated methyl (sometimes it is a ketolactone), with one or two tetrahydrofurans (THF) located along the hydrocarbon chain and a determined number of oxygen groups (hydroxyl, acetoxyls, ketones, epoxy). Most of the acetogenins found in *A. muricata* contain a THF ring, although acetogenins have also been reported with two adjacent or nonadjacent THF rings. Acetogenins are linear and may have one or two epoxy groups. Fig. 2 shows the six basic chemical structures of acetogenins reported for *A. muricata*. Some studies suggested that its bioactivity depends on its structure (Landolt et al., 1995). Annonacin was the most abundant acetogenin reported in both, leaves (Liaw et al., 2002) and fruit (Champy et al., 2005, 2009) of *A. muricata,* but has also been reported in seeds (Wu et al., 1995a), peel (Jaramillo et al., 2000) and roots (Champy et al., 2004). The contents of acetogenins in leave extracts range from 3.38 to 15.05 mg/g measured by A ^{1}H NMR, while HPLC-MALDI quantified 0.299 mg/g (Machado et al., 2014). Acetogenins are considered the main bioactive compounds of the Annonaceae family (Alali et al., 1999). Some studies have shown that acetogenins are more cytotoxic than alkaloids and rotenone, a synthetic cytotoxic compound. Acetogenins and alkaloids are widely studied in a controversial form, due to their therapeutic potential versus neurotoxic activity.

3.3. Phenolic compounds

Thirty-seven phenolic compounds have been reported to be present in *A. muricata* (Table 2). The important phenolic compounds found in *A. muricata* leaves include quercetin (Nawwar et al., 2012) and gallic acid (Correa-Gordillo et al., 2012). The presence of flavonoids and lipophilic antioxidant compounds such as tocopherols and tocotrienols has been reported to be present in the pulp (Correa-Gordillo et al., 2012). In different studies, when organic or aqueous extracts have been used, the quantity of extractable total phenols is considerably different. This is important to mention because the most common medicinal use is aqueous infusion and the majority of phenols are soluble in water. Phenolic compounds are considered as the major phytochemicals responsible for the antioxidant activity (George et al., 2014).

3.4. Other compounds

Other compounds such as vitamins, carotenoids, amides, cyclopeptides and megastigmanes have also been identified in *A. muricata* (Table 2). Vitamins and carotenoids have been found in leaves, seeds and fruit pulp (Correa-Gordillo et al., 2012; Vijayameena et al., 2013). The presence of the amide N-p-coumaroyl tyramine (Wu et al., 1995c) and cyclopeptides (Li et al., 1998; Wélé et al., 2004) has been reported in the seeds and showed to have anti-inflammatory and anti-tumor effects. Megastigmanes are present in leaves of *A. muricata* but had no cytotoxic or antioxidant activity (Matsushige et al., 2011). Examples of chemical structures of these compounds are shown in Fig. 3.

On the other hand, 37 volatile compounds have been identified in the fruit pulp of *A. muricata*, and most of these compounds are aromatic and aliphatic esters (Cheong et al., 2011). In addition, 80 essential oils, mainly sesquiterpenes derivates (Kossouoh et al., 2007; Thang et al., 2012), have been identified in the leaf and have shown cytotoxic activity against MCF-7 (human breast carcinoma) cell line (99.2% kill at 100 μg/ml) (Owolabi et al., 2013). The study of volatiles of *A. muricata* is promising because of their bioactivity.

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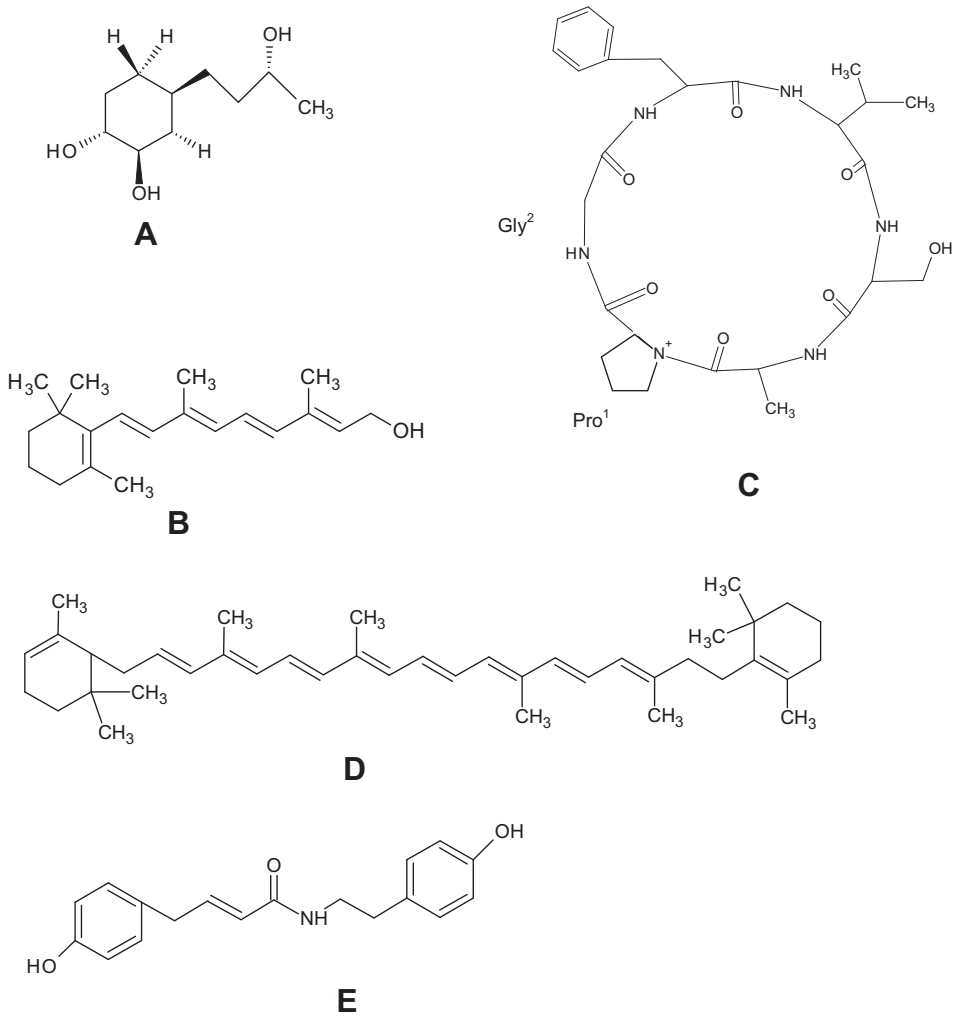

Figure 4 Chemical structure of some compounds present in *A. muricata*. (A) Megastigmane type. (B) Vitamin type. (C) Cyclopeptide type. (D) Carotenoid type. (E) Amide type. Representative compounds are found in Table 2 for numbers 194, 205, 198, 204 and 212 respectively.

4. Pharmacological activities

From the 50 reports of pharmacological studies we have reviewed for this manuscript, about 66% corresponded to *in vitro* studies, 32% to *in vivo* studies in murine models, and 2% to clinical studies. Regarding the type of extracts used, 84% corresponded to maceration of any part of the plant in organic solvents and 16% corresponded to aqueous preparations.

4.1. In vitro studies

Most of the *in vitro* studies correspond to cytotoxic activity (30%) followed by antiprotozoal activity (23%) and insecticidal activity (18%). The remaining 29% was conformed to antioxidant activity and antimicrobial and antiviral activities, among others (Table 3).

4.1.1. Cytotoxic activity

The increasingly popular use of *A. muricata* as an anticancer treatment reported ethnobotanically may be related to reports of its selective cytotoxic activity (George et al., 2012). This bioactivity is considered selective as some of the extracts studied *in vitro* were shown to be more toxic to cancer cell lines than to normal cells (Betancur-Galvis et al., 1999; Dai et al., 2011; George et al., 2012; Valencia et al., 2011; Gavamukulya et al., 2014). Nawwar et al. (2012) reported that 1.6 μg/ml and 50 μg/ml from hydroalcoholic extract of *A. muricata* leaves increased the viability of non-cancerous cells while 100 μg/ml did not alter their viability. This selective activity has also been reported to induce healing. In tumor cells, healing time is increased (Torres et al., 2012), whereas in rodents, healing time of induced wound decreases (Padmaa et al., 2009). Likewise, in the study of other bioactivities, the type of extract is decisive in the results obtained. Organic solvents, pentanoic and ethanolic, were the most active *A. muricata* extracts against cancer cells grown *in vitro*. In these extracts, activity has been reported to be 10 and 4.5 times higher, respectively, than the activity of the aqueous extract in the A375 cell culture (Ménan et al., 2006). According to Osorio et al. (2007), extracts with $LC_{50} < 10$ μg/ml can be classified as highly cytotoxic while the National Cancer Institute (Pieme et al., 2014) suggested that plant extracts with LC_{50} values $\leqslant 20$ μg/ml are suitable for cancer

Table 3 Pharmacological activities of *A. muricata* extract evaluated *in vitro*.

Activity	Plant part	Solvent	Test model	Effect	References
Cytotoxic	Leaf	H_2O:EtOH 40%	K562	MIC = 7 mg/ml	Oviedo et al. (2009)
			ECV-304	MIC = 2 mg/ml	
	Peri	MeOH	U-937	MEC > 1 mg/ml	Jaramillo et al. (2000)
		Hex		MEC = 1 mg/ml	
		EtOAc		MEC = 0.1 mg/ml	
	Dried fruit	H_2O:Cet 50%	MCF-10A	IC_{50} > 200 μg/ml	Dai et al. (2011)
			BC MDA-MB-468	IC_{50} = 4.8 μg/ml	
			MDA-MB-231	IC_{50} > 200 μg/m	
			MCF-7	IC_{50} > 200 μg/m	
	Leaf	EtOAc	U-937	LC_{50} = 7.8 μg/ml	Osorio et al. (2007)
	Stem	EtOAc		IC_{50} = 10.5 μg/ml	Valencia et al. (2011)
		MeOH		IC_{50} = 60.9 μg/ml	
		Hex		IC_{50} = 18.2 μg/ml	
		EtOAc		IC_{50} = 28.1 μg/ml	
		MeOH		IC_{50} = 38.5 μg/ml	
		Hex		IC_{50} = 15.7 μg/ml	
	Leaf	EtOH	VERO	IC_{50} < 0.00022 mg/ml	Quispe et al. (2006)
			H460	IC_{50} < 0.00022 mg/ml	
			C-678	IC_{50} < 0.00022 mg/ml	
	Leaf/ stem	DMSO	PC FG/COLO357	IC_{50} = 200 μg/ml	Torres et al. (2012)
			PC CD18/HPAF	IC_{50} = 73 μg/ml	
	Leaf	*n*-But	MDA-MB-435S	IC_{50} = 29.2 μg/ml	George et al. (2012)
			HaCaT	IC_{50} = 30.1 μg/ml	
			WRL-68	IC_{50} = 52.4 μg	
		H_2O:EtOH	HaCat	1.6 to 50 μg/ml increase cellular activity, 100 μg/ml not change cell behavior	Nawwar et al. (2012)
		H_2O	A375	IC_{50} > 500 μg/ml	Ménan et al. (2006)
		EtOH		IC_{50} = 320 μg/ml	
		Pen		IC_{50} = 140 μg/ml	
		EtOH	MCF-7	ED_{50} = 6.2 μg/ml	Calderón et al. (2006)
			H-460	ED_{50} = 4.0 μg/ml	
			SF-268	ED_{50} = 8.5 μg/ml	
	Leaf	EtOH	MDBK	CC_{50} = 20x10–4 μg/ml	Betancur-Galvis et al. (1999)
	Seed			CC_{50} = 24x10–5 μg/ml	
	Leaf	EtOAc	HeLa	15.62 μg/ml = 11.37% inh	Astirin et al. (2013)
		EtOH + H_2O		15.62 μg/ml = 3.97% inh	
		Chl		15.62 μg/m l = 18.42% inh	
		n-Hex		15.62 μg/ml = 21.41% inh	
		n-Hex	HT-29	IC_{50} = 14.93 μg/ml	Moghadamtousi et al. (2014)
		EtOAc		IC_{50} = 4.29 μg/ml	
		MeOH		IC_{50} > 100 μg/ml	
		n-Hex	HCT-116	IC_{50} = 12.26 μg/ml	
		EtOAc		IC_{50} = 3.91 μg/ml	
		MeOH		IC_{50} > 100 μg/ml	
		n-Hex	CCD841	IC_{50} = 42.19 μg/ml	
		EtOAc		IC_{50} = 34.24 μg/ml	
		MeOH		IC_{50} > 100 μg/ml	
		EtOH	Spleen cell	IC_{50} > 750 μg/ml	Gavamukulya et al. (2014)
			EACC	IC_{50} = 335.85 μg/ml	
			MDA	IC_{50} = 248.77 μg/ml	
			SKBR3	IC_{50} = 202.33 μg/ml	
			T47D	IC_{50} = 17.15 μg/ml	Rachmani et al. (2012)
	Leaf	EtOH	HL-60	IC_{50} = 14 μg/ml	Pieme et al. (2014)
	Twigs			IC_{50} = 49 μg/ml	
	Roots			IC_{50} = 9 μg/ml	
	Leaf	Hex	Capan-1	IC_{25} = 7.8 μg/ml	Mohamad et al. (2015)
	Com leaf	DMSO		IC_{25} = 0.9 μg/ml	
Antiprotozoal	Leaf	H_2O	*Plasmodium falciparum*	IC_{50} = 240 μg/ml	Ménan et al. (2006) and
		EtOH	(chloroquine-sensitive	IC_{50} = 52 μg/ml	Nguyen-Pouplin et al.
		Pen	strain)	IC_{50} = 18 μg/ml	(2007)
		H_2O	*Plasmodium falciparum*	IC_{50} = 230 μg/ml	
		EtOH	FcM29	IC_{50} = 49 μg/ml	

(*continued on next page*)

Table 3 (*continued*)

Activity	Plant part	Solvent	Test model	Effect	References
		Pen		IC_{50} = 16 μg/ml	
		EtOH	*Plasmodium falciparum*	IC_{50} = 7.43 μg/ml	Boyom et al. (2011)
		MeOH	strain W2	IC_{50} = 3.55 μg/ml	
		Ip		IC_{50} > 10 μg/ml	
		Hex		IC_{50} = 2.03 μg/ml	
		H_2O		IC_{50} > 10 μg/ml	
	Twig	EtOH		IC_{50} = 8.56 μg/ml	
		MeOH		IC_{50} = 4.11 μg/ml	
		Hex		IC_{50} > 10 μg/ml	
		H_2O		IC_{50} > 10 μg/ml	
	Flow	EtOH		IC_{50} = 5.12 μg/ml	
		MeOH		IC_{50} = 2.92 μg/ml	
		H_2O		IC_{50} > 10 μg/ml	
	Peric	EtOH		IC_{50} = 6.87 μg/ml	
		MeOH		IC_{50} = 4.3 μg/ml	
		Ip		IC_{50} > 10 μg/ml	
		H_2O		IC_{50} > 10 μg/ml	
	Pulp	EtOH		IC_{50} = 6.01 μg/ml	
		MeOH		IC_{50} = 5.17 μg/ml	
		Pp		IC_{50} = 4.42 μg/ml	
		H_2O		IC_{50} > 10 μg/ml	
	Seed	EtOH		IC_{50} = 3.02 μg/ml	
		MeOH		IC_{50} = 2.42 μg/ml	
		Pp		IC_{50} > 10 μg/ml	
		H_2O		IC_{50} > 10 μg/ml	
	Leaf	Hex	*Plasmodium falciparum*	IC_{50} = 7 μg/ml /38 μg/ml	Osorio et al. (2005)
		EtOAc	F32/W2	IC_{50} = 8 μg/ml /10 μg/ml	
		MeOH		IC_{50} = 9 μg/ml/36 μg/ml	
	Stem	Hex		IC_{50} = 11 μg/ml/38 μg/ml	
		EtOAc		IC_{50} = 40 μg/ml/34 μg/ml	
		MeOH		IC_{50} = 32 μg/ml/26 μg/ml	
	Leaf	MeOH	*Plasmodium falciparum* 3D7	IC_{50} = 0.715 μg/ml	Yamthe et al. (2015)
	Peri	EtOH	*Plasmodium falciparum*	IC_{50} = 1.01 μg/ml	Boyom et al. (2011)
	Root		strain W2	IC_{50} = 0.79 μg/ml	
	Steam			IC_{50} = 1.45 μg/ml	
	Peri	MeOH	*Leishmania braziliensis*	MEC > 1 mg/ml	Jaramillo et al. (2000)
		Hex		MEC > 1 mg/ml	
		EtOAc		MEC = 0.1 mg/ml	
	Leaf	Hex	*Leishmania sp.*	IC_{50} > 100 μg/ml	Osorio et al. (2007)
		EtOAc		IC_{50} = 25 μg/ml	
		MeOH		IC_{50} > 100 μg/ml	
	Stem	Hex		IC_{50} = 76.3 μg/ml	
		EtOAc		IC_{50} = 63.2 μg/ml	
		MeOH		IC_{50} = 98.6 μg/ml	
	Leaf	EtOH	*Biomphalaria glabrata*	500 ppm, 100% mort	Luna et al. (2005)
	Leaf	EtOAc	*Trypanosoma cruzi*	IC_{50} = 40.2 μg/ml	Valencia et al. (2011)
		MeOH		IC_{50} > 200 μg/ml	
		Hex		IC_{50} > 200 μg/ml	
	Stem	Hex		IC_{50} = 91 μg/ml	
		EtOAc		IC_{50} = 93.5 μg/ml	
		MeOH	*Entamoeba histolytica*	IC_{50} > 200 μg/ml	
	Bark	EtOH		MIC = 63 mcg/ml	Ross (2010)
	Leaf	H_2O	*Haemonchus contortus*	12.5% extract 90% of larvae mot	Ferreira et al. (2013)
Insecticidal	Seed	EtOH	*Spodoptera litura* larvae	5% extract, 18–96% inh	Leatemia and Isman (2004)
		PE	*A. aegypti*	18.75 ppm, 15% mort	Morales et al. (2004)
			An. albimanus	4.7 ppm, 85% mort	
			A. aegypti	37.5 ppm, 3% mort	
			An. albimanus	9.4 ppm/, 2.5% mort	
	Leaf and Bark	H2O	*A. aegypti*	5% extract, 99% mort	Sanabria et al. (2009)
	Flow	EtOH/	*A. aegypti*	CL_{50} = 3.33 mg/ml	Bobadilla et al. (2005)

Table 3 (*continued*)

Activity	Plant part	Solvent	Test model	Effect	References
	Seed	H2O		CL_{50} = 0.02 mg/ml	
	Leaf			CL_{50} = 8.25 mg/ml	
	Stem			CL_{50} = 19.21 mg/ml	
	Root			CL_{50} > 50 mg/ml	
	Leaf	EtOH	*Plutella xylostella*	5 mg/ml by 12 days: 100% larvae mort	Prédes et al. (2011)
		EtOH	*Callosobruchus maculatus Fabricius*	1 g/l, 40.8% mort	Adeoye and Ewete (2010)
	Seed	EtOH/*n*-Hex	*A. aegypti*	LC_{50} = 73.77 ppm	Komansilan et al. (2012)
		EtOH	*Cx. Quinquefascia-tus*	1 ml extract, 22% mort	Raveloson et al. (2014)
		DicMet		1 ml extract, 22% mort	
		H_2O		20% extract, 11.5% mort	
		DicMe	*Ae. albopictus*	1 ml extract, 25% mort	
Repellent	Seed	EtOH	*C. gestroi* Wasmann	20% extract, 15.75% mort	Acda (2014)
Antioxidant	Juice	NR	ABTS	6.09 µM of Tr/g	Almeida et al. (2011)
			DPPH	1.36 µM of Tr/g	
	Pulp	NR	FRAP	503 µmol/l/g	Correa-Gordillo et al. (2012)
			ORAC	14.51 µmol of Tr/g	
			ABTS	287.67 µmol of Tr/g	
			DPPH	2.88 µmol of Tr/g	
			Lipid peroxidation	3.5% with 10 µM GAE	
	Leaf	MeOH	DPPH	IC_{50} = 221 µg/ml	
		EtOH	DPPH	IC_{50} = 70 µg/ml	
			ABTS	IC_{50} = 305 µg/ml	
			Lipid peroxidation	IC_{50} = 455 µg/ml	
			Follow nitric oxide radical	IC_{50} = 350 µg/ml	
			Follow superoxide radical	IC_{50} = 155 µg/ml	
	Leaf	H_2O:EtOH (3:1)	ORAC assay	14269537.4 µM Tr/g	Nawwar et al. (2012)
	Fresh leaf	H_2O	DPPH	SC50 = 10.1 mg/l	Alitonou et al. (2013)
	Leaf	*n*-But	DPPH	400 µg of extract, 60% inh	George et al. (2012)
	Fresh-leaf	EtOH	ABTS	219.2 µmol of Tr/100 g	Vit and Santiago (2014)
	Dried-leaf	MeOH		182.3 µmol of Tr/100 g	
	Pulp	EtOH		280.2 µmol of Tr/100 g	
		MeOH		160.8 µmol of Tr/100 g	
	Seed	EtOH		306 µmol of Tr/100 g	
		MeOH		193.4.2 µmol of Tr/100 g	
		EtOH		131.2 µmol of Tr/100 g	
		MeOH		86.6 µmol of Tr/100 g	
	Pulp	MeOH	DPPH	5 mg of pulp, 75.39% inh	Boakye et al. (2015)
Antibacterial	Peel	H_2O	*S. aureus*	50 µL/dish, DIH = 14 mm	Viera et al. (2010a)
			V. cholera	50µL/dish, DIH = 17 mm	
			E. coli (river)	50µL/dish, DIH = 18 mm	
	Leaf	EtOH	*S. aureus*	MIC = 128 mg/ml	Bussmann et al. (2010) Bento et al. (2013)
		H_2O:EtOH	*E. coli* EC27	MIC > 1024 µg/ml	
		H_2O/ MeOH	*B. subtilis*	400 mg/ml, DIH = 18.5/19.5m	Solomon-Wisdom et al. (2014)
			S. aureus	400 mg/ml, DIH = 17.7/20.5m	
			K. pneumonia	400 mg/ml, DIH = 16.0/18.0m	
			S. typhimurium	400 mg/ml, DIH = 16.5/16.5m	
			E. coli	400 mg/ml, DIH = 17.5/16.5m	
			S. pyogenes	400 mg/ml, DIH = 0/17.2 m	
	Seed, Stem	MeOH	*E. coli* C600	MIC > 1024 µg/ml	Yasunaka et al. (2005)
			S. aureus 209P	MIC > 1024 µg/ml	
	Leaf	H_2O	*M. tuberculosis* H37Rv	5 mg/ml of extract, 82% inh	Radji et al. (2015)
			M. tuberculosis MDR	5 mg/ml of extract, 50% inh	
		EtOH	*S. thypimurium*	MIC = 4096 µg/ml	Roger et al. (2015)
			S. thypimurium A	MIC = 2048 µg/ml	
			S. thypimurium B	MIC = 4046 µg/ml	

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Table 3 (*continued*)

Activity	Plant part	Solvent	Test model	Effect	References
Antiviral	Stem	EtOH	*Herpes simplex* HSV-1 strain #753166	MIC = 1 mg/ml	Padma et al. (1998)
	Leaf	EtOH	Spleen cell	IC_{50} > 750 μg/ml	Gavamukulya et al. (2014)
			EACC	IC_{50} = 335.85 μg/ml	
			MDA	IC_{50} = 248.77 μg/ml	
			SKBR3	IC_{50} = 202.33 μg/ml	
		EtOH	T47D	IC_{50} = 17.15 μg/ml	Rachmani et al. (2012)
	Leaf	EtOH	HL-60	IC_{50} = 14 μg/ml	Pieme et al. (2014)
	Twigs			IC_{50} = 49 μg/ml	
	Roots			IC_{50} = 9 μg/ml	
	Leaf	Hex	Capan-1	IC_{25} = 7.8 μg/ml	Mohamad et al. (2015)
		DMSO		IC_{25} = 0.9 μg/ml	
	Leaf	H_2O	BPH-I	IC_{50} = 1.36 mg/ml	Asare et al. (2014)

NR, no reported; **Cell line:** ECV304, Human leukemia carcinoma cells; FG/COLO357 and CD18/HPAF, Pancreatic cancer cells; U937, Histiocytic lymphoma cell line; HeLa, Uterine cervical cancer cell line; MDA-MB-435S, Breast carcinoma cells; HaCat, immortalized human keratinocytes; WRL-68, normal human liver cells; MBDK, Bovine cell line; MCF-7, human breast carcinoma; K562, Human bladder carcinoma cells; H-460, Human large lung cell carcinoma; S-F-268, glioma; CCD841, normal human colon epithelial cells; HT-29 and HCT-116, colon cancer cell. VERO, kidney epithelial cells; C-678, stomach cancer cells; EACC: Ehrlich Ascites Carcinoma Cells; SKBR3: breast adenocarcinoma cell line; T47D, breast cancer cells; HL-60, human promyelocytic leukemia; Capan-1, pancreatic cancer cells; BPH-I, human benign prostate cells. **Concentration**: MEC: minimum effective concentration; MIC, minimum inhibitory concentration; IC_{50}, medium inhibitory concentration; DIH, Diameter of inhibitory halo (mm); SC_{50}, medium scavenging activity; ED_{50}, medium effective dose; CC_{50}, 50% cytotoxic concentration; CL_{50}, 50% lethal concentration; inh, inhibitory; Ip, Interface precipitate. **Extract**: *n*-but, butanol; Chl, chloroform; EtOAc, ethyl acetate; EtOH, ethanol; Hex, hexane; *n*-hex, *n*-hexane; H2O, water; MeOH, methanol; PE, petroleum ether; Pen, pentane. **Chemical**: Tr, trolox; GAE, gallic acid equivalent. **Activity**: FRAP, Power reduction of iron; ORAC, Oxygen radical absorbance capacity; ABTS, Radical cation capture 2,2-azino-bis(3-ethylbenzthiazoline)-6 ammonium sulfonate; DPPH, 1,1-diphenyl-2-picrylhydrazyl radical activity**. Plant part**: flow, flower; peric, pericarp. Inh, inhibition; mor, mortality; MDR, multi drug resistant.

drugs from plants. Ethyl acetate *A. muricata* leaf extract showed inhibition of the U-937 cell line with 7.8 μg/ml (Osorio et al., 2007). Although *A. muricata* extracts exhibit good cytotoxicity, there are plants with more cytotoxic effect, like *Thevetia ahouai* with LC_{50} < 1 μg/ml. Both plant species are used in Latin American countries to treat cancer (Calderón et al., 2006). The hexane extract of leaves had the highest content of flavonoids and the most effective inhibition of cell proliferation than the methanol or chloroform extracts (Mohamad et al., 2015). Moghadamtousi et al. (2015c) and Pieme et al. (2014) proposed that the mechanism of action of the extract implies the disruption of mitochondrial membrane to arrest cells in G0/G1 phase, and the induction of apoptosis suppressing the migration and invasion of cancer cells. Pieme et al. (2014) suggested that *A. muricata* extracts induce apoptosis by Reactive Oxygen Species (ROS), and downregulates Bcl-2 proteins. Bax protein Bcl-2 are anti-apoptotic proteins that suppress the function of apoptosis, while Bax are proteins that mediate the leakage of pro-apoptotic factors, including cytochrome c, Ca^{2+} and the mitochondrial protein Smac/DIABLO into the cytosol through dimerization and translocation to the outer mitochondrial membrane; a property that was also observed for acetogenins (Asare et al., 2014).

The acetogenins with antitumor and anticancer activity have also been studied *in vitro* assays, and cytotoxic effects against more than 15 cancer cell lines have been used (Alonso-Castro et al., 2011; Chang and Wu, 2001; Kim et al., 1998a, 1998b; Ko et al., 2011; Liaw et al., 2002; Quispe et al., 2006; Torres et al., 2012; Zeng et al., 1996). Isolated acetogenins have demonstrated selective cytotoxic effects (Moghadamtousi et al., 2015c). Acetogenins bioactivity has been related to their molecular structure (Landolt et al., 1995; Nakanishi et al., 2003). The two adjacent THF rings acetogenins are the most active (Table 2) (Castillo-Sánchez et al., 2010; Nakanishi et al., 2003; Yang et al., 2010), especially bullatacin and squamocin (Table 2), which have been reported mainly in the seeds (Landolt et al., 1995; Nakanishi et al., 2003). The mechanism of the acetogenin cytotoxic action is the inhibition of the mitochondrial complex I (Lannuzel et al., 2003), and the inhibition of ubiquinone-linked NADH oxidase in the plasma membranes of cancerous cells causing apoptosis (Alali et al., 1999). Torres et al. (2012) demonstrated that *A. muricata* extracts suppressed phosphorylation of the key molecules involved in the extracellular signal-regulated kinase (ERK) and the phosphatidylinositol 3'kinase (PI3 K/Akt) pathway which play a crucial role in the proliferation and survival of pancreatic cancer cells. Also, plant extract inhibited the expression of glucose transporter and glycolytic enzymes, all of which lead to the reduction of glucose uptake and ATP production by PC cells (Torres et al., 2012).

Biochemical apoptosis implied a transverse redistribution of phosphatidylserine (PS) on the outer plasma membrane arises during early apoptosis (Moghadamtousi et al., 2015c). Other events in apoptosis are the complex cascade of caspases. Annomuricin E caused depletion of mitochondrial membrane potential (MMP) leading to opening of mitochondrial permeability transition pores and further release of pro-apoptotic proteins, such as cytochrome c from the mitochondria to the cytosol, resulting in the formation of the apoptosome and the activation of caspase 9 and caspase 3/7, which have been linked to the mitochondrial death pathway. *A. muricata* extracts isolated Annomuricin E downregulates Bcl-2 proteins

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and upregulates Bax protein. This finding confirms that Annonacin E-induced apoptosis was through the mitochondrial-mediated pathway (Moghadamtousi et al., 2015c). McLaughling (2008) suggested that selective cytotoxicity of *A. muricata* is due to the enhanced ATP demand of cancer cells with respect to normal cells.

4.1.2. Anti-protozoal activity

A. muricata extracts and some of their isolated compounds have shown effectiveness against protozoans responsible for human diseases (Table 3), as is the case of the genera *Plasmodium* (Boyom et al., 2011), *Leishmania* (Osorio et al., 2007), *Biomphalaria* (Luna et al., 2005), *Trypanosoma*, and *Entamoeba* (Ross, 2010), responsible for malaria, leishmaniasis, schistosomiasis, chagas, and amebiasis diseases, respectively. The anti-plasmodic effect has particular interest due to the necessity for antimalarial drugs in tropical areas. Methanol extract of this species has shown inhibition of this parasite *in vitro* but with less effectivity than the commercial drugs chloroquine and artemisinin (Boyom et al., 2011). The highest effectiveness was found in seed extracts (Boyom et al., 2011). It has also been reported that alkaloids (Fofana et al., 2011, 2012), acetogenin, anonaine, and gallic acid (Yamthe et al., 2015) isolated from *A. muricata* had antiplasmodial activity. It has been demonstrated that phenolic compounds inhibit the activity of β-ketoacyl-ACP-reductase (FabG), β-hydroxyacyl-ACP-dehydratase (FabZ) and enoyl acyl-ACP reductase (FaBI), important enzymes for fatty acid biosynthesis in *P. falciparum* that compromises its growth (Tasdemir et al., 2006). In the case of FabG, phenols like luteolin act as noncompetitive inhibitor of FabG with respect to acetoacetyl-CoA as well as NADPH, while in FabZ, luteolin acts as competitive inhibitor of the substrate crotonyl-CoA (Tasdemir et al., 2006).

Methanolic and ethyl acetate extracts of *A. muricata* peel showed higher antileishmanial activity than the commercial compound Glucantime® (Jaramillo et al., 2000) used to treat diseases caused by different strains of protozoa.

The trypanocidal activity of *A. muricata* was found in extracts from different plant parts and in different solvents, although its effectiveness was 100 times lower than the commercial trypanocide benznidazole (Osorio et al., 2007; Valencia et al., 2011). Extracts of *A. muricata* also have antiparasitic activity against the metazoan or helminth *Haemonchus contortus*, a gastrointestinal parasite of sheep (Ferreira et al., 2013). The extracts of *A. muricata* were active against eggs, infective larvae and adult forms of the parasite, and the effect was comparable to that obtained with using the anthelmintic drug, levamisole (Ferreira et al., 2013).

Isoquinoline alkaloids are strongly implicated in the inhibition of an essential antioxidant enzyme of *Leishmania* and *Trypanosoma*, trypanothione reductase. This enzyme protects the parasites from ROS generated by the host defense cells (Tempone et al., 2005).

4.1.3. Insecticidal, larvicidal and repellent activity

A. muricata showed insecticidal activity from seed, leaves, barks, stems, roots and flowers (Bobadilla et al., 2005; Leatemia and Isman, 2004; Prédes et al., 2011). Ethanolic extracts inhibited insect larvae of *Aedes aegypti* (Bobadilla et al., 2005; Morales et al., 2004; Sanabria et al., 2009), *Anopheles albimanus* (Morales et al., 2004), and insects that affect plants such as *Spodoptera litura* (Leatemia and Isman, 2004), *Callosobruchus maculatus* and *Plutella xylostella* (Prédes et al., 2011). *A. muricata* seed extracts have shown the most active insecticidal activity (Bobadilla et al., 2005; Morales et al., 2004; Sanabria et al., 2009), probably due to its content of chemical compounds such as alkaloids, fatty acids and acetogenins. The insecticidal action of soursop alkaloids has not been fully studied. Fatty acids are toxic to insects in different manners: by inhalation of volatile compounds, by contact with film at the surface of water, and by penetration due to the amphibolic property of some compounds (Raveloson et al., 2014). New technologies, such as nano science, are exploring the development of environmentally friendly, effective, inexpensive and easy to apply mosquito control products. For this purpose, green silver nanoparticles synthesized using aqueous crude extract of *A. muricata* show larvae toxicity of *Aedes aegypti* (Santhosh et al., 2015).

Acetogenins have *in vitro* activity on larvae of *Myzus persicae*, *Leptinotarsa decemlineata*, *Blattella germanica*, *Aedes aegypti*, *Rhodnius prolixus*, and *Rhodnius pallescens* (Castillo-Sánchez et al., 2010; Guadaño et al., 2000). In studies that have evaluated the insecticidal activity of 44 acetogenins isolated from different species of *Annona*, there was a relationship between the acetogenin structure and their toxicity to mosquito larvae. As such, compounds with adjacent bis-tetrahydrofuran rings and three hydroxyls were more active than compounds with a mono-tetrahydrofuran ring. The majority of the active acetogenins evaluated in a study by Isman and Akhtar (2007) were equitoxic to the commercial compound rotenone (LC_{50} = 1.2 ppm). Some studies have suggested that the insecticidal mechanisms of acetogenins are due to THF ring having strong interaction with the interface of lipid bilayers, and alkyl spacer between the γ-lactone and hydroxylated THF ring moieties elicited potent inhibitory activities on the NADH oxidase, resulting in the inhibition of mitochondrial complex I (Guadaño et al., 2000; Isman and Akhtar, 2007), and thus damaging the respiration chain and the integrity and function of the cell. Using the insecticidal activity of isolated acetogenins as a base, commercial products were developed but failed mainly because their mechanism of action involves inhibition of mitochondrial electron transport with a specific action at complex I, thus becoming detrimental to other organisms. In the case of other plants, using crude extracts can be more promising than the development of products using individually isolated compounds as active ingredient (Isman and Akhtar, 2007).

4.1.4. Antioxidant activity

Natural antioxidants from plant species have gained interest due to their protective effect against oxygen-derived from free radicals involved in the development of many diseases such as cancer, cardiovascular affections, arthritis, as well as degenerative illness such as Parkinson and Alzheimer (Almeida et al., 2011). Several antioxidant screenings have been conducted on *A. muricata* (Table 3). Correa-Gordillo et al. (2012) compiled studies on the antioxidant activity of *A. muricata* considering different assays, the different plant parts, and the different solvents used. Some of the methods used for determining the total antioxidant capacity included the free radical scavenging capacities using DPPH

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and the ABTS+ assays, determination of oxygen radicals by the ORAC assay, reduction power by the FRAP assay and β-carotene bleaching.

The antioxidant activity has been evaluated in fresh and frozen pulp, juice, and fresh or dried leaves. The pulp antioxidant activity measured by ABTS, FRAP and ORAC suggested that the antioxidant compounds from *A. muricata* are mainly lipophilic, and the mechanism of action is by hydrogen donation (Correa-Gordillo et al., 2012).

The composition of the extract varies depending on the solvent used. For example, methanolic, ethanolic, *n*-butanolic and aqueous leaf extracts showed different antioxidant activity measured by DPPH. For instance, the aqueous extract of fresh leaves of *A. muricata* was 1000 times less active than the commercial antioxidant butylated hydroxytoluene (Alitonou et al., 2013). A positive correlation between antioxidant activity and the total polyphenol content was reported (George et al., 2012). Antioxidant activities of phenols, flavonoids, vitamins and carotenoids in *A. muricata* are summarized in Table 2.

4.1.5. Antibacterial and antiviral activities

A. muricata showed antibacterial activity against gram-positive and gram-negative bacteria, comparable with the standard antibiotic streptomycin (Table 3). Its bioactivity efficacy depends on the kind of solvent used in the extraction. For example, ethanolic and methanolic extracts of *A. muricata* showed antibacterial activity against *Staphylococus aureus,* while the peel aqueous extract did not show such activity. In addition to the direct antimicrobial activity, a modulatory activity has also been reported. The combination of ethanolic extract and antibiotic treatment increased the potentiation of the antibiotic against multidrug-resistant strains of *E. coli* and *S. aureus* (Viera et al., 2010; Bento et al., 2013; Solomon-Wisdom et al., 2014). Ethanolic extracts from stem and bark of *A. muricata* also showed antiviral activity *in vitro* against the *Herpes simplex* virus (Padma et al., 1998).

Antimicrobial bioactivity of *A. muricata* extracts is attributed to flavonoids, steroids and alkaloids present in the plant extracts (Radji et al., 2015). The mechanism of action is probably due to a synergism of these compounds. It has been reported that some alkaloids have the ability to bind with DNA of microorganisms and inhibit RNA synthesis (Roger et al., 2015), and have shown antimicrobial activity by glycosidase inhibition (Mohanty et al., 2008). It has also been reported that flavonoids act by inhibiting both cytoplasmic membrane function and DNA synthesis, such as quercetin that binds to GyrB subunit of *E. coli* DNA gyrase and inhibits the enzyme ATPase activity. Phenylphenol was reported to bind to membrane protein or hydrogen with vital proteins such as microbial enzymes and inhibit and change their functions (Radji et al., 2015).

With respect to antiviral bioactivity, it is known that plant extracts interfere with HIV-I replication at an early step of the virus. In the first step, plant extracts interfere with virus entry into the host cell by reduction of input viral RNA and by interfering with the function of the envelope proteins that diminish the infectivity of viral particles. This indicates that plant extracts have virucidal activity and act before the interaction with the host cell. Also, plant extracts inhibit attachment of virus to the host cell. It is demonstrated that antiviral activity of plant extracts is mediated by polyphenol compounds (Helfer et al., 2014).

4.2. In vivo studies of extracts and isolated compounds

The most encountered *in vivo* studies were hypoglycemic, antitumorigenic, hepato and gastro protective studies. The pharmacological activities of *A. muricata* extracts evaluated *in vivo* are summarized in Table 4.

4.2.1. Hypoglycemic activity

A. muricata leaf extracts showed hypoglycemic activity in murine models (Adewole and Caxton-Martins, 2006). In these studies, the effect of aqueous and methanolic extracts of *A. muricata* leaves on reducing the concentration of blood glucose in rats with diabetes induced with streptozotocin (STZ) was evaluated, and the histology and biochemistry of the pancreas were observed. Pancreatic β-cells in rats that were administered with extracts of *A. muricata* did not show the alterations that are normally found in diabetic rats. An increase in the antioxidant enzymatic activity and insulin content in pancreatic serum was reported. Near normal blood glucose levels, body weight, food and water intake, lipid profile and oxidative defense were achieved after a month of daily treatment with *A. muricata* extract, which could prevent the deleterious effect of STZ by its antioxidant and protective effect of pancreatic β-cells (Florence et al., 2014). It has also been reported that there is a positive correlation between tannins, flavonoids and triterpenoids content and the inhibition of α-glucosidase. Flavonoids inhibit α-glucosidase through hydroxylation bonding and substitution at β ring (Hardoko et al., 2015). This inhibition decreases carbohydrate hydrolysis and glucose absorption, and inhibits carbohydrates metabolism into glucose (Hardoko et al., 2015).

Additionally, glycemic index (GI) and glycemic load (GL) have been reported for *A. muricata* fruit. GI indicates the effect of the content and type of carbohydrates of a food on blood glucose content, while GL estimates how much the food will raise blood glucose level after eating it. GI and GL are considered low for *A. muricata*, which agrees with its hypoglycemic potential (Passos et al., 2015).

4.2.2. Anti-cancer activity

Ethyl acetate extract of *A. muricata* leaves showed chemopreventive properties on azoxymethane-induced colonic aberrant crypt foci in rats (Moghadamtousi et al., 2015c). As acetogenins, the extract downregulates PCNA and Bcl-2 proteins, upregulates Bax protein and restores the levels of the antioxidant enzymes. An excessive ROS generation results in the production of lipid radicals such as malondialdehyde (MDA), and an elevated concentration of MDA was observed in patients suffering from colorectal cancer (Moghadamtousi et al., 2015c). *A. muricata* extract treatment reduced MDA formation in colon tissue, confirming its protective effect against oxidative stress.

4.2.3. Anti-tumorigenic activity

Anti-tumoral activity has been reported for extracts and some isolated acetogenins of *A. muricata*. Hamizah et al. (2012)

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Table 4 Pharmacological activities of *A. muricata* extracts evaluated *in vivo*.

Activity	Plant part	Solvent	Dose	Test model and results	References
Hypoglycemic	Leaf	H_2O	100 mg/kg p.o. by 25 days	Reduction of blood glucose (4.7 mmol/l) in diabetes mellitus rats	Adewole and Caxton-Martins (2006)
		H_2O	100 mg/kg p.o. by 25 days	Increase of serum insulin glucose (12.2 μU/ml) in diabetes mellitus rats	
		MeOH	100 mg/kg, daily for two weeks	Reduction of blood glucose (4.22 mmol/l) in diabetes mellitus rats	Adeyemi et al. (2009)
		H_2O	100 mg/kg, daily for 28 days	Reduction of blood glucose (80.75 mg/dl) in diabetes mellitus rats	Florence et al. (2014)
	Stem bark	EtOH	100 mg/kg, daily for 14 days	Reduction of blood glucose (187 mg/dl) in diabetes mellitus rats	Ahalya et al. (2014)
Anti-cancer	Leaf	EtOH	100 mg/kg/4 wk	Restoration of colon total protein in cycas-induced colorectal carcinogenesis in rats	Okolie et al. (2013)
	Leaf	EtOAc	500 mg/kg/8 wk	72.5% of ACF inhibition in AOM induced colorectal carcinogenesis in rats	Moghadamtousi et al. (2015c)
Anti-tumorigenic	Dried fruit	H_2O:Cet 50%	200 mg/kg/35 wk	32% growth inhibition (weight) of breast tumor induced by MDA-MB-468 cell in rats	Dai et al. (2011)
	Leaf/ Stem	H_2O	50 mg/kg/35 days	59.8% growth inhibition of pancreatic tumor induced by CD18/HPAF cell in rats	Torres et al. (2012)
	Leaf	EtOH/H_2O	30 mg/kg bwt	0% of incidence of initiation and promotion of tumors induced in mouse skin	Hamizah et al. (2012)
Anti-diarrhea	Leaf	MeOH	25 a 200 mg/kg, vo	13.94% of inhibition of activated charcoal transit in mouse	Salinas et al. (2011)
Gastroprotective	Leaf	EtOH 80%	300 mg/kg	92.8% of inhibition of total area of gastric lesion in rats	Roslida et al. (2012)
	Leaf	EtOAc	400 mg/kg	Reduction of ulcer index in ethanol-induced ulcerogenesis in rats	Moghadamtousi et al. (2014)
Hepato-protective	Leaf	H_2O	400 mg/kg twice daily for 7 days:	Reduction of bilirubin level (5.68 μmol/l) in rats hyperbilirubinemia induced	Arthur et al. (2012a)
	Leaf	H_2O	50 mg/kg	97% of protection versus hepatotoxicity induced in rats by CCl_4	Arthur et al. (2012b)
	Leaf	H_2O	100 mg/kg	100% of protection versus hepatotoxicity induced in rats by acetaminophen	
Anti-inflammatory	Leaf	H_2O	1.5 mg/kg	71.12% reduction of plant edema induced in mouse model	Poma et al. (2011)
	Leaf	EtOH	400 mg/kg	Reduction of volume (0.47 ml) of carrageenan-induced paw edema in rats	Sousa and Vieira (2010)
Anti-nociceptive	Leaf	EtOH 80%	10 mg/kg op	53.92% prolongation of reaction time of mice exposed to the hot plate	Roslida et al. (2012)
	Leaf	EtOH 80%	300 mg/kg	95.3% inhibition of abdominal writhes of mice induced by 0.6% acetic acid	
	Leaf	EtOH 80%	100 mg/kg	47.36% of reduction time spent licking on formalin-induced in mice	
	Leaf	EtOH	400 mg/kg	41.41% inhibition of acetic acid-induced writhing in mice	Sousa and Vieira (2010)
	Leaf	EtOH	400 mg/kg	Increase the latency time (13.25 min) in mice	
	Leaf	EtOH	400 mg/kg	45% inhibition of formalin-induced nociception in mice	
Anxiolytic-like effect	Leaf	EtOH 40%	0.5 g/kg, vo:	45% reduction of time reaction in Albino mice/ elevated plus maze	Oviedo et al. (2009)
Hypotensive	Leaf	H_2O	48.53 mg/kg	Reduction of blood pressure (57.7 mm Hg) in rats	Nwokocha et al. (2012)
Wound healing	Stem bark	EtOH	4% in ointment/12 days	88.58% reduction of area of open wound produced in rats	Padmaa et al. (2009)
	Leaf	EtOAc	10% in cream, two applications a day per 15 days	77% of wound closure in rats	Moghadamtousi et al. (2015b)

NR, Not reported; EtOH, ethanol; H_2O, water; MeOH, methanol; EtOAc, ethyl acetate; Cet, cetone; CCl_4, carbon tetrachloride; wk, week; ACF, aberrant crypt foci; AOM, azoxymethane.

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reported that the ethanolic extract of *A. muricata* leaves showed greater anti-tumor activity in murine models than curcumin, a known natural chemopreventive. This extract has shown protective effect in biochemical events and in morphological changes in induced colorectal carcinogenesis. Aqueous extract of commercial powder capsules containing leaf and stem of *A. muricata* also showed anti-tumorigenic and anti-metastatic activities on pancreatic tumors in murine models (Torres et al., 2012). Breast tumor in rats was reduced by treatment for 5 weeks with *A. muricata* fruit extract (Dai et al., 2011). The mechanism of action suggests the inhibition of multiple signaling pathways that regulated metabolism, metastasis, induction of necrosis and cell cycle arrest (Torres et al., 2012; Dai et al., 2011), has been shown in cytotoxic mechanism. Antitumor activity was also reported for two acetogenin isolates of *A. muricata* (Ko et al., 2011; Wang et al., 2002). Ko et al. (2011) reported that bullatacin at doses of 400 mg/kg was able to reduce a tumor induced in rodents 300 times better than the commercial drug Taxol (paclitaxel). Meanwhile, annonacin at doses of 10 mg/kg reduced tumor size induced in murine models comparable to the commercial drugs cisplatin and adriamycin (Wang et al., 2002). A study by Yang et al. (2015) demonstrated that crude leaf extract showed more *in vitro* inhibition of prostate cancer proliferation and more effect on tumor growth-inhibition than flavonoid-enriched extract. This report suggests that the effectivity of crude extract is probably due to a synergistic interaction between flavonoids and acetogenins.

4.2.4. Hepatoprotective and gastroprotective activities

Arthur et al. (2012a, 2012b) studied the hepatoprotective activity of the leaf aqueous extract of *A. muricata*. They reported that the extract was effective against hyperbilirubinemia or jaundice with similar effect to silymarin (*Silybum marianum*). The extract reduced the harmful effect and preserved the hepatic physiological mechanism of the liver damaged by a hepatotoxin such as paracetamol (Acetaminophen), a drug widely used as antipyretic and analgesic, which can cause liver damage if taken in excessive (Arthur et al., 2012b). This study suggests that soursop extract reduces bilirubin levels due the glucosides present in the extract, which might be converted into glucuronic acid, conjugating with bilirubin for excretion, or because the extract active regulators increase the activity of enzymes, synthesis of transporter, and steps related to bilirubin clearance pathway (Arthur et al., 2012b).

Ethyl acetate and ethanol extracts from leaf of *A. muricata* showed protective gastric effect like omeprazole in ethanol-induced ulcerogenesis in rats (Moghadamtousi et al., 2014; Roslida et al., 2012). Antiulcer potential of *A. muricata* is probably through its antioxidant compounds that increase the mucosal nonprotein sulfhydryl group content (Roslida et al., 2012). The excessive production of gastric acid in patients with ulcers can reduce the level of gastric wall mucus (GWM). *A. muricata* extract caused attenuation in gastric acidity and retrieved the loss in GWM like proton pump inhibitors drugs as omeprazole but in less proportion. Additionally, the antioxidant effect of *A. muricata* extract can play an important role in the gastroprotection. The ROS produce oxidative damage to the gastric mucosa. *A. muricata* extract restores the activity of enzymes such as glutathione (GHS), catalase (CAT), nitric oxide (NO), superoxide dismutase (SOD), malondialdehyde (MDA) and prostaglandin E2 (PGE-2) that reduces cellular ROS. Histopathological analysis showed that the extract protects the gastric tissue from hemorrhagic lesion associated with attenuation of leukocyte infiltration and submucosal edema (Moghadamtousi et al., 2014).

4.2.5. Anti-inflammatory and anti-nociceptive activities

Anti-inflammatory activity similar to the activity presented by indomethacin, which is a nonsteroidal anti-inflammatory, has been reported (Poma et al., 2011; Sousa and Vieira, 2010). The antinociceptive effect of ethanolic and hydroalcoholic extracts of *A. muricata* has been reported using various chemical and thermal nociceptive models. *A. muricata* produced antinociception action of activity in both neurogenic and inflammatory phases (Roslida et al., 2012). Metabolites of arachidonic acid (called icosanoids) are involved in inflammation process (Poma et al., 2011). These metabolites are produced via cyclooxygenase and lipoxygenase when a cell is activated by mechanical trauma, cytokines, growth factors or other stimuli. It has been proposed that the mechanism of antinociception may be by inhibition of cyclooxygenase (COX) and lipoxygenases (LOX) and other inflammatory mediators by flavonoids present in the plant extract (Poma et al., 2011).

4.2.6. Anxiolytic and anti-stress activities

The anxiolytic and the anti-stress effects were more effective in the alkaloid fraction than in the crude hydroalcoholic extracts (Oviedo et al., 2009). It is possible to attribute this bioactivity to the alkaloid compounds; especially because two of the isolated alkaloids (anonaine and asimilobine) have relaxing activity. These compounds can influence the central nervous system via the $5HT_{1A}$ receptor. The $5HT_{1A}$ receptor binds with the endogenous neurotransmitter serotonin and is involved in the modulation of emotion (Hasrat et al., 1997a, 1997b). This bioactivity can validate the reason for the traditional use of *A. muricata* as sedative.

4.2.7. Hypotensive activity

Leaf extract of *A. muricata* caused a dose-dependent reduction in mean arterial pressure (MAP) in normotensive rats (Nwokocha et al., 2012). The suggested hypotensive mechanism of action of aqueous extract of *A. muricata* did not involve the endothelial or nitric oxide-dependent pathways. Studies suggested that plant extracts lower blood pressure through the blockage of calcium ion channel, and this Ca^{+} antagonism is further demonstrated by its ability to relax high K^{+} induced contractions (Nwokocha et al., 2012). The hypotensive effect has been attributed to alkaloids such as coreximine, anomurine, and reticulin, and some essential oil components such as β-caryophyllene (Nwokocha et al., 2012).

4.2.8. Wound healing

Bark and leaf extracts showed elevation in wound contraction compared with wound without treatment (Padmaa et al., 2009; Moghadamtousi et al., 2015b). Wound healing consists of four complex phases: coagulation, inflammation, proliferation and maturation. *A. muricata* accelerates some of these phases. In

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inflammatory phase the protein expression of heat shock proteins (Hsp70) is important for healing due to their role in cell proliferation. *A. muricata* induced upregulation of Hsp70 in wound tissues. In this phase the inflammatory cells produce cytokines and free radicals that in great quantity can produce lipid peroxidation in wound. Tissues treated with *A. muricata* extracts showed elevated activity of CAT, GPx and SOD that protect tissue against oxidative damage to accelerate the wound healing process. Additionally, *A. muricata* extracts reduce MDA, the biomarker of lipid peroxidation that can cause defect in endothelial cells, fibroblast and collagen metabolism necessary for wound healing. During the maturation phase, the collagen accumulation and fibroblast proliferation occurred. *A. muricata* extracts elevated the deposition of collagen fibers in the wound as observed in histological analysis (Moghadamtousi et al., 2015c).

4.3. Clinical studies

Ethanolic extracts of *A. muricata* leaves have been clinically evaluated in relation to their hypoglycemic activity. Arroyo et al. (2009) conducted a randomized, parallel grouped, double blind phase II clinical trial, in patients with type 2 diabetes mellitus. Groups of patients were given 1, 2 or 3 capsules of ethanol extract from *A. muricata* leaves (180 mg) plus 5 mg of glibenclamide for 30 days, and another group only received glibenclamide. The results of this study showed a decrease in the blood glucose or glycemia level in patients receiving extract of *A. muricata* compared to patients who did not receive it. Side effects were reported in 11% of patients (five patients) receiving *A. muricata* extract. Two of them mentioned burning pain in epigastrium, one was associated with nausea, and the remaining three reported nausea (Arroyo et al., 2009). Compounds responsible for the hypoglycemic activity found in the *A. muricata* leaf extracts could be flavonoids and alkaloids, which are present in the leaves and the fruit (Table 2).

Additional to the clinical study described above, two cases of anticancer evaluations have been reported (Hansra et al., 2014; Yap, 2013). In one of them, tumor markers showed that a breast cancer patient has been stable and had no side effects after therapy for 5 years (Hansra et al., 2014). Therapy consisted in taking 227 gm of leaves decoction of *A. muricata* (10–12 dry leaves in water for 5–7 min) daily and Capecitabina (2500 mg PO) 2 weeks on one week off (Hansra et al., 2014). The other case of study involves the disappearance of the malignancy with substantial regression of colon tumor cells in a patient who combined lifestyle modifications with the intake of some herbal extracts and nutraceuticals. The therapy included the daily ingestion of 5 g of powered leaf and seed of *A. muricata* extract (Yap, 2013).

5. Toxicology

Considerable information, both formal and informal, is available on the relation of the consumption of *A. muricata* with the appearance of an atypical Parkinson's disease (Caparros-Lefevre et al., 2002; Lannuzel et al., 2006). The toxicity reported for the extracts is variable depending on the plant part used, and the solvent employed (Table 5).

5.1. Acute toxicity

Aqueous extracts showed a LD_{50} > 5 g/kg, while methanolic and ethanolic extracts of leaves, flowers and pulp had a LD_{50} of > 2 g/kg (Sousa and Vieira, 2010), which are considered non-toxic according to the guidelines of OECD (http://www.oecd.org/chemicalsafety/testing/oecdguidelinesforthetestingofchemicals.ht). The median lethal dose of aqueous extract of leaves is above the expected consumption for a human, which is about 211 mg/kg per day, considering that an average person consumes one cup of tea three times per day (Arthur et al., 2011). Therefore, for a human to reach the lethal dose of consumption of soursop leaf infusion would require consuming more than 71 cups of tea a day. For toxicity in organs, Arthur et al. (2011) reported that doses greater than 5 g/kg of aqueous extract might cause kidney damage, unlike the 1 g/kg dose that showed hypoglycemic and hyperlipidemia properties. The most toxic extracts that have been reported are methanol extracts of pericarp, fruit pulp or seed (Boyom et al., 2011). *A. muricata* pulp consumed for 28 days showed no

Table 5 Neurotoxicity and mutagenicity of acetogenins and alkaloids of *A. muricata*.

Activity	Compound	Dose	Test model and results	References
Mutagenicity	Annonacin Squamocin	1000 µg/plate:	No mutagenic according Ames test	Guadaño et al. (2000)
Neurotoxicity	Coreximine	EC_{50}: 13 µM	Viability reduction of mesencephalic dopaminergic neurons	Lannuzel et al. (2003) and Hôllerhage et al. (2009)
	Reticuline	EC_{50}: 304 µM		
	Annonacin	EC_{50}: 0.018 µM		
	Annonacin	50 nM	Induced concentration-dependent neuronal cell loss, reduction brain ATP levels in rat striatal neurons cell	Escobar-Khondiker et al. (2007)
	Solamin	EC_{50}: 1210 nM	Viability reduction of rat striatal neurons cell	Hôllerhage et al. (2009)
	Annonacin	EC_{50}: 60.8 nM		
	Annonacinone	EC_{50}: 189.7 nM		
	Isoannonacin	EC_{50}: 121.3 nM		
	Annonacin	3800 and 7600 µg/kg for 28 days	Reduction brain ATP levels, neuronal cell loss and gliosis in the brain stem and basal locomotive ganglia in rats	Champy et al. (2004)
	Annonacin	7600 µg/kg/day for 28 days	Neurodegeneration in male Lewis rats	Lannuzel et al. (2006)

EC_{50}: Median effective concentration

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effect in blood hematology and serum biochemistry (Syahida et al., 2012). A study that evaluated the toxicity of crude leaf extract and its flavonoid and acetogenins enriched extracts shows that acetogenins-enriched extract was more toxic than others (Yang et al., 2015). This study suggested that whole extract could pose similar bioactive properties of its fractions or isolated constituents, but without their toxicity.

5.2. Neurotoxicology

The association of the consumption of fruit and homemade preparations of *A. muricata* with the appearance of atypical Parkinsonism in the Caribbean Island of Guadeloupe is based on a case study published in 1999 (Caparros-Lefevre et al., 2002). This association has also been reported in New Caledonia and Caribbean patients living in London (Shaw and Höglinger, 2008). From these studies, assessment of the neurotoxic effect of the main bioactive compounds of *A. muricata* alkaloids and acetogenins was initiated. It was evident that some of the isolated compounds induce neurotoxicity and neurodegenerative diseases in murine models (Table 5).

The reticuline and coreximine alkaloids and solamin, annonacinone, isoannonacinone and annonacin acetogenins were shown to be toxic to dopaminergic cells by impairing energy production (Escobar-Khondiker et al., 2007; Hôllerhage et al., 2009; Lannuzel et al., 2002, 2003, 2006). Annonacin toxicity was greater than the toxicity of the pesticide rotenone, which was used as a positive control. Champy et al. (2005) and Lannuzel et al. (2006) reported that in murine models annonacin enters the brain parenchyma, decreases ATP levels and induces neurodegeneration in the basal ganglia. According to these authors, this neurodegeneration induced no change in the behavior or locomotor activity in rodents.

Regarding the neurotoxicity, seven acetogenins have been evaluated using mesencephalic dopaminergic neurons, rat striatal neurons cells and laboratory rats (Table 5). Champy et al. (2005) reported that annonacin and reticuline, which are the most abundant acetogenin and alkaloid in *A. muricata*, respectively, are neurotoxic. Annonacin is about 1000 times more toxic for neuronal cell cultures than reticuline, and 100 times more potent than 1-methyl-4-phenylpyridinium (MPP), a known neurotoxin that causes Parkinsonism in humans and animal models. This study was conducted by administering isolated annonacin to laboratory rats intravenously. The amount administered to rats was determined by estimating the amount of annonacin a human would consume by ingesting fruit or canned nectar daily for one year. Neurotoxicity studies of annonacin suggest that there is a need for a long exposure to this molecule to observe the effect in murine models, while pharmacokinetic studies estimated low bioavailability of this compound. In this regard, AVIS (l'Agence Francaise de Sécurité des Aliments) in 2010 issued a statement which concluded that on the basis of available experimental data, it is not possible to say that cases of atypical parkinsonian syndromes observed in Guadeloupe are linked to consumption of species belonging to Annonaceae family.

6. Conclusions

A. muricata is widely used in traditional medicine to treat illness such as diarrhea, dysentery and fever, pain, respiratory and skin illness, internal and external parasites, bacterial infections, hypertension, inflammation, diabetes and cancer. Decoctions of bark, root, seed or leaf are the most widely used preparations. *In vitro* and *in vivo* studies support the majority of the traditional uses but lack clinical validation. Among the traditional uses that have not shown scientific validation yet are the effectivity in treating respiratory tract, heart and kidney affections, treatment to animal bites and stings, and obesity treatments.

More than 200 phytochemicals have been identified in this plant, mainly acetogenins, alkaloids and phelos. These phytochemicals have shown pharmacological activities such as antimicrobial, antiprotozoan, antioxidant, insecticide, larvicide, selective cytotoxicity to tumoral cells, anxiolytic, anti-stress, anti-ulceric, wound healing, anti-icteric, hepatoprotective, and hypoglycemic. New phytochemicals are been identified in soursop.

Mechanisms of action of the plant extracts and phytochemicals have been proposed. Cytotoxicity implies the disruption of mitochondrial membrane to arrest cells in G0/G1 phase, and the induction of apoptosis, the inhibition of multiple signaling pathways that regulate metabolism, induction of metastasis and necrosis of cancer cells. Mechanism of action of antioxidant activity is by hydrogen donation, while antimicrobial action is because of some phytochemicals having the ability to bind with DNA and inhibiting RNA synthesis and by glycosidase inhibition lacking cytoplasmatic membrane function. Mechanisms of action of antinociception may be by inhibition of cyclooxygenase and lipoxygenase enzymes and other inflammatory mediators. Hypotensive mechanism is thought to be through the blockage of calcium ion channel. Mechanisms of action of other bioactivities have not been completely elucidated, such as anxiolytic, antistress and hypoglycemic activities.

Some phytochemicals, such as acetogenins, have shown neurotoxicity *in vitro* and *in vivo* studies. More research is needed to quantify the amount of neurotoxic compounds and to determine the level of human exposure. Metabolic studies are also necessary to determine whether digestive processes decrease or increase bioactivity and/or neurotoxicity of the active compounds. These studies have been extended to whole extract used in medicinal treatments.

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