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A.M. Quílez, M.A. Fernández-Arche, M.D. García-Giménez, R. De la Puerta

PII: S0378-8741(18)31967-6
DOI: https://doi.org/10.1016/j.jep.2018.06.014
Reference: JEP11403

To appear in: *Journal of Ethnopharmacology*

Received date: 30 May 2018
Accepted date: 14 June 2018

Cite this article as: A.M. Quílez, M.A. Fernández-Arche, M.D. García-Giménez and R. De la Puerta, Potential therapeutic applications of the genus *Annona* Local and traditional uses and pharmacology, *Journal of Ethnopharmacology,* https://doi.org/10.1016/j.jep.2018.06.014

Potential therapeutic applications of the genus *Annona:* Local and traditional uses and pharmacology.

Quílez, A.M., Fernández-Arche, M.A. García-Giménez, M.D., De la Puerta, R.*

Pharmacology Department, School of Pharmacy. Seville University. C/Profesor García González, 2; 41012. Sevilla. Spain

***Corresponding autor:** De la Puerta R.;Tel.: +34(9)54566722 , puerta@us.es

Abstract

Ethno-pharmacological relevance:
Annona species (*Annonaceae)* have long been used as traditional herbal medicines by native peoples in tropical areas. In different countries they are used against a large variety of illnesses, such as parasitic and infectious diseases, cancer, diabetes, peptic ulcers, and mental disorders.

Aim of the study:
This review aims to achieve a comprehensive understanding of the research conducted so far on the local and traditional uses, pharmacological activities, mechanism of actions of active compounds, toxicity, and possible interactions with other drugs of the *Annona* species. Through analysis of these findings, evidences supporting their applications in ethno-medicines are described. We discuss the possible research opportunities and stand out the weak points in our knowledge that deserves further investigation.

Material and methods:
Information on ethno-medicinal uses and pharmacological activities of the *Annona* genus was collected. The main scientific biomedical literature databases (Cochrane, PubMed, Scopus, Lilacs, SeCiMed, Elsevier, SpringerLink, Google Scholar, SciFinder) were consulted. The search covered all the literature available until September 2017. National and regional databases of Herbal Medicine and Complementary and Alternative Medicine were also revised in order to explore further data. For a better understanding of the therapeutic importance of these species, we have classified the pharmacological activities within each group of disorders. The International Classification of Diseases (ICD), used from WHO Member States, was chosen as the reference classification.

Results:

From among the 27 species revised, four species are highlighted for their important pharmacological activities in most of the groups of illnesses: *A. muricata, A. squamosa, A. senegalensis,* and *A. cherimola*. Many investigations have been performed with extracts from the leaves, bark, fruit and seeds and have shown a wide range of pharmacological activities, such as antiprotozoal, antitumoural, antidiabetic, hepato-protective, anti-inflammatory and anxiolytic activities. The chemistry on the annonaceous acetogenins (ACGs) has been extensively investigated due to their potent antitumoural activity. Many of the assays were carried out with the isolated acetogenins in different lines of tumour culture cells and were found effective at very low doses even in multidrug-resistant tumours, and hence constitute promising compounds in the treatment of different types of cancers. No studies were found with extracts rich in acetogenins in the clinical field.

Conclusions:

The experimental results from the pharmacological research enable the validation of their traditional uses in several of the groups of diseases in the countries of origin and reveal these plants to be a valuable source for therapeutic molecules. However, more toxicity assays and clinical trials would be necessary to establish optimal and safe doses of consumption on the application of these medicinal plants.

Abbreviations

ABTS: 2,2-Azinobis-3-Ethylbenzothizoline-6-Sulphonate; ACGs: Acetogenins; AEF: Acetogenin-Enriched Fraction; ATP: Adenosine Triphosphate; COX: Cyclooxygenase; CYP: Cytochrome P450; DNA*:* Deoxyribonucleic Acid; DPPH: 1,1-Diphenyl-2-Picrylhydrazyl; EC_{50}: Effective Concentration 50; $ED_{50:}$ Effective Dose 50; EEG*:* Electroencephalogram; EU-SA: Ethnomedicinal Use and Significant Activity; FAME: Fatty Acid Methyl Esters; FEF: Flavonoid-Enriched Fraction; GABA: Gamma-aminobutyric Acid; GC-FID: Gas Chromatography-Flame Ionization Detector; GC-MS: Gas Chromatography-Mass Spectrometry; GLE: Graviola Leaves Extract; HPLC-MS: High-performance Liquid Chromatography-mass Spectrometry; HT: Hydroxytryptamine; IC_{50}: Inhibitory Concentration 50; ICD: International Classification of Diseases; LC_{50}: Lethal Concentration 50; LD_{90}: Lethal Dose 90; LPS: Lipopolysaccharide; MIC: Minimum Inhibitory Concentration; MPO: Myeloperoxidase Enzyme; MTT: 3-(4,5-diMethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NADH: Nicotinamide Adenine Dinucleotide; NCI: National Cancer Institute; NIH: National Institute of Health: NO: Nitric Oxide; ORAC: Oxygen Radical Absorbance; PAF: Platelet Activating Factor; PMA: Phorbol Myristate Acetate; Ppm: Parts per million; RCT: Randomized Double-Blind Placebo-Controlled Pre-Post-Trial; SA: Significant Activity; SAR: Structure–Activity Relationship; Syn.: Synonym; T&CM: Traditional and Complementary Medicine; Taas: Total annonaceous

acetogenins; THF: Tetrahydrofuran; TPA: 12-O-Tetradecanoylphorbol-13-acetate; WHO: World Health Organization

Key words:

Annona species, *Annonaceae*, ethno-medicinal uses, pharmacology, acetogenins, toxicity, interactions.

1. INTRODUCTION

Traditional systems of medicine offer a large number of plants with various medicinal and pharmacological relevancies and hence represent a valuable source of new bioactive molecules (Mishra et al., 2013). To integrate phytopharmaceuticals into basic healthcare, it is necessary to use and scientifically authenticate herbal products of a more medicinally useful nature (Heinrich, 2007).

The recent publication of the *WHO Traditional Medicine Strategy* 2014-2023, describes the course for Traditional and Complementary Medicine (T&CM) in the next decade (WHO, 2013) and shows important considerations regarding the need for integration of traditional medicine into public health systems. Among these considerations, we highlight the increasing demand on public healthcare services and the need for contributions to ensure that all people have access to care.

On the other hand, major changes in the lifestyle of the population have caused certain chronic diseases to increase, such as cardiovascular diseases, metabolic syndrome, diabetes mellitus, and cancer. In industrialized and developing countries, these illnesses have reached epidemic proportions. Gastrointestinal disorders, allergy and inflammatory disease processes cause discomfort and reduce the quality of life. The socio-economic implications of these ailments, such as the high cost for public health systems, are cause for concern (Barbalho et al., 2012a).

The *Annona* species have been used as a natural medicine by native people of various cultures for a wide variety of illnesses. There are a large number of studies on pharmacological activities of this genre in literature. Different parts of the species are used, however leaves and seeds have long-established uses, including applications against parasites, inflammatory processes, diabetes and cancer (Lim, 2012), (Mishra et al., 2013). Those species commanding a large number of studies can be highlighted: *A.muricata, A.squamosa, A. cherimola, A.senegalensis, A.montana, A.glabra, A.crassiflora*, *A.reticulata, and A.coriacea*.

Many bioactive compounds and phytochemicals have been identified. The main specific class of constituents of the *Annona* species are acetogenins (ACGs) extensively investigated for their antitumoural effects. Acetogenins also exhibit immunosuppressive, pesticidal, antiprotozoal,

antimicrobial, antimalarial, anthelmintic, and antiviral effects and have successful applications and commercial products for the treatment of oral herpes and treating infestations of head lice, fleas and ticks (Asare et al., 2015; Barbalho et al., 2012a). Furthermore, alkaloids, essential oils, flavonoids, and terpenoids, among others, have been reported as contributing towards several of the detected pharmacological activities of these species (Barbalho et al., 2012a).

In this review, we have carried out a revision of the local medicinal uses and the pharmacological activities of the species of the genus *Annona*, according to the following criteria:

- To evaluate whether traditional assertions of Annona species have been validated scientifically by pre-clinical and clinical studies.
- To evaluate whether modes of action of extracts and fractions of Annona species have been established.
- To evaluate whether Annona species have been investigated for acute and chronic toxicity studies and possible interactions.

The main databases of scientific biomedical literature (Cochrane, PubMed, Scopus, Lilacs, SeCiMed, Elsevier, SpringerLink, Google Scholar, and SciFinder) were consulted. The search covered all the literature available until September 2017. The inclusion criteria were that these studies were from SCI journals derived from including preliminary keywords such as *Annona,* local and traditional uses, pharmacological activities, and chemical constituents; subsequently, we used the appropriate keywords for each activity, chemical compound, and mechanism of action or diseases. Studies with no specified information on a particular *Annona* species or for veterinary or agriculture uses were excluded, as were those that failed to meet the quality criteria required in pharmacology studies. Finally, more than 300 papers were selected for inclusion in this review. National and regional databases of Herbal Medicine and Complementary and Alternative Medicine were also revised in order to explore further data. Tertiary scientific sources, such as Pharmacopoeias, books, thesis, and technical reports, were also investigated and compared with pertinent information.

2. Botanical and biogeographical aspects

The *Annonaceae* family has 112 genera and approximately 2,500 species (Mabberly, 1997) dispersed around the planet. The majority of these species are found in the tropics although a few exceptions are found growing in temperate zones. This family includes trees, bushes and lianas divided into two large subfamilies: Annonoidae, which comprises the *Annona, Guatteria, Xylopia, Uvaria, Artabotrys,* and Monodoridae genera, which in turn includes the genera *Isolona* and *Monodora*. Only a few of the species produce edible fruits, which are mainly found in wild species, although certain species have been cultivated.

There are about 119 species described in the genus *Annona,* of which about 109 are local from tropical America and 10 from tropical Africa. All the cultivated species are American, with the exception of *A. senegalensis* which is African (Geurts, 1981; Pinto et al., 2005). On the southeast coast of Spain (Granada and Málaga), *A. cherimola* is cultivated for food purposes. This country is the world's first commercial producer of *A. cherimola* fruit (Gonzalez, 2013).

In relation to its botanical characteristics, the *Annona* species are shrubs or small trees, of 5 to 11 m in height depending on various factors, such as species, climate, type of soil, and crop managing. They are moderately erect and often spread naturally with grey-brown bark which is frequently rough or furrowed. Generally, *Annona* stems are ferruginous to greyish, and tomentose when young but later becoming glabrous (León, 1987).

3. Pharmacological activities and local and traditional uses

The long list of the ethnomedicinal uses for this genus identified through pharmacological research is shown in Tables 1-5. The information covered includes the *Annona* species, local name, biographical distribution, part used, pharmacological activity and compound or extract evaluated with the references. The pharmacologically validated uses have been emphasized. References are given in the column of the table where pharmacological activities are described. In the column where the information on compounds or extracts is presented, references are only included when it is a phytochemical report. All the species names in the tables are validated taxonomically with the exception of *A. cuneata* and *A. diversifolia*, since this is how they are denominated in all the research work (their accepted names are also included in the table). The accepted synonyms of all the species are likewise included.

To enable a clearer understanding of the therapeutic importance of these species, they have been classified according to their pharmacological activities into different groups of diseases, which are presented in Table 6. The International Classification of Diseases (ICD) used by the WHO Member States was chosen as the reference classification system (ICD-10, 2016). For each of these classes, the species that have shown a significant pharmacology activity are highlighted in the column called SA (significant activity), while in the column denominated EU-SA (ethnomedicinal use and significant activity) are those that have validated their traditional use, in addition to their pharmacological activities. These species in this column are those which could provide a source of most immediate phytomedicines.

3.1. Infectious and parasitic diseases

3.1.1. Antifungal: *A. glabra* L., *A. coriacea* Mart., *A. cornifolia* A. St-Hil. and *A. crassiflora* Mart.

Ethanol extracts of the leaves of *A. crassiflora* and *A. coriacea* were tested against 52 strains of *Candida albicans*. The *A. crassiflora* was effective against all the microorganisms and showed the greatest antifungal effect. Methanol extracts from *A. cherimolia,* also manifested the strongest action against *Candida albicans* and other dermatophytes (*Trichophyton mentagrophytes* and *Trichophyton rubrum*) (Silva et al., 2001; Navarro-García et al., 2003).

In the case of *A. cornifolia,* the fatty acid methyl esters (FAME) isolated from its seeds were active against 12 clinical strains of the pathogenic fungus *Paracoccidioides brasiliensis* and were also effective in the bioautographic assay against *Cladosporium sphaerospermum* (Lima et al., 2011).

3.1.2. Antimicrobial: *A. ambotay* Aubl.*, A. chirimola* Mill.*, A. diversifolia* Saff.*, A. glabra* L.*, A. muricata* L.*, A. pickelii* (Diels) H. Rainer*, A. salzmannii* A. DC.*, A. senegalensis* Pers.*, A. squamosa* L.*, A. vepretorum* Mart.

A. squamosa is the most studied species among the group. By disc diffusion method an extract of this plant was shown to be active against *Neisseira gonorrhoeae* clinical isolated and World Health Organization (WHO) strains (Shokeen et al., 2005). Besides, a recent research identified potential applications for this species in the treatment and prevention of foodborne bacterial diseases (Dholvitayakhun et al., 2012; 2013).

The essential oils from the leaves of three species from the northeast of Brazil, *A. pickelii, A. salzmannii* and *A. vepretorum*, have shown antioxidant, antimicrobial and lavicidal activities. They were analyzed by GC-MS and GC-FID and sesquiterpenes were predominatly identified in their composition (Costa et al., 2011a, 2012; Di stasi and Akiko, 2002; Paulo et al., 2002)*,* what supports the use of these plant in the original countries.

A. muricata pods aqueous extract was active against *S. aureus* and *V. cholera* (Vieira et al., 2010; Di stasi and Akiko, 2002). On the other hand, *A. senegalensis* showed noteworthy antidiarrhoeal properties in-vivo and in-vitro models (Suleiman et al., 2008), in addition to the antimicrobial activity (Okoye et al.,2012; More et al., 2008; Magassouba et al., 2007; Lino and Deogracious, 2006).

Table 1. Pharmacological activities and local and traditional uses of *Annona* species

Specie taxa ***Annona***	Local name	Biogeographical distribution	Used part	Traditional Use	Pharmacological activity	Extract/compound evaluated
ambotay Aubl. **Syn.** *ambotay* subsp *occidentalis* R.E.Fr	Pinaioua, enviratataia	Southamerican tropical rain forest	Trunkwood	Febrifuge (French Guaiana)	Antimicrobial. Takahashi et al. (2006), Sandoval et al. (2002), Di Stasi and Akiko, (2002), Grenand et al.	Alkaloids De Oliveira et al. (1987). Ethanol and benzene extract Flavonoids

				(1987).		
x atemoya Mabb.	Pinnaple sugar apple, anón, chirimorinón, manzana dulce	Australia, Formosa, Palestina, cultivated in Tropics	Seed	Antitumoural. Selective cytotoxicity (HepG2). (Yi et al. 2014), Chiu et al. (2003), Chih et al (2001).	ACG Bullatacin Alkaloid Tryptamine-derived amides. Wu et al. (2005). Ethanolic extract	
bullata A. Rich.		Endemic of Cuba	Bark	Antitumoural. Selective cytotoxicity (HT-29, A-549, MCF-7/wt, MCF-7/Adr). Lim, (2012), Ram and Kumari, (2001), Gu et al. (1993, 1994, 1995), Hui et al. (1989, 1990, 1992).	THF ACGs (2, 4-cis and trans-32-hydroxybullatacinone [1 and 2], 2, 4-cis and trans-31-hydroxybullatacinone [3 and 4], 2, 4-cis and trans)-30-hydroxybullatacinone [5 and 6], bullatacin, bullatacinone). Diterpene 16 alpha-hydroxy-(-)-kauranoic acid. Ethanolic extract. ACGs (32-hydroxybullatacin, 31-hydroxybullatacin, 30-hydroxybullatacin, 2,4-cis and trans-28 hydroxybullatacinone, bullatencin, 4-deoxyasimicin, uvariamicins). Isoquinolin alkaloids (R)-annonain, liriodenine. Sandoval and Helmut, (1986).	

ACGs: Acetogenins; THF: Tetrahydrofuran; **Syn.:** Synonym

Table 1.Cont.

Specie taxa ***Annona***	Local name	Biogeographical distribution	Used part	Traditional Use	Pharmacological activity	Extract/compound evaluated
coriacea Mart. **Syn.** *coriacea* var.: *amplexicaulis*	Araticum, marolino, marolo	Brazilian cerrado and caatinga	Leaf Root Seed	Anti-helmintic Chronic diarrheia Inflammation Leishmani	Antifungical. Silva et al. (2001). Antiinflammatory. Coelho et al. (2006).	ACGs (annoheptocins A-B, coriacyclodienin, coriacycloenin).

S. Moore *cuneata* R.E.Fr. *pygmaea* Warm.				asis Malaria Rheuma	Antitumoural. Selective cytototoxicity (cell lines: VERO and KB). Meneses da Silva et al. (1996). Insecticidal. Coelho et al. (2007). Leishmanicid al. De toledo et al. (2011), Siqueira et al. (2011). Trypanocidal. Siqueira et al. (2011).	Silva et al. (1997a, 1997b, 1996). Crude extracts 14-kDa lectin. Coelho et al. (2003). Diterpenoid 9ß H-pimaradienic Onan and Mcphail, (1978). Essential oils Sesquiterpens (Bicyclo-germacrene), monoterpenes (β-pinene, pseudolimonene). Ethanol extracts ACGs (coriacin, 4-deoxycoriacin, coriaheptocins A-B, coriadienin, gigantecin), terpenoids (3-4 hardwickiico dihydro acid, annonalide, podocarp-7-en-6- ß-lacton).
cornifolia A. St-Hil. **Syn.** *walkeri* S. Moore		Bolivian and Brazilian savannah	See d	Antiulcerative (green fruit)	Antifungical. Lima et al. (2011). Antioxidant. Lima et al. (2010). Cytotoxic. Lima et al. (2009).	ACGs (9-hydroxyfolianin, folianin B, asimicin, bullatacin). Ethanol extract Fractions and pure ACGs. Fatty acid methyl esters (FAME)
crassiflora Mart. **Syn.** *macrocarpa* Barb. Rodr. *rodriguesii* Barb. Rodr.	Araticum-mirim	Brazilian Cerrado	Leaf Root bark Root wood	Analgesic Antimicrobial Antirheumatic Carminative Digestive Edible fruit	Antiinflammatory. Chemopreventive Rocha et al. (2015). Antimicrobial Takahashi et al. (2006). Antifungical	ACG Araticulina

			Seed	Inflammation	Silva et al. (2001), Lima and Farias, (1999). Larvicidal De Omena et al. (2007), Rodrigues et al. (2006). Molluscicidal. Dos Santos and Sant´Ana, (2001).

Table 1.Cont.

Specie taxa ***Annona***	Local name	Biogeographical distribution	Used part	Traditional Use	Pharmacological activity	Extract/compound evaluated
cuneata (Oliv.) R.E. Fr. **Aceppted name** *stenophylla* subsp. *cuneata* (Oliv.) N.Robson		Congo	Root bark Stem bark	Asthenia Female sterility Hernia Parasitic infections Venereal diseases.	Antioxidant Khallouki et al. (2011).	Essential oils Khallouki et al. (2002). Methanol extract Phenolic compounds
densicoma Mart.	Jaca-do-mato, graviola-do-mato	Amazonia (Brazil, Peru, Venezuela), Guyana, French Guyana, Surinam	Leaf Stem bark		Antitumoural. Selective cytotoxicity Ho et al. (1992), Cassady et al. (1990), Xu et al. (1989), McCloud et al. (1987).	Aqueous/methanol fraction Dicloromethane Extract Essential oils Andrade et al. (2007). Ethanol crude extract Polyketides (annonacin-10-one, isoannonacin, isoannonacin-10-one). Ethanol extract Linear polyketides (10, 13-tram-13,14-erythro-densicomaci, 10,13-tram-13, 14-threo-densicomacin, 8-hydroxyannonacin, annonacin goniothalamicin).
dioica A. St.-Hil. **Syn.** *dioica* var. *mattogrossensis* R.E.Fr.		Cerrado, Pantanal (Brazil)	Leaf	Diarrhea Rheumatism	Antioxidant, hypoglycaemic, antiproliferative, anti-inflammatory Formagio et al. (2013a).	Crude methanol extract Ethyl acetate fraction Flavonoids Hydromethanol fraction
diversifolia Saff. **Aceppted name** *macroprophyl*	Ilama, papausa, white anona, yi ye fan li zhi	Tropical forest of Mesoamerica, China	Leaf Seed	Arthritic pain Anti-spasmodic	Anticonvulsant (González-Trujano et al. 2006b, 2001,).	ACGs (laherradurin, cherimolin-2). Alkaloidal

lata Donn.Sm.					Antinociceptive Carballo et al. (2010). Antitumoural. Selective cytotoxicity (HeLa, SW-480) Schlie-Guzmán et al. (2009). Antifungical De la Cruz-Chacón et al. (2011). Antimicrobial Luna-Cazares and Gonzalez-Esquinca, (2010). Anxiolytic González-Trujano et al. (2006a). Neuroprotective Cano-Europa et al. (2010).	extracts Aporphine alkaloids Liriodenine Ethanol crude extract Hexane and acetone fractions (palmitone and flavonoids). Hexanic extract. ACG Rolliniastatin-2

Table 1. Cont.

Specie taxa ***Annona***	Local name	Biogeographical distribution	Used part	Traditional Use	Pharmacological activity	Extract/compound evaluated
glauca Schumach.& Thonn. **Syn.** *glauca* var. *minor* Robyns & Ghesq.	Dangan, mampihege, mandé sunsun, tangasu	West Tropical Africa (Senegal, Ghana) and Suriname	Root Seed	Arachnicides Blennorrhoea Diuretic Fish-poisons Insecticides	Leishmanicidal Trypanocidal Waechter et al. (1998).	Cyclic peptides Glaucacyclopeptide A, B. Wélé et al. (2006, 2005).
haematantha Miq.		Southamerican tropical rain forest	Root	Febrifuge	Leishmanicidal Waechter et al. (1997).	Hexanic extract α, β-unsaturated delta-lactone (argentilactone).
hypoglauca Mart. **Syn.** *tessmannii* Diels		Southamerican tropical rain forest			Antitumoural. Selective cytotoxicity (MCF-7). Suffredini et al. (2007).	Aqueous or organic extract

jahnii Saff. **Syn.** *Guaricensis* Pittier		Cerrado (Brazil) and Amazonia (Brasil, Venezuela)	Twig		Antitumoural. Selective cytotoxicity (A-549, A-498, HT-29, MCF-7, PC-3, PACA-2). Colman-Saizarbitoria et al. (1998).	ACG Annojahnin
montana Macfad. **Syn.** *montana f. marcgravii* (Mart.) Porto	Mountain soursop, shan di fan li zhi, false graviola, araticum grande, jacá do Pará,	Southamerican tropical rain forest, Southern Asia, Amazonia, Mata Atlántica, Pantanal	Leaf Pulp juice Seed Stem Twig	Against snake bite Against obesity	Anti-inflammatory Chuang et al. (2008). Antiplatelet aggregation Giulietti, (2006). Antitumoural. Selective cytotoxicity (hep2, 1A9). Alvarez Colom et al. (2009), Liaw et al. (2004, 2005), Wang et al. (2000, 2001), Mootoo et al. (2000), Wu et al. (1995a), Jossang et al. (1991). Hipoglycaemic, hipolipidemic Barbalho et al. (2012b).	Acid amide N-trans-caffeoyltyramine. Alkaloids Ethanolic and methanolic extract Cyclopeptides (cyclomontanins A-D, annomuricatin C, (+)-corytuberine). Mono-THF ACGs (tucupentol, montalacins A-J, cis-annoreticuin, molicin A-B, anmontanins A-C, montanacins B-E-G-H-J, 34-epi-montanacin H-J, annomonysvin). Lignans Linear ACGs Monhexocin 5-6 Terpens

Table 1.Cont.

Specie taxa ***Annona***	Local name	Biogeographical distribution	Used part	Traditional Use	Pharmacological activity	Extract/compound evaluated
pickelii (Diels) H. Rainer **Syn.** *Rollinia pickelii* Diels		Brazil	Leaf		Antioxidant, antimicrobial, larvicidal (*Aedes aegypti*) Costa et al. (2011).	Essential oils Sesquiterpens (bicyclogermacrene, E-caryophyllene, delta-cadinene, α-copaene, α-humulene, allo-aromadendrene).
purpurea Moc. & Sessé ex Dunal **Syn.** *involucrata* Baill. *manirote* Kunth prestoei Hemsl.	Sincollo, soncoyo	Mesoamerica (Mexico, Caribbean, Central America, Venezuela, Colombia, Belize), Formosa	Leaf Root Stem Seed		Antitumoural and trypanocidal Costa et al. (2013). Antiplatelet aggregation Chang et al. (2000), Chang et al. 1998a, 1998b).	Bis-THF ACGs (purpuracenin, purpurediolin, purpurenin). Aporphine alkaloids 7-Dehydroaporphine alkaloids. Pyrimidie- β-carboline alkaloid. Annomontine.
reticulata L.	Bullock's-heart, custard-apple, anona blanca, anona, niiu xin fan li zhi	Tropical forest of Meso and Southamerica, Southern Asia, Africa, Madagascar	Aerial parts Bark Fruit Leaf Root Seed Stem bark	Anticonceptional Blood dysentery Cold Estomach each Fainting spinal disorders. Fever Hysteria Influenza Mental depression Skin diseases Unhealthy ulcers Wounds	Anxiolytic. Rejón-Orantes et al. (2011). Antitumoural. Selective cytotoxicity Camacho et al. (2003), Chavez and Mata, (1998, 1999), Soneto and Jacobson, (1971). Trypanocidal. Camacho et al. (2003).	Aqueous and Metanolic extract Metanolic extract Alkaloids (promucosine, romucosine F, romucosine G) Oxoaporphines ACGs (annonacin, annoreticuin, annoreticuin-9-one, bullatacin, squamocin, cis-/trans-bullatacinone, cis-/trans-murisolinon, rolliniastatin I-2, solamin, annomonicin). Tam et al. (1993).
.					Antibacterial. Antidiabetic. Antiovulatory Jamkhande and Wattamwar, (2015), Chavan et al. (2014), Pathak and Zaman, (2014), Antihelmintic activity Chavan et al. (2014), Jamkhande and Wattamwar, (2015). Anti-inflammatory, analgesic, SNC depressant activity Jamkhande and Wattamwar, (2015), Chavan et al. (2012, 2014).	Alkaloids Tetrahydroisoquinoline Alkaloid. Aminoacyl triesters of squamocin 1 Aqueous and ethanolic extracts Essential oils (camphene, α-copaene, β-elemene, β-caryophyllene, β-bisabolene, δ-cadinene germacrene D). Gamma-lactone ACG Cis-/trans-isomurisolenin Isoflavonoids and flavonoids Kaur-16-en-19-oic acid Sesquiterpene fraction (copaene, patchoulane, 1H-cycloprop (e) azulene). Triterpenoid Annonaretin A

					Antioxidant Thang et al. (2013b), Baskar et al. (2007). Antypiretic (Jamkhande and Wattamwar, 2015)- Antitumoural. Selective cytotoxicity (Caco-2, Hep G2, T24, KB 3-1,) Jamkhande and Wattamwar, (2015). Suresh et al. (2011), Duval et al. (2005), Yuan et al. (2003, 2006), Chang et al. (1993, 1998c), Cassady et al. (1990) Antiulcer Jamkhande and Wattamwar, (2015). Cardiotonic activity Insecticidal. Postcoital Antifertility Pathak and Zaman, (2014).	

Table 1. Cont.

Specie taxa ***Annona***	Local name	Biogeographical distribution	Used part	Traditional Use	Pharmacological activity	Extract/compound evaluated
salzmannii A. DC.		Brazil	Bark Leaf		Antioxidant, antimicrobial and larvicidal (Aedes aegypti) Costa et al. (2011), Di Stasi and Akiko, (2002), Paulo et al. (1992). Antitumoural and trypanocidal Costa et al. (2013).	Benzylisoquinoline alkaloids (reticuline, anonaine, laurelliptine, isoboldine). Essential oils. Sesquiterpens (α-copaene, δ-cadinene, germacrene D, (E)-caryophyllene, bicyclogermacrene).

sclerophylla Saff. **Syn.** *sulcata* Urb.	Endemic of Cuba	Leaf Stem	Antimicrobial Sandoval et al. (2002).	Organic extracts. Alkaloids (isocorypalmin, liriodenin), (-)-kaur-16-en-19-oic acid, (-)-kauran-16a-o1 (AU).
spinescens Mart.	Brazil	Trunk bark Roots	Cytotoxic, leishmanicidal, trypanocidal Giulietti, (2006), Queiroz, (1996).	Metanolic extract. ACGs (araticin, almunequin, bullatanocin, carolins -A-B-C, desacetiluvaricina, isodesacetiluvaricina, neoannonina, squamocina, squamocina-K,spinescina), alcaloids (anonaina bracteolin, norbracteolin, liriodenin, nordomesticin, norosin-shunin, pessoin, reticulin, spinosin, stepharin). Queiroz et al. (1996, 1998).
spraguei Saff. **Syn.** *uncinata* Sprague	Tropical forest of Mesoamerica	Seed	Mitochondrial complex I inhibitory Gallardo et al. (1998). Leishmanicidal Rocha et al. (2005).	Chloroform extract Nitrogenated ACGs 10-Oximeguanacone
sylvatica A. St.-Hil. *Syn.* *Rollinia sylvatica (A. St.-Hil.) Martius*		Leaf	Anti-inflammatory, antitumoural Formagio et al. (2013b).	Essential oils Sesquiterpenes (hinesol, z-caryophyllene, β-maaliene, γ-gurjunene, ledol, silphiperfol-5-en-3-ol, cubecol-1-epi muurola-3,5-dien).
vepretorum Mart.		Leaf	Antimicrobial, trypanocidal Costa et al. (2012).	Essential oils (bicyclogermacrene, spathulenol, alpha-felandrene, ȧ-pinene, (E)-β-ocimene, germacrene D, p-cymene).

Table 2. Pharmacological activities and local and traditional uses of *Annona cherimola* Mill.

Specie taxa ***Annona***	Local name	Biogeographical distribution	Used part	Traditional Use	Pharmacological activity	Extract/compound evaluated
cherimola Mill.	Cherimola, cherimoya, chirimoya, custard apple, mao ye fan li zhi	Tropical America and Asia, Gabon, cultivated in Spain and Australia	Aerial parts Fruit Leaf Root Seed Stem	Abortion Anti-anxiety Bronquitis Cough Diarrheia Flu Hypercholesterolemia Infections Intestinal diseases Painful inflammations Parasitic Tranquilizing Twist Ulcers	Antidepressant Martinez-Vazquez et al. (2012). Antifungical Navarro-García et al. (2003). Antimicrobial Takahashi et al. (2006). Antiprotozoal (*E. Histolytica, G. Lamblia*) Calzada et al. (2006). Antitumoural. Selective cytotoxic (KB, MIA PaCa-2, PC-3, HT-29, MCF-7, A-498). De Pedro et al. (2013), Quispe et al. (2009), García-Aguirre et al. (2008), Barrachina et al. (2004), Wélé et al. (2004), Son et al. (2003), Kim et al. (2001a, 2001b), Woo et al. (1999a, 1999b). Antihypercholesterolemic Falé et al. (2013). Antiulcerative Castillo-Juarez et al. (2009). Antiviral Betancour-Galvis et al. (1999). Anxyolitic Lopez-Rubalcava et al (2006). Insecticidal. Alvarez Colom et al. (2010). Vasodilatador Chuliá et al. (1995a, 1995b).	ACGs (aporphine, itrabin, molvizarin, squamocin, mixture of epimers). Bis-tetrahydrofuranic ACGs (cherimolin-1, motrilin, aherradurin, tucumanin). MonoTHF ACGs (cis-annonacin and the mixture of (2,4)-cis-and trans-isoannonacins). Aqueous extract Alkaloid extract Alkaloids (roemerine anonaine, dehydroroemerine). Cyclic heptapeptide Cherimolacyclopep-tide C. Ethanolic extract Mono THF ACGs (annomolin annocherimolin, annomocherin, annonacin, annomontacin). Hexanic extract Palmitone, beta-sitosterol, beta-cariophyllene, beta-selinene, alpha-cubebene, linalool. Methanol Extract Cyclic heptapeptide (cherimolacyclo-peptide C), THF ACGs (annocherin and a mixture of (2,4)-cis-and trans-annocherinone

s).

.ACGs: Acetogenins; THF: Tetrahydrofuran; **Syn.:** Synonym

Table 3. Pharmacological activities and local and traditional uses of *Annona muricata* L.

Specie taxa ***Annona***	Local name	Biogeographical distribution	Used part	Traditional Use	Pharmacological activity	Extract/compound evaluated

muricata L. **Syn.** *muricata var. borinquensis* Morales *muricata* f. *mirabilis* R.E.Fr.	Brazilian pawpaw, soursop, guanábana, graviola, araticum grande, catuche, Ci Guo Fan Li Zhi, Mullu Raama Phala, corossol.	Tropical forest of Meso-America, Asia and Africa	Bark Fruit, Leaf Root Root bark Seed Stem bark	Ailments Antihelmintic Antiscorbutic Asthma Antispasmodic Bedbugs. Cancer Cough Cystitis Dermatosis Diabetes Diuretic Eczema Emetic Febrile seizures Headaches Head lice Hematuria Hypertension Inflammation Rheumatism Insomnia Lactation Livers disorders Neuralgia Parasitic infections Rash Ring worm Skin ruptions Sudorific Tonic Toothache Urethritis	Anti-arthritic Chan et al. (2010). Antidepresssant, sedative, antistress Hasrat et al. (1997), Padma et al. (1997). Anticonvulsivant (N'gouemo et al. 1997). Antidiabetic. Moghadamtousi et al. (2015a), Florence et al. (2014), Karou et al. (2011), Adeyemi et al. (2010), Adeyemi et al. (2008). Anti-inflammatory Ishola et al. (2014), Chan and Roslida, (2012). Anti-hyperglycemic Adeyemi et al. (2008). Antimicrobial. Vieira et al. (2010), Di Stasi and Akiko, (2002). Antinociceptive Moghadamtousi et al. (2015a), De Sousa et al. (2010), Roslida et al. (2012, 2008). Antimalarial Moghadamtousi et al. (2015a), Mohd Abd Razak et al. (2014). Antileishmanial, trypanocidal Vila-Nova et al. (2013, 2011), Osorio et al. (2007), Jaramillo et al. (2000). Antioxidant. Moghadamtousi et al. (2015a), George et al. (2015), Gavamukulya et al. (2014), Nawwar et al. (2012), Correa Gordillo et al. (2012), Baskar et al. (2007). Anti-	ACGs 10 different groups (cis-annonacin, muricins A-G, muricatretocin A –B, longifolicin, corossolin, corossolone, solamin, muricin H, muricin I, cis annomontacin, murisolin, annomutacin, annocatacin A-B, muricatocins A-C, annomuricins C and E, annomuricin C, annohexocin, murihexocin A-C, muricoreacin, muricapentocin, gigantetrocin A, annopentocins A-C, cis and trans annomuricin-D-ones, 2,4-trans and cis-10R-annonacin-A-ones, muricatocins A-B, annomuricins A-B). Leboeuf et al. (1981,1982). Annoreticuin-9-one, cis-annoreticuin, sabadelin. Ragasa et al. (2010). Amide N-p-coumaroyl tyramine Aqueous extract Aqueous ethanol extract Flavonol triglycoside, quercetin 3-O-α-rhamnosyl-(1″″→6″)-β-sophoroside. Ethanolic extract

					ulcerogenic, gastroprotective Moghadamtousi et al. (2015a, 2014b), Roslida et al. (2012). Antiviral (HSV-1) Padma et al. (1998). Hepatoprotective Moghadamtousi et al. (2015a), Adewole and Ojewole, (2009), Padma et al. (1999).	

ACGs: Acetogenins; THF: Tetrahydrofuran; **Syn.:** Synonym

Table 3. Cont.

Specie taxa ***Annona***	Local name	Biogeographical distribution	Used part	Traditional Use	Pharmacological activity (cont.)	Extract/compound evaluated (cont.)

muricata L. **Syn.** *muricata* *var.* *borinquensis* Morales *muricata* f. *mirabilis* R.E.Fr.		Hypotensive Nwokocha et al. (2012). Larvicidal (Dengue fever vector) Grzybowski et al. (2013). Molluscicidal Dos Santos and Santana, (2000, 2001). Wound healing. Moghadamtousi et al. (2015a, 2015b), Antitumoural.Selective cytotoxicit MCF-7/Adr, skin papillomagenesis, MDA-MB-435S, PC , HaCaT, MMPs, H-460, MDA-MB-468, MCF-7, SF-268, Hep-G (2), HT-29, KB, Vero, Hep 2, A-549, PC-3, PACA-2, HL-60, FG/COLO357, CD18/HPAF, HCT-116, BPH-1. Yang et al. (2015, Asare et al. (2015), Moghadamtousi et al. (2015, 2014a), Pieme et al. (2014), Sun et al. (2014), Mishra et al. (2013), Lim, (2012), Hamizah et al. (2012), George et al. (2012), Torres et al. (2012), Dai et al. (2011), Ribeiro et al. (2010), Quispe et al. (2006), Arroyo et al. (2005), Chang et al. (2003, 2001), Liaw et al. (2002), Chang and Wu, (2001), Kim et al. (1998a,1998b), Oberlies et al. (1997), Zeng, (1996), Wu et al. (1995b, 1995c, 1995d, 1995e).	Essential oils Monoterpens, sesquiterpenes and alcohols (α-pinene, β -pinene, ρ-mentha-2, 4(8)-diene, β –elemene, germacrene D, δ-cadinene, β-caryophyllene, epi-α-cadinol, α-cadinol). Thang et al. (2013b). Ethyl acetate extract Isoquinoline alkaloids Reticuline (main), coclaurine, coreximine, atherosperminine, stepharine, annonaine, nornuciferine, asimilobine, anomurine, anomuricine. Lyophilized fruit extract Methanolic extract N-butanolic extract

Table 4. Pharmacological activities and local and traditional uses of *Annona senegalensis* Pers.

Specie taxa ***Annona***	Local name	Biogeographical distribution	Used part	Traditional Use	Pharmacological activity	Extract/compound evaluated
senegalensis Pers. **Syn.** *senegalensis* var. *deltoides* Robyns & Ghesq. *senegalensis* var. *porpetac* (Boivin ex Baill.) Diels	Wild custard apple, pomme canelle de Senegal, muroro	Tropical Africa, Cape verde,Comoros, Madagascar	Leaves, seed ,stem bark ,root bark	Antihelmintic Cancer Cardiovascular diseases Diabetes Diarrhea Epilepsy Febrile seizures Gout Infectious diseases Inflammations Mental disorders Painful Sleeping sickness Snake bite	Anticonvulsant. Okoye et al. (2013). Antidiabetic Nyarko et al. (2005). Antidiarrhoeal Suleiman et al. (2008). Antidote.Antidrepanocytary (Sabbir et al. 2014), Emmanuel, et al, (2014), Mpiana et al. (2007), Adzu et al. (2005). Antihelmintic Ndjonka et al. (2011), Fall et al. (2008), Alawa et al. (2003). Anti-inflammatory Yeo et al. (2011). Antimalarial. Lame et al. (2015), Ajaiyeoba et al. (2006), Fall et al. (2003). Antimicrobial Okoye et al. (2012), More et al. (2008), Magassouba et al.(2007), Lino and Deogracious, (2006). Antioxidant Bangou et al. (2011). Antitumoural. Selective cytotoxicity (MCF-7, PC-3, KB and VERO). Fatope et al. (1996), You et al. (1995), Sahpaz et al.	ACGs Aqueous extract Tannin, phlobatanin, saponins, ent-kaurenoids (1-4). Aqueous herbal extract ADD-199 Aporphine alkaloid (-)-roemerine Chloromethylenic extract. Squamocine Ethanolic extract Terpenoids, coumarins, flavonoids, tannins, alkaloids, quinones. Ethyl-acetate fraction Diterpenoid (kaur-16-en-19-oic acid (KA). Methanol-methylene extract Lipophilic fraction, kaurenoic acid. Methanolic extract

		(1994), Durodola, (1975). Cytotoxic Ahmed et al. (2010), Sowemimo et al. (2007), Ajaiyeoba et al. (2006), Sahpaz et al. (1996). Hepatoprotective Ajboye et al. (2010). Insecticidal Ajaiyeoba et al. (2006), N´Tinkeu et al. (2004). Leishmanicidal Sahpaz et al. (1994). Trypanocidal Ogbadoyi et al. (2007, 2008), Freiburghaus et al. (1996), Sahpaz et al. (1994), Igweh and Onabanjo, (1989).	Mono THF ACGs (annose negalin, annogalene), essential oils.

ACGs: Acetogenins; THF: Tetrahydrofuran; **Syn**.: Synonym

Table 5. Pharmacological activities and local and traditional uses of *Annona squamosa* L.

Specie taxa ***Annona***	Local name	Biogeographical distribution	Used part	Traditional Use	Pharmacological activity	Extract/compound evaluated
squamosa L. **Syn.** *squamosa* f. *parvifolia* Kuntze	Sweetsop, custard or sugar apple,chirimoya, saramuyo, pinha, fruta do conde, attier, fan li zhi , sitapha, atis	Tropical America, Africa, Asia and Australia		Analgesic Antihelmintic Antiinflammatory Antimicrobial Antirheumatic Cancer Carminative Digestive Headache	Acaricidal, insecticidal and larvicidal (Madhumitha et al, 2012), (Kamaraj et al, 2011). Analgesic and anti-inflammatory Chavan et al. (2011), Chavan et al. (2010), Yeh et al, (2005). Antibacterial Dholvitayakhun et al. (2013), Dholvitayakhun et al. (2012), Shanker et al. (2007), Mukhlesur Rahman et al. (2005),Shokeen et al.(2005). Antidiabetic Agarwal, (2014), Ranjana and Tripath, (2014). Kaur et al. (2012), Kaleem et al. (2008), Panda and Kar, (2007a), Kaleem et al. (2006), Gupta et al. (2005a, 2005c),	BisTHF-ACGs (2,4-cis and trans - squamolinone, 2,4-cis and trans-9-oxoasimicinone, bullacin B, squamotacin). THF-ACGs (squadiolins A and B, squafosacin B, 2, 4-cis and trans-mosinone A, mosin B, mosin C, bullatacin, bullatacinona, squamona, tetrahydrosquamone). Aporphine alkaloids Aqueous extract Chloroform fraction N-methyl-6, 7-dimethoxyisoquinolone Crude extract Essential oils Monoterpens, sesquiterpenes and alcohols (α-pinene, limonene, β-cubebene, β-caryophyllene, spathulenol, caryophyllene oxide, α-cadinol. Thang et al. (2013b) Ethanolic extract Ent-kaur-16-en-19-oic acid, 15, 16-epoxy-17-hydroxy-ent-kau-ran-19-oic acid, annosquamosin

					Shirwaikar et al. (2004a). Antigenotoxicity Suresh et al. (2008). Anti-head lice Intaranongpai. et al. (2006). Anti-HIV Wu et al. (1996). Antileishmanial Vila-Nova et al. (2011). Antilipidemic Gupta et al. (2008). Antimalarial Singh et al. (2015), Kihampa et al. (2009), El Tahir et al. (1999). Antioxidant Nandhakumar and Indumathi, (2013), Mariod et al. (2012), Sultana, (2008), Gupta et al. (2008), Panda and Kar, (2007b), Shirwaikar et al. (2004b), Yang et al. (2004). Antiplatelet aggregation Yang et al. (2002). Anti-psoriatic Saelee et al. (2011). Antithyroidal Panda and Kar, (2007b).	B, 12, 15-cis-squamostatin-A and bullatacin, annosquacins A-D, annosquatin A and annosquatin B.

ACGs: Acetogenins; THF: Tetrahydrofuran; **Syn**.: Synonym

Table 5. cont.

Specie taxa ***Annona***	Local nam	Biogeographical distribution	Used part	Traditional Use	Pharmacological activity (cont.)	Extract/compound evaluated

	e		
squamosa L. **Syn.** *squamosa* f. *parvifolia* Kuntze		Antitumoural. Selective cytotoxicity Adult T-cell leukemia/lymphoma (ATL), 95-D lung, A2780 ovarian cancer cells, MCF-7, Hep G2 and 3B hepatoma, H (22), A-549, MDA-MB-231, K-562, AK-5, HL60, PACA-2, PC-3, AD-5. Wang et al. (2014), Yang et al, (2014), Nakano et al. (2013), Sun et al. (2012), Taylor et al. (2012), Chen et al. (2011, 2012a, 2012b), Liaw et al. (2008), Pardhasaradhi et al. (2004, 2005), Zhu et al. (2001), Hopp et al. (1996, 1997, 1998), Li et al. (1990). Antiulcer Yadav et al. (2011). Antyhyperglicemic Davis et al. (2012). Biopesticide Grover et al. (2009) Blood-feeding parasiticide Madhumitha et al. (2012), Kamaraj et al. (2011) (2010), Senthilkumar et al. (2009), Saxena et al. (1999). Contraceptive Singh et al. (2012), Damasceno et al. (2002), Mishra et al. (1979), Vohora et al. (1975). Hepatoprotective Thattakudian Sheik Uduman et al. (2011). HypogliceGonzaet al. (2005a, 2005b, 2005c).	Ethyl acetate extract Hexane extract Methanolic extract Cyclic octapeptide Cyclosquamosin Organic extract Petroleum ether extract 8-Acetoxy-ent-kaur-16-ene, caryophyllene oxide, 16-beta, 17-dihydroxy-ent-kauran-19-oic acid.

				Immune-stimulant Soni et al. (2012). Renoprotective Deshmukh and Patel, (2011). Vasorelaxant Morita et al. (2006). Wound healing Ponrasu and Saguna, (2012).

Table 6. *Annona* species potentially useful in different group of diseases

Diseases (International Statistical Classification of Diseases (**ICD**),	**Species potentially useful**	**Pharmacological Activity**	**S.A**	**EU-SA**
Infectious				
	A.cornifolia	Antifungical	X	
	A.crassiflora	Antifungical	X	
	A.glabra	Anti-HIV	X	
	A.cherimola	Antifungical, Antiviral		X
	A.muricata	Antimicrobial		X
	A.senegalensis	Antimicrobial		X
	A.squamosa	Antimicrobial		X
Parasitic				
	A.cherimola	Antiprotozoal (*Entamoeba histolytica*)		X
	A.coriacea	Antileishmanial, Trypanocidal		X
	A.crassiflora	Against Dengue, Yellow fever and Chikungunya vector	X	
	A.glabra	Dengue, yellow fever, chikungunya vector	X	
	A.haematantha	Antileishmanial	X	

A.foetida	Antileishmanial, Trypanocidal		
A.muricata	Antileishmanial, Trypanocidal, Antimalarial, Molluscicidal (schistosomiasis)		X
A.pickelii	Trypanocidal	X	
A.purpurea	Trypanocidal	X	
A. salzmanniii	Trypanocidal	X	
A.senegalensis	Antileishmanial, Trypanocidal, Antimalarial, Antihelmintic		X
A. spinescens	Antileishmanial, Trypanocidal	X	
A.squamosa	Antileishmanial, Antimalarial, Molluscicidal (schistosomiasis)		X
A.vepretorum	Trypanocidal	X	

SA: Significant Activity; **EU-SA**: Ethnomedicinal Use and Significant Activity

Table 6. Cont.

Diseases (International Statistical Classification of Diseases (**CDI**),	**Species potentially useful**	**Pharmacological Activity**	**S.A**	**EU-SA**
Neoplasm				
	A.bullata	Antitumoural. Selective cytotoxicity (A-549, HT-29, , MCF-7/wt, MCF-7/Adr)	X	
	A.cherimola	Antitumoural. Selective cytotoxic (A-498, KB, HT-29, MCF-7, MIA PaCa-2, PC-3)		X
	A.glabra	Antitumoural. Selective cytotoxicity (A-498, CEM, CEM/VLB, Hep G2, MCF-7, PC-3, PACA-2, SMMC-7721)	X	
	A. jahnii	Antitumoural. Selective cytotoxicity (A-549, A-498, HT-29, MCF-7, PC-3, PACA-2)	X	
	A.montana	Antitumoural. Selective cytotoxicity (1A9, Hep2)	X	
	A.muricata	Antitumoural.Selective cytotoxicit (A-549, BHP-1, CD18/HPAF, FG/COLO357, HaCaT, H-460, Hep-G(2), HCT-116, HT-29, Hep 2 KB, MCF-7/Adr, K562, MDA-MB-435S, MMPs, MDA-MB-468, MCF-7,PACA-2, PC-3, PC , SF-268, Skin papillomagenesis, Vero)		X
	A. reticulata	Antitumoural. Selective cytotoxicity (Caco-2, Hep G2, T24, KB 3-1)	X	
	A.senegalensis	Antitumoural. Selective cytotoxicity (MCF-7, PC-3, KB, VERO)		X
	A.squamosa	Antitumoural. Selective cytotoxicity (Adult T-cell leukemia/lymphoma (ATL), A2780, A-549, AK-5, 95-D lung, Hep G2 and 3B Hepatoma, H(22), HL60, MCF-7, MDA-MB-231, K-562, PACA-2, PC-3)		X
Metabolic, nutritional and endocrine				
	A.cuneata	Antioxidant	X	
	A.dioica	Antioxidant, hypoglycaemic	X	
	A.montana	Hypoglycaemic, hipolipidaemic	X	
	A.muricata	Antidiabetic, hypolipidaemic, protective action on pancreatic β-cells, hepatoprotective, antioxidant		X
	A. pickelii	Antioxidant	X	
	A.reticulata	Antidiabetic, antiovulatory		X

A. salzmannii	Antioxidant	X	
A.senegalenseis	Antidiabetic, hepatoprotective		X
A.squamosa	Antioxidant, hepatoprotective, contraceptive, antidiabetic, hypolipidaemic, antioxidant and protective action on pancreatic β-cells and against metabolic syndrome		X

SA: Significant Activity; **EU-SA**: Ethnomedicinal Use and Significant Activity

Table 6. Cont.

Diseases (International Statistical Classification of Diseases (CDI),	**Species potentially useful**	**Pharmacological Activity**	**S.A**	**EU-SA**
Nervous system				
	A.diversifolia	Anxyiolitic, anticonvulsivant, neuroprotective	X	
	A.muricata	Antidepresssant, anticonvulsivant,antistress, sedative		X
	A.cherimola	Anxyiolitic		X
	A.purpurea	Anxyiolitic	X	
	A. senegalensis	Anticonvulsant		X
Digestive system				
	A.cherimola	Anti-*Helicobacter pylori*		X
	A.muricata	Anti-ulcer, Gastroprotective		X
	A.squamosa	Anti-ulcer, Anti-secretory		X
	A. senegalensis	Antidiarrhoeal		X
Osteomuscular system and conective tissue				
	A.dioica	Anti-inflammatory		X
	A.diversifolia	Antinociceptive		X
	A.coriacea	Anti-inflammatory		X
	A.glabra	Anti-inflammatory		X
	A.montana	Anti-inflammatory		X
	A.muricata	Analgesic, Antinociceptive, Anti-inflammatory, Anti-arthritic		X
	A.reticulata	Analgesic, Anti-inflammatory		X
	A.senegalenseis	Anti-inflammatory		X
	A.squamosa	Analgesic and anti-inflammatory		X
	A.sylvatica	Anti-inflammatory	X	

SA: Significant Activity; **EU-SA:** Ethnomedicinal Use and Significant Activity

3.1.3. Antiprotozoal: antileishmanial, trypanocidal, antimalarial

The protozoal diseases, such as leishmaniasis, trypanosomiasis and malaria, are a cause of considerable mortality and morbidity throughout the world, affecting millions of persons every year. There are an important number of ethnopharmacological records of the use of the species of

Annona for the treatment of these diseases, especially with those from Brazil.

Antileishmanial*: A. haematantha* Miq., *A. muricata* L.*, A. spraguei* Saff., *A. squamosa* L.

In the treatment of cutaneous leishmaniasis a α,β-unsaturated delta-lactone (argentilactone) from the hexane extract of the roots of *A. haematantha*, produced the same efficacy as the reference drug (N-methylglucamine antimonite). This compound was able to reduce parasite loads in the lesion by 96% and the parasite burden in the spleen by 50% (Waechter et al., 1997).

Moreover, a chloroform extract of the seeds of *A. spraguei* showed activity against *L. braziliensis, L. infantum and L. panamensis* (Saez et al., 1998).

Some pure compounds as alkaloids and acetogenins isolated from leaves of *A. squamosa* and seeds of *A. muricata* were found to exert a potent action against promastigote and amastigote forms of *L. chagasi.* The IC_{50} against promastigotes was 23.3μg/mL for alkaloids and it was in a range of 25.9 to 37.6 μg/mL for acetogenins; in the amastigote assay, the IC_{50} values was between 13.5 to 28.7μg/mL (Vila-Nova et al., 2011).

Trypanocidal*: A. pickelii* (Diels) H. Rainer*, A. purpurea* Moc. & Sessé ex Dunal*, A. salzmanniii* A. DC*., A. vepretorum* Mart.

The methanolic extract from the seeds of *A. purpurea* provided IC_{50} values below 10 μg/mL against *Trypanosoma brucei brucei* (trypomastigote forms) (Camacho et al.,2003).

As it was mentioned in the antimicrobial section, in several studies, Costa and coauthors have shown the significant activities of the essential oils from the leaves of the other three species of *Annona (pickelii, salzmanniii* and *vepretorum)*. The essential oils showed potent trypanocidal activity (against epimastigote forms) with values of IC_{50} lower than 100 μg/mL, being the most active the oil from *A. pickelii* with an IC_{50} value of 27.21 μg/mL. As it was observed in the antitumour assay, the significant trypanocidal activity could be attributed to the high concentration of bicyclogermacrene. These results obtained in these studies are considered to be very promising by the authors (Costa et al., 2012; 2013).

Antileishmanial and trypanocidal*: A. coriacea* Mart.*, A. foetida* Mart*., A. muricata* L.*, A. senegalensis* Pers.*, A. spinescens* Mart*.*

Volatile oil from the leaves of *A. coriacea* presented an effective anti-leishmanial and trypanocidal activity. The oil showed more potent activity against *Leishmania chagasi* (IC_{50} 39.93 μg/mL). The terpenes (*E*)-caryophyllene together with δ-cadinene are markers of the essential oil of Annonaceae and showed a significant activity against *L. donovani* promastigotes with an IC_{50} of 19 and 4 μg/mL respectively, the authors suggested the contribution of these compounds to the anti-leishmanial activity showed by the *A. coriacea* oil (Siquiera et al., 2011).

In an assessment of the plants from the Brazilian cerrado (savanna) widely used in ethnomedicine, an alcoholic extract of *A. coriacea* showed the best activity against the promastigote forms of *L. amazonensis* (IC_{50}: 175 µg/mL). Brazilian cachaça was used as the extractor liquid (De Toledo et al., 2011).

Besides, Costa and collaborators isolated from the bark of *A. foetida* the alkaloids pyrimidine-β-carboline, N-hydroxyannomontine, together with other alkaloids as annomontine, O-methylmoschatoline and liriodenine. They were all effective against the promastigote forms of *L. braziliensis* (Costa el al., 2006). Subsequently, liriodenine and annomontine were also isolated from the branches of *A.foetida* and showed a potent trypanocidal effect when evaluated against epimastigote and trypomastigote forms of *T. cruzi* (Costa el al., 2011).

Previously, anonaine and liriodenine, isolated from another species *A. spinescens* have already showed significant activity against promastigote forms of *L braziliensis, L. amazonensis and L. donovani* and anonaine and acetyl-bracteolina against trypomastigote forms of *T. cruzi* (Queiroz, 1996).

Furthermore, two acetogenins, annonacinone and corossolone isolated from the seeds of *A. muricata* (soursoup) showed leishmanicidal activity in promastigote forms of the three species tested (*L. donovani, L. mexicana and L. major*). The isolated compounds were also tested against promastigote and amastigote forms of *L. chagasi* (responsible for American visceral leishmaniasis) and results suggested soursop as a potential source of leishmanicidal agents (Vila-Nova et al., 2013; 2011). In fact, the ethyl acetate extract of soursop pericarp was more active than the reference substance (glucantime) when it was tested against *L. braziliensis* and *L. panamensis* promastigotes (Jaramillo et al., 2000). Subsequently, Osario and coauthors demonstrated similar results for *L. braziliensis*, *L. amazonensis* and *L. donovani* testing the same extract from the leaves, which showed activity against epimastigote of *T. cruzi* showing an IC_{50} value of 25 µg/mL (Osorio et al., 2007).

Several studies support the claims of Nigerian Traditional Medicine practitioners regarding the efficacy of *A. senegalensis* against trypanosomiasis in man (Ogbadoyi et al., 2007). The administration of crude and partially purified of an aqueous extracts from the leaves of this species at 200 mg/kg body weight to mice, experimentally infected with *T.brucei,* cured the experimental infection. However, the pre-treatment of healthy mice it did not show prophylactic effects. Furthermore, an aqueous extracts of the stem bark of *A. senegalensis* also cured this infection in mice. Thus, an aqueous root extract of this plant showed to be therapeutically effective against *T. brucei* in mice at 27.8 mg/kg per oral administration. Chemical tests revealed that this root plant extract contained alkaloids, saponins and tannins.

In addition, a combination of a methanolic extract from the leaves of *Annona senegalensis* and *Eucalyptus camaldulensis* completely cured an experimental *T. brucei* infection in mice (Ogbadoyi et al., 2008). All these results showed the positive action of *A. senegalensis* against *T.*

brucei in mice, thus validating the claims of Nigerian practitioners of Traditional Medicine when use the species against trypanosomiasis in man (Ogbadoyi et al., 2007; Igweh and Onabanjo, 1989).

Previously, several extracts of *Annona senegalensis* (Annonaceae) seeds demonstrated to have antiparasitic activity.The acetogenins extracted from *A. senegalensis* seeds also showed activity against *L. major, L. donovani and T. brucei brucei* (Sahpaz et al., 1994).

Antimalarial*: A. muricata* L. (soursop, graviola)*, A. squamosa* L. (custard apple) *and A. senegalensis* Pers. (wild custard apple)*.*

Much research has been developed in the antimalarial properties of *Annona* species, being the three above mentioned species (*muricata, squamosa, and senegalensis*) the most active. In a study by Mohd Abd Razak, extracts of different polarity from *A. muricata* leaves showed significant antiplasmodial activities against the blood stage of chloroquine resistant *P. falciparum* (EC_{50} < 10 µg/mL) with minor cytotoxicity (Mohd Abd Razak et al., 2014). On the other hand, a pentane extract of *A. muricata* leaves was assayed against two strains of *Plasmodium falciparum*: the Nigerian chloroquine-sensitive strain and FcM29-Cameroon (chloroquine-resistant strain); a promising antiplasmodial effect was obtained with an IC_{50} value of 16 and 8 µg/mL after 72 h, respectively. Moreover, the leaves extract showed a 67% inhibition against an asynchronous F32 strain of *P. falciparum*. In addition, another study on different extracts of *A. muricata* leaves and stems confirmed the reported cytotoxic effects against the chloroquine-sensitive (F32) and -resistant (W2) *P. falciparum*. The authors state these findings substantiated the traditional use of *A. muricata* as an antimalarial agent (Moghadamtousi et al., 2015a).

Related to *A. squamosa,* a study of the methanolic extract from the leaves showed high antiplasmodial activity with an IC_{50} value of 2 and 30 µg/mL in 3D7 and Dd2 chloroquine sensitive strain respectively (El Tahir et al.,1999). Furthermore, a recent systematic exploration of the ex vivo blood stage antiplasmodial potential of medicinal plants, to corroborate their traditional usage against malaria in India, has shown the highest antiplasmodial activity (against both chloroquine-sensitive Pf3D7 and chloroquine resistant PfINDO strains of *P. falciparum*) (Pf3D7 IC_{50}≤5 µg/ml) from ethanol extracts of custard apple leaves (Singh et al., 2015).

The effective antimalarial properties of *A. senegalensis* were demonstrated by Ajaiyeoba and collaborators that showed a dose-dependent effect for the methanol extract of the leaves. It manifested a 91.1 % activity at 800 mg/kg weight of mice compared to the reference drug chloroquine disphosphate, which showed a chemosuppression of 96.2% (Ajaiyeoba et al., 2006). In addition, an extract from the roots of *A. senegalensis* showed an interesting activity on the chloroquine-resistant strain of *P. falciparum* (Fall et al., 2003). These results support the traditional use of this vegetal species for the treatment of malaria. In relation to vector control, N-hexane and chloroform fractions of methanol crude leaves extract of wild custard apple were toxic on the immature stage of the mosquito species tested. For these findings it could be considered

and utilized for future immature mosquito vectors control (Lame et al., 2015).

Most of the research on the custard apple antimalarial activity is aimed at their larvicidal effect. On this line of investigation, Madhumitha and collaborators suggest that the biodegradable compounds from fruit peel of the custard apple may be an option to conventional synthetic chemicals, particularly as an integrated approach for the control of medically important vectors as *Anopheles subpictus* and *Culex quinquefasciatus* (Madhumitha et al., 2012). Likewise, the bark ethyl acetate and methanol extract of *A. squamosa* has the potential to be used as an ecofriendly method for the control of the instar larvae of malaria vector as *An. subpictus*, and *An. Stephensi* (Liston) and lymphatic filariasis vector as *Cx. Tritaeniorhynchus and Cx. Quinquefasciatus* (Kamaraj et al., 2011; 2010). According to, crude extracts from the stem and root barks are promising as larvicides against *An. gambiae* s.s. Giles mosquitoes (Kihampa et al., 2009). These findings also support the use of this medicinal plant against malaria-like conditions for the control of vectors.

Similarly, an investigation into the larvicidal and mosquitocidal properties of *An.* stephensi (Liston) against larvae and adults of 11 commonly available medicinal plants (including the custard apple) found that all the medicinal plants and the mixture were active. The authors stated that the larval mortality with the combined treatment was between 80% and 100%. Senthilkumar and collaborators pointed out that these plant extracts were easy to prepare and could be safe for mosquito control which might be used directly as larvicidal and mosquitocidal agents in small volume aquatic habitats or breeding sites in close vicinity to human dwellings (Senthilkumar et al., 2009).

3.1.4. Dengue, yellow fever, chikungunya vector control (*Aedes aegypti*)*: A. glabra* L.*, A. crassiflora* Mart.*, A. muricata* L.*, A. pickelii* (Diels) H. Raine*, A. salzmanniii* A. DC. *, A. squamosa* L.

The larvicidal activity against *A. aegypti* larvae of the essential oil from the leaves of *A. salzmannii* and *A. pickelii,* was also tested by Costa and coworkers and showed a significant activity likely mediated by the high content in sesquiterpene compounds (Costa et al., 2011). Different investigations have demonstrated that ethanol extracts from root bark, root wood of *A. glabra* and seeds from *A. crassiflora* have shown significant activity against vector larvae (LC_{50} < 100 µg/mL) (De Omena et al. 2007; Rodrigues et al., 2006; De Mendonça et al., 2005).

In a subsequent study, *A. muricata* seed and *Piper nigrum* fruit ethanolic extracts as phytopesticide combination enriched in acetogenins and piperamides, respectively, were synergistically used as larvicides against the dengue, yellow fever and chikungunya vector *A. aegypti* (Grzybowski et al., 2013).

3.1.5. Schistosomiasis vector control: *A. muricata* L. and *A. squamosa* L.

Dos Santos and Santana carried out a research for plant molluscicides for the vector control of schistosomiasis with application in the industry. In these experiments ethanolic extracts from different parts of six species of the Annonaceae family were evaluated against adult forms and egg masses of *Biomphalaria glabrata.* The majority of analyzed extracts showed lethal properties to this snail*,* some of them with significant LD_{90} values (<20 ppm) as shown by *A. crassiflora*, *A. glabra*, *A.muricata* and *A. squamosa*. Especially effective were the latter two species (leaves and root respectively) for presenting additional toxicity toward snail egg masses (Dos Santos and Santana, 2001; 2000).

3.2. Neoplasms

3.2.1. Antitumoural acetogenins

Some isolated compounds and extracts from different parts of the plant in the *Annona* species have shown antitumoural activity, but a set of phytochemicals, Annonaceous acetogenins (ACGs), have proved to be effective against multidrug resistant tumours and have selective cytotoxicity. These lipophilic molecules are long-chained (C-35/C-37) fatty acids derivatives and are only found in the Annonaceae family. They have an aliphatic chain with one or two tetrahydrofuran (THF) rings and a terminal butyrolactone. Related to the mechanism of action, they seem to exhibit their potent bioactivities through a decrease of ATP levels via inhibiting complex I of mitochondria and inhibiting the NADH oxidase of plasma membranes of tumour cells. Therefore, they show ATP driven resistance mechanism. Although most of the ACGs have high potencies among several solid human tumour cell lines, some of the derivatives within the different structural types and some positional isomers showed remarkable selectivity among several different cell lines (tables 1-5).

A great number of studies have reported the selective cytotoxic potency of ACGs for several human tumour cell lines. A wide review of all the data reveals different general tendencies depending on the tumour cell line. Against lung, breast and colon carcinoma in human cells (A-459, MCF-7 and HT-29 respectively) the most potent groups of acetogenins (considering DE_{50} values) are some of the bis-adjacent tetrahydrofuran (THF) α, α'-dihydroxylated acetogenins type as asimicin, **squamocin** (figure 1) and panalicin. However, this is significantly different against human prostate adenocarcinoma (PC-3), human pancreatic carcinoma (MIA PaCa-2) and human kidney carcinoma (A-498) cells, where the mono-THF ACGs are the strongest series (Zafra-Polo et al., 1998). This fact could be explained because the different tumour cell lines show notable differences in their susceptibility to the same ACG_s. There are multiple factors involved in cell death caused by enzymatic inhibitors of mitochondrial complex I (such as ACGs), from the access of the toxic compound to the target enzyme to the defensive cellular mechanism against this poisoning (Bermejo et al., 2005).

Recent research about three newly isolated and elucidated ACGs (muricins J, K, and L), all C-35 with a mono-tetrahydrofuran ring and four

hydroxyls, shows that their antiproliferative activity against human prostate cancer PC-3 cells manifested inhibition with the following potency: muricin K > muricin L > muricin J, which indicates that the structure–activity relationship (SAR) of ACGs is not only affected by the number of hydroxyl groups, but also by the positions of these groups (Sun et al., 2014).

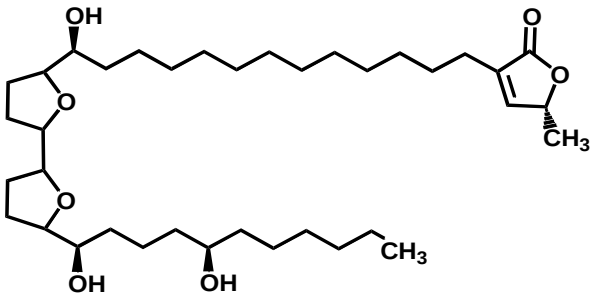

Figure 1. Squamocin

Related to the mechanism of action of **bullatacin** (Figure 2) (present in several species of Annona genus), it is known its action by inhibiting the complex I of mitochondria and the NADH oxidase of plasma membrane in tumor cells and depletion of ATP levels, nevertheless it was also investigated that bullatacin causes an upregulation of radical oxygen species and interferes in the cell apoptosis pathway, resulting in an inhibition of the growth of 50% of grown multidrug resistance cancerous cells at extremely low concentrations in vitro (Liang et al., 2009).

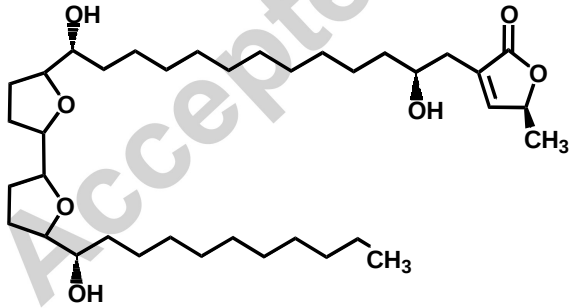

Figure 2. Bullatacin

From this information it can be deduced that acetogenins exert a strong selective antitumour effects in a wide range of cancer cell lines: colon, lung, ovarian, breast, liver, leukemia and lymphomas. They have demonstrated to be effective at very low doses; however the effect depends on the number of hydroxyls and their position in the chain, as well as the number of tetrahydrofuran rings in their structures. Thus, as it is reported

by some authors, all these features supported the ACGs as potential molecules for the design of a new class of antitumoural agents with a innovate mechanism of action different from conventional antitumoural drugs (Tundis et al, 2017).

3.2.2 Antitumoural Annona species: *A. muricata* L., *A. squamosa* L., *A. cherimola* Mill., *A. senegalensis* Pers.

Seventeen *Annona* species have shown significant anti-tumour, anticancer and selective toxicity against several different types of cancer cells. The species of *Annona* and the selective types of tumour cell lines are specified in tables 1-5. We will comment on those that are active against multidrug resistant tumours or have more studies about selective cytotoxicity and its action mechanisms.

A. muricata L. (soursop, graviola)

Different authors reported about the plant screening program by the National Cancer Institute (NCI) in 1976 that found *A. muricata* leaves and stem showed active cytotoxicity against cancer cells (Mishra et al., 2013; Barbalho et al. 2012a; Lim, 2012). The collaboration between the Purdue University (West Lafayette, Indiana), the National Cancer Institute (NCI) and the National Institute of Health (NIH) has provided, at least, nine international patents relating to the use of acetogenins and the antitumoural and insecticide properties (Lima, 2008; McLaughlin and Hopp, 1998, 1999; McLaughlin et al., 1996; McLaughlin and Hui, 1993).

Plenty of studies report the significant antiproliferative effects of different extracts of the plant and isolated AGEs towards various cancer cell lines, as it can be found in the reviews available (Moghadamtousi et al., 2105a; Mishra et al., 2013).

Researches on different cell lines of prostate cancer (PC) showed that soursop extracts inhibit multiple signaling pathways that regulate metabolism, cell cycle, survival, and metastatic properties of PC cells (Sun et al.,2014). Besides, an aqueous extract of *A. muricata* leaves expressed, possibly through apoptosis, antiproliferative effects on BPH-1 cells and reduces prostate size (Asare et al., 2015). Other authors agree with this possible mechanism of action, suggesting that the ethanol extracts from different parts and the ethyl acetate extract of the leaves of this medicinal plant, presented strong antiproliferation potential and could induce apoptosis through loss of membrane mitochondrial potential and G0/G1 phase cell arrest (Moghadamtousi et al., 2015a; Pieme and col., 2014; Moghadamtousi et al., 2014a).

The most studied acetogenins from the leaves of *Annona muricata* L that have shown antitumoural activity are **annonacin** (Figure 3), **muricatocin A** (Figure 4) and **annomuricin A** (Figure 5). The first one was active against various cancer cell lines including skin cancer cell lines at

very low dosages, acting as a mitochondrial complex I inhibitor (Yuan et al., 2003), (Gonzalez-Coloma et al., 2002). The other two acetogenins caused significant cell death in A-549 human lung tumour cell line (Wu et al., 1995a; 1995b; 1995c).

However, many of the *in vitro* studies in cell lines with phytochemical compounds are not conclusive due to lack of data on bioavailability. This has been recently improved with a novel method where the serum from patients, who ingested daily during 8 weeks, a supplement from an extract of *A. muricata,* was tested versus a colorectal cancer cell line. Thirty patients participated in this randomized double-blind placebo-controlled pre-post-trial (RCT) and it could be detected that the serum from the patients taking the extract showed cytotoxicity against the cancer cell line compared with the placebo control group (Indrawati et al., 2017).

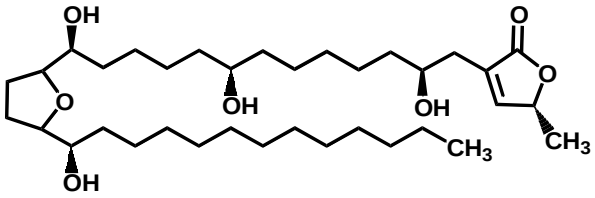

Figure 3. Annonacin

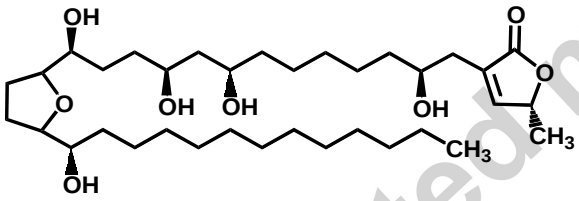

Figure 4. Muricatocin A

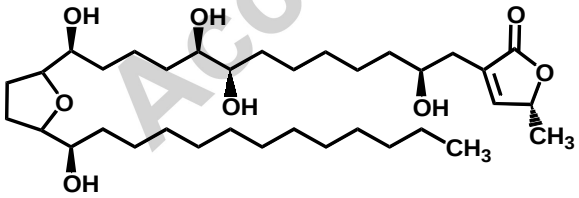

Figure 5. Annomuricin A

Recently an important investigation conducted by Yang and collaborators showed a phytochemical synergy among the constituents of the extract of graviola leaves (GLE). The authors compared its flavonoid-enriched (FEF) and acetogenin-enriched (AEF) fractions in prostate cancer. The concentration of rutin and quercetin-3-glucoside was higher in FEF than GLE, however, GLE had higher inhibition in human prostate tumour xenograft action than FEF. In fact, AEF showed superior *in vitro* and *in vivo*

efficacy, although, due to the toxicity, caused the death of the mice. GLE comprises of other phytochemical group of compounds, in addition to acetogenins. It could be deduced that all together they might act synergistically optimizing its effectiveness. The authors emphasize the importance of evaluating the nature of interactions among the phytochemicals of soursop leaves to develop appropriate dose regimens for prostate cancer management to achieve optimal therapeutic benefits (Yang et al., 2015).

On the other hand, a case study of a 66-year old woman showed an example of possible complementary use with anti-tumour drugs. Metastatic breast cancer was stabilized with the combine use of a decoction of the leaves of soursop and Xeloda^{R} (capecitabine) (Hansra et al., 2014).

Different formulations from different manufacturers of *A. muricata* leaves are available in the U.S. market in health food stores. The ethyl acetate-soluble fraction containing ACGs has been formulated as a tablet, for use as a cancer adjuvant therapy (Elisya et al., 2014). The proposed dose of soursop leaves has been 2-3 g, taken 3 or 4 times daily (Sun et al., 2014).

A. squamosa L. (custard apple)

The efficacy and safety of a standardized *A. squamosa* seeds extract (containing 12, 15-cis-squamostatin-A and bullatacin) was verified by Chen´s group (Chen et al., 2012). The extract showed significantly higher anti-tumour activity against the MCF-7 and HepG2 cells. Furthermore, the anti-tumour effect of the extract was also investigated by in vivo mice bearing H22 hepatoma cells transplantation tumour model. Compared with cyclophosphamide the extract inhibited the growth of these tumour cells in mice with a maximum inhibitory rate of 69.55% and no side-effects were observed, suggesting that the extract of custard apple seeds may be a potential candidate for a novel anti-liver cancer drug.

Wang and colleagues (Wang et al., 2014) have found significant anticancer activity on human epidermoid carcinoma cell line KB-3-1 and colon cancer cell line HCT-116 in the crude and ethyl acetate extract. Besides, specific selectivity, against certain tumour cell lines and an antigenotoxic effect of the ethanolic and aqueous extracts in 7,12 dimethylbenz(a)anthracene (DMBA) in golden Syrian hamsters was demonstrated (Suresh et al., 2008).

With regards to the antitumour action mechanism, several authors (Pandey and Barve, 2011; Pardhasaradhi et al., 2005; Pardhasaradhi et al., 2004; Zhu et al., 2001) suggest that aqueous and organic extracts from defatted seeds of *A. squamosa* and the active compound squamocin induce apoptosis in tumour cells through oxidative stress. Aqueous extracts of custard apple seeds showed significant antitumour activity *in vivo* against the AD-5 tumour. Yang and collaborators have demonstrated the activity of total annonaceous acetogenins (TAAs) against human hepatocarcinoma by two effective mechanisms: the arrest of cell cycle at G phase and induction

of apoptosis dose- and time-dependently through mitochondrial and recipient pathways (Yang et al., 2014).

On the other hand, the potency of mono-tetrahydrofuran (THF) ring acetogenins (2,4-cis and trans-mosinone A, mosin B, mosin C and annoreticuin-9-one) and bis-adjacent THF-ring acetogenins (bullacin B) from the bark have shown a potency ranging from 10-100 times and nearly a million that of adriamycin against different human tumour cell lines respectively (Hoop et al., 1997; Hoop et al., 1996).

A. cherimola Mill. (cherimola, chirimoya)

As with the custard apple, it is possible to obtain from the cherimola seeds several mono-THF acetogenins (cherimolin-1, motrilin, laherradurin , annomolin, annocherimolin annomocherin, annonacin, annomontacin, cis-annonacin and the mixtures of (2,4)-cis-and trans-isoannonacins, bis-THF ACGs (tucumanin) and a mixture of epimers (annomolon A and 34-epi-annomolon A and of annomolon B and 34-epi-annomolon B) that show specific selectivity against different tumour cell lines and manifest a potent inhibition of mitochondrial complex I (De Pedro et al., 2013; Kim, 2001a; Kim, 2001b; Woo et al.,1999a, 1999b; Barrachina et al., 2004; Son et al., 2003)(Table 2). All these acetogenins also showed substantial cytotoxicity, with a potency comparable to or higher than Adriamycin against several tumour cell lines. They were isolated from an ethanolic or a methanolic extract.

But another phytochemical, cherimolacyclopeptide C, a new cyclic heptapeptide from a methanol extract of the seeds, manifested a very significant in vitro cytotoxic activity against KB cells (IC_{50} value of 0.072 µM) (Wélé et al., 2004).

A. senegalensis Pers. (wild custard apple)

Cancer is treated by Nigerian traditional healers with the barks of the roots of the wild custard apple. An active compound, named $C/M_{2,}$ isolated from this rootbark manifested a strong antitumour activity against sarcoma 180 ascites tumour cells. The daily dose, optimized at 100 mg/kg and administered intraperitoneally (i.p.) to mice, showed a complete inhibition tumour, survival for 60 days or more and no toxicity to the host. The 200 mg/kg dose did not present toxicity to the test mice (Durodola, 1975).

The aporphine alkaloid (-)-roemerine isolated from the leaves of the wild custard apple improved the reponse produced by vinblastine. Without the presence of vinblastine, (-)-roemerine did not show significant cytotoxicity against multidrug-resistant KB-V1 or KB-3 cells (ED_{50} > 20 µ/mL). This alkaloid appears to function by interacting with P-glycoprotein as indicated by its ability to inhibit ATP-dependent [^{3}H] vinblastine binding to multidrug-resistant KB-V1 cell membrane vesicles (You et al., 1995).

Another five species of Annona have been investigated in order to examine their selective cytotoxicity: *A.bullata, A.glabra, A. jahnii, A.montana and A.reticulata*. The culture cell lines and the isolated compounds or extracts from these species are described in tables 1 and 6.

3.3. Metabolic, nutritional and endocrine diseases

3.3.1. Antioxidant activity

Seven species have shown remarkable results for this activity: *A. cuneata* (Oliv.) R.E. Fr. (synonym of *A. stenophylla* subsp. cuneata (Oliv.) N.Robson)*, A. dioica* A. St.-Hil*, A. glabra* L *, A. muricata* L.*, A. pickelii* (Diels) H. Rainer*, A. salzmannii* A. DC. and *A. squamosa* L*.*

Most of the plant extractions for the antioxidant assays were done with polar solvents as water, methanol and ethanol. Thus, the methanolic extract of the root bark of *A. cuneata* exhibited potent antioxidant capacity with an IC_{50} of 1.38 mg/mL of raw extract in the hypoxanthine/xanthine oxidase assay and using spectroscopic methods a wide range of polyphenolic compounds mainly phenolic acids were identified (Khallouki et al., 2011) and among the different tested fractions of the methanol extract of *A.dioica* leaves, the ethyl acetate and the hydromethanol fractions showed stronger activities, with an IC_{50} of 8.53 and 10.57 µg/mL, respectively in the 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay. The antioxidant activity may be associated with the presence of the flavonoids quercetin and kaemferol (Formagio et al., 2013a).

In a recent study, three ent**-**kaurene diterpenoids isolated from the fruits of *A. glabra* showed a potent (7*β,*17-dihydroxy-ent-kaur-15**–**en-19-oic acid 19-O-*β*-D-glucopyranoside ester) and significant(7*β*, 16*α*, 17-trihydroxy-ent-kauran-19-oic acid and 16*β*,17-dihydroxy-ent**-**kauran-19-al) inhibitory activity against nitric oxide (NO) production in LPS-stimulated RAW 264.7 macrophages with an IC_{50} of 0.1, 0.39, and 0.32 µM, respectively (Nguyen et al., 2015).

In another recent study the methanolic and aqueous extracts of the leaves of *A. muricata* revealed that both extracts manifested significant ($p<0.05$) radical scavenging activities. The methanolic extract showed a better protection against H_2O_2-induced DNA damage than the aqueous extract (George et al., 2015). In the same way, other studies have shown an important *in vitro* antioxidant activity of the ethanolic and water extracts of graviola leaves, providing the reducing power of 216.41 µg/mL GAE (gallic acid equivalent) for the water extract and 470.51 µg/mL GAE for the ethanolic extract (Gavamukulya et al., 2014). This could explain why *A. muricata* leaves accelerate wound healing in rats via antioxidant defense (Moghadamtousi et al., 2015). Previously, Baskar and collaborators demonstrated using different *in vitro* assays that the ethanolic extract of the leaves at 500 µg/mL showed maximum scavenging activity (90.05%) of ABTS (2,2-azinobis-(3-ethylbenzothizoline-6-sulphonate) radical cation followed by the scavenging of hydroxyl radical (85.88%) and nitric oxide (72.60%) at the same concentration. *A. muricata* extracts showed a higher *in vitro* antioxidant activity compared to leaves of *A. squamosa* and *A. reticulata,* its role as an effective free radical scavenger can be important in its therapeutic effects (Baskar et al., 2007).

However, two studies disagree with the previous authors. Nawwar and collaborators studied the constitutive phenolics compounds of *A.*

muricata in aqueous ethanol extracts of the leaves in association with its antioxidant effect. They assayed the effect on HaCaT human keratinocytes and its capability to reduce the interleukin 6 (Il-6) excretions after UVB radiation and observed that Il-6 production after UV irradiation was not influenced by this species leaves extract (Nawwar et al., 2012). Also, in the same year, other authors undertook a review of the antioxidant activity of the graviola and its potential active compounds, concluding that the leaves, the juice and the wine from the plant, did not contain high activity or concentration of antioxidants (Correa Gordillo et al., 2012).

On the other hand, the essential oil of *A. pickelii* and *A. salzmannii* manifested, in the oxygen radical absorbance (ORAC) and DPPH antioxidant assays, a significant capacity. In both essential oils, sesquiterpenes were the major terpenes. Bicyclogermacrene (45.4%), (E)-caryophyllene (14.6%), and *α* -copaene (10.6. %) are the main compounds in *A. pickelii*. In the case *A. salzmannii* standed out bicyclogermacrene (20.3%), (E)-caryophyllene (19.9%), delta-cadinene (15.3%), *α*-copaene (10.0%) and allo-aromadendrene (5.7%) (Costa et al., 2011).

For *A. squamosa* (custard apple) we have found several studies which examined the properties of various parts of this plant. In an *in vitro* study of the methanol and aqueous extracts of the fruit an important antioxidant activity was manifested by the first one, clearly due to a higher content of flavonoids and polyphenolic compounds (Nandhakumar and Indumathi, 2013). Others authors reported the effects of extracts obtained from different parts of the plant (leaves, bark, roots, and seeds) showing a good antioxidant activity from this species when it was evaluated by the oxygen radical absorbance (ORAC) capacity and the MTT assay(Mariod et al., 2012).

With respect to the enzyme inhibitory activity against lipoxygenase and acetylcholinesterase, crude extracts of fruit pulp and seeds of *A. squamosa* were investigated. The petroleum ether extracts of seeds exhibited higher inhibition (52.7%) of lipoxygenase activity at a concentration of 40 µg/200mL than the crude ethanolic extract of fruit pulp and seeds. The latter was also bioassayed for acetylcholinesterase inhibition and it was found ineffective (Sultana, 2008). The extract of the seeds also was investigated for its possible ameliorative effect in the regulation of hyperthyroidism in a mouse model and the effects of quercetin isolated in this extract suggested the involvement of this phytochemical in the mediation of antithyroidal activity of custard apple seed extract (Pand and Kar, 2007).

Different antioxidant models of screening were applied to study the free radical scavenging potential of *A. squamosa* leaves, when the ethanolic extract was tested at 1 mg/mL. The maximum scavenging of the radical cation ABTS observed up to 99.07% followed by the scavenging of the stable radical DPPH (89.77 %) and the nitric oxide radical (73.64%). The authors (in accordance with Baskar et al. for *A. muricata*) suggested that these findings support the therapeutic applications of the plant in traditional medicine (Shirwaikar et al., 2004b; Baskar et al., 2007).

Eleven ent-kauranes were obtained from the fresh stems of *A.squamosa*, and subjected to assays on the generation of superoxide anion (O_2^-) by human neutrophils. Most of them could significantly decrease O_2^- production. Any ent-kaurane manifested an inhibitory effect on nitric oxide generation, in response to formyl-L-methionyl-L-leucyl-L-phenylalanine (fMLP/CB) but not to phorbol myristate acetate (PMA) stimulation (Yang et al., 2004).

3.3.2. Anti-hyperglycemic-Antidiabetic: *A. dioica* A. St.-Hil*., A. montana* Macfad*., A. muricata* L.*, A. reticulata* L. *, A. senegalenseis* Pers. and *A. squamosa* L.

The oral administration of the crude methanol extract (100 mg/kg) and ethyl acetate extract (15 mg/kg) of *A. dioica* leaves in non-diabetic rats caused a hypoglycaemic effect by inhibition of the increase of glucose levels. According to the authors, this effect is due, at least in part, to the presence of flavonoid derivatives of quercetin and kaempferol in both extracts (Formagio et al., 2013a).

Moreover, it was reported that the juice of the leaves of the Brazilian species *A.montana* decreased glycaemia, lipids and body weight in the treated Wistar rats and moreover increased high-density lipoprotein-cholesterol (HDL-c) levels (Barbalho et al., 2012b). Author suggested that this species have beneficial effects in the prevention of diabetes mellitus and dyslipidemia and may thus contribute to the prevention of cardiovascular diseases.

On the other hand, *A. muricata* aqueous extract, at 100 and 200 mg/kg, administered orally showed antidiabetic activity in a study with normal and streptozotocin-induced diabetic rats. This activity can be explained by the hypolipidaemic effect and improvement in the metabolism of glucose due to antioxidant and protective action on pancreatic β-cells (Florence et al., 2014). In regards to this protective activity, Adeyemi et al. agree with previous researchers in a study with methanolic extracts in similar conditions. The results (100 mg/Kg dose) revealed regeneration of the β -cells of the pancreatic islet of rats treated with an extract of soursop (Adeyemi et al., 2010; Adeyemi et al., 2008).

Besides, this species showed a coadjuvant hypoglycemiant effect in a clinical study. Capsules with an ethanolic extract of *Annona muricata* leaves (180 mg) plus glibenclamide was administered during thirty days demonstrating that a glycaemic control in type 2 diabetic patients improved compared to a patient group receiving only glibenclamide (Arroyo et al., 2009).

An ethnobotanical investigation carried out interviewing african traditional healers highlighted the use of *A. muricata* and *A. senegalensis* for the treatment of diabetes. In a study, in the Togo Central Region about the use of plants for the treatment of diabetes mellitus and hypertension, *A. muricata* was the species most cited of 29 antidiabetic recipes using both, on its own and as an ingredient of antidiabetic herbal formulation from 3 or

4 species. *A. senegalensis* was also cited but used only in a formulation of 3 and 4 species (Karou et al., 2011).

The antihyperglycaemic effect of a methanolic extract of *A. reticulata* leaves was investigated using oral glucose tolerance tests in glucose loaded mice. Serum glucose level was reduced by 56.1% at a dosis of 400 mg/kg body weight. Overall results showed that leaves of *A. reticulata* possess significant and potent antihyperglycaemic activity (Jamkhande and Wattamwar, 2015).

Finally, the most studied species for antidiabetic activity is *A. squamosa* (custard apple). Panda and Khar (Panda and Khar, 2007a), in their study of the mechanism of action of its antidiabetic activity in a hexane extract and in an active constituent (quercetin-3-O-glucoside) of the leaves, suggested that the leaves exert its action by modulating insulin signaling through inhibition of protein-tyrosine phosphatase 1B (PTP1B) (Davis et al., 2012) and that the antidiabetic effects were probably due to the stimulation of insulin secretion and/or free radical scavenging properties of its active compounds. Another recent study, in streptozotocin induced diabetic rats, evaluated the effect of a hexane extract of this species. Doses of 100 and 400 mg/kg body weight increased insulin levels when compared with glimepiride (1 mg/kg). In addition, inhibited alpha-glucosidase activitywhen compared with acarbose (10 mg/kg). The authors suggested the hypoglycaemic activity is affected at two levels: by secreting insulin and also inhibiting the intestinal enzymes responsible for glucose metabolism (Ranjand Tripathi, 2014).

Gupta and collaborators have conducted several studies on the hypoglycemic and antidiabetic effect of the fruit pulp and an ethanolic and an aqueous extracts of the leaves of the *A. squamosa* (Gupta et al., 2005a). The water extract manifested hypoglycaemic and antidiabetic effects, acting with a high margin of safety, on different targets: enhancing insulin levels from pancreatic islets, increasing utilization of glucose in muscle and inhibiting the glucose output from the liver and reversing the abnormal lipid profile seen in diabetic animals. The authors concluded that this extract obtained from *A.squamosa* leaves could be useful to mantain suitable blood sugar and cholesterol levels. Other authors also support the antidiabetic claims of the aqueous custard apple extract compared with standard glibenclamide (Shirwaikar et al., 2004a).

With respect to the fruit pulp of *A. squamosa*, Gupta´s group observed that feeding diabetic animals between 2.5 and 5.0 g/kg body weight improved their glucose tolerance and the urine sugar, urine protein and glycohemoglobin was removed in diabetic rabbits. In addition, the utilization of dietary protein body weight, as well as the ratio of gain in body weight per gram of protein consumed, had augmented. The ethanolic extract also presented satisfactory results in fasting blood glucose (FBG) reduction (52.7%) and urine sugar (75%) as in the lipid profile: total cholesterol (TC) (49.3%) with increase (30.3%) in high-density lipoprotein (HDL) and decrease of 71.9 and 28.7% in low-density lipoprotein (LDL) and triglycerides (TG) levels, respectively. These activities are also promising for using in the control of metabolic syndrome (Gupta et al., 2005b, 2005c).

Finally, Ponrasu and Suguna study provides important information about the effect of an ethanolic extract of custard apple leaves on wound repair in streptozotocin-nicotinamide-induced diabetic rats. The histopathological evidence showed that treated wounds to heal much faster-improving rates of epithelization and wound contraction (Ponrasu and Suguna, 2012). The authors highlight the important activity on the acceleration of normal and diabetic wound healing through topical application.

All the above effects were confirmed in a recent randomized, open-label controlled study carried out in 25 diabetic patients using an extract of powdered custard apple leaves. The extract appears to exert its effect by raising the utilization of glucose by the muscles and improving the insulin level from pancreatic islets, significantly affected total cholesterol, LDL and insulin levels ($p < 0.01$ each). The authors concluded that *A. squamosa* can be used to control blood sugar levels with no adverse effects (Agarwal et al., 2014).

3.3.3. Hepatoprotective: *A.muricata* L*., A. senegalensis* Pers. and *A. squamosa* L*.*

Related to the hepatoprotective effects, the aqueous extracts of the leaves of *A. muricata* showed a protective, beneficial effect on hepatic tissues subjected to STZ-induced oxidative stress in rats.This effect is possibly due to the indirect improvement of the production of endogenous antioxidants and insulin and to the reduction in lipid peroxidation (Adewole and Ojewole, 2009). Padma and collaborators manifested, in albino rats with hepatotoxicity induced by carbontetrachloride, that the aqueous extract (100 µg/kg) caused a lowering in liver and brain total protein content and a preventive effect in rising of liver and brain lipid peroxidation and serum transaminases (Padma et al., 1999).

A. senegalensis leaves are used in different African countries in liver diseases. A study, about plants in Nigerian folklore medicine, validated the use of this species suggesting an antioxidant and drug detoxification effects. In rats, its aqueous extract showed the ability to scavenge free radicals *in vitro* and reversal of CCl_4-induced hepatocellular damage (Ajboye et al., 2010).

On the other hand, a methanolic extract of *A. squamosa* protected against isoniazid and rifampicin-induced oxidative liver injury in rats. The effect of extract was compared with a standard drug, silymarin. (Thattakudian Sheik Uduman et al., 2011).

3.3.4. Contraceptive: *A. reticulata* L. and *A. squamosa* L.

Ayurvedic medicine uses stem and leaves extracts of *A. reticulata* as an uterotonic drug. The seed extract manifested postcoital antifertility effect (Pathak and Zaman, 2014).

Singh and collaborators evaluated *in vitro* (using healthy human spermatozoa) and *in vivo* (in rats) the spermicidal effect of a hydroalcoholic extract from the seeds of *A. squamosa*. As a vaginal gel (HerbOshield™) this phytodrug showed, safely and effectively, spermicide activity in rats. After 20 seconds a complete immobilization of human spermatozoa was showed (100mg/mL, dose) and the treated animals demonstrated a 100% contraceptive effect as compared to nonoxynol-9-containing marketed formulation (Gynol II^{R}) that manifested only 67% contraceptive effect *in vivo.* The authors propose its development as a potential vaginal contraceptive for future use in humans (Singh et al., 2012).

Moreover, an evaluation of the anti-implantation activity of custard apple (*A. squamosa*) extracts has been found to have significant effects (Mishra et al., 1979), though in another study the effects of the custard apple extract on early pregnancy in rats showed that seed aqueous extract did not interfere with the reproductive performance of pregnant rats (Damasceno et al., 2002).

3.4. Digestive system diseases

3.4.1. Anti-ulcer: *A. cherimola* Mill., *A. muricata* L., A. *reticulata* L. and *A. squamosa* L.

A. cherimola is one of the species that has shown high anti-*Helicobacter pylori* activity. Methanolic extracts of its leaves and stem gave a significant inhibitory effect (MIC < 15.6 µg/mL) when it was measured by *in vitro* activity (Castillo-Juarez et al., 2009).

In addition, in the research carried out by Moghadamtousi and collaborators it was shown the gastroprotective effects of ethyl acetate extract of *A. muricata* leaves against ethanol-induced gastric injury models in rats. In addition, a pretreatment of rats with the extract caused a significant reduction in the level of malondialdehyde, as a marker for oxidative stress, associated with an increase in prostaglandin E2 activity and a significant reduction of the ulcer lesion index of rats pretreated, which was comparable to omeprazole. According to the authors, the protective activity on gastric wall mucus and suppressive effect against oxidative damage, manifested by this extract, are important evidence for its possible antiulcer potential (Moghadamtousi et al., 2014b). Other authors showed the significant decrease in the ulcerative lesion produced by the ethanol extract of *A. muricata* in rats in a dose-dependent manner. Authors suggested that tannins, flavanoids and triterpenes from the ethanolic extract of soursop leaves can elevate the mucosal non-protein sulfhydryl group content (Roslida et al., 2012).

Besides, an aqueous extract of *A. reticulata* leaves (100 mg/kg and 200 mg/kg) was investigated using ethanol and indomethacin-induced ulcer models in rats. Significant dose-dependent reduction in ulcer index was observed in rats treated with the extract and the reference standard drug, famotidine (3 mg/kg). The extract and famotidine also showed a significant decrease in acid volume and content. The extract showed a significant

improvement in glutathione and pH level as compared to vehicle-treated groups of rats. The study suggested that the significant antiulcer activity of aqueous extract of *A. reticulata* leaves may be due to cytoprotective, antisecretory and antioxidant potential of the phytoconstituents present in the extract (Jamkhande and Wattamwar, 2015).

In other studies, *A. squamosa* twigs have also demonstrated significant anti-ulcer effect. Thus, chloroform and hexane fractions attenuated ulcer formation in cold restraint, pyloric ligation and histamine models in rats and displayed anti-secretory activity *in vivo* through reduced free, total acidity and pepsin in pyloric ligation. Custard apple manifested a clear cytoprotection protection in alcohol and aspirin models and enhanced mucin level in pyloric ligation (Yadav et al., 2011).

Although the experimental researchs have shown promising results, there is not any clinical trial, so far, on the antiulcer treatment with these four species of *Annona*.

3.4.2. Antidiarrhoeal: *A.senegalensis* Pers.

The antidiarrhoeal properties of a methanol stem bark extract of *A. senegalensis*, using both *in vivo* and *in vitro* models, were investigated. The extract was safe at doses up to 5000 mg/kg and significant and at the dose of 10 mg/kg ($p<0.05$) decreased intestinal transit time in Swiss albino mice Concentrations of 0.2-3.2 mg/mL of the extract attenuated spontaneous contractions of the isolated rabbit jejunum, and those induced by acetylcholine in a concentration-dependent fashion. According to the authors, the study validates the use of the stem bark extract of this species in the treatment of diarrhoea (Suleiman et al., 2008).

3.5. Osteomuscular system and connective tissue diseases

3.5.1. Anti-inflammatory, antinociceptive, anti-arthritic, analgesic: *A. coriacea* Mart., *A. crassiflora* Mart., *A. dioica* A. St.-Hil., *A. diversifolia* Saff., *A. glabra* L., *A. montana* Macfad., *A. muricata* L., *A. reticulata* L., *A. senegalensis* Pers., *A. squamosa* L., *A. sylvatica* A. St.-Hil.

Annonas are consumed as fresh fruits, but are also widely used in folk medicine for treating pain and other inflammatory disorders. Several species of *Annona* and isolated compounds from the extracts have been investigated in relation to these properties.

In this sense, the methanolic extract of *A. crassiflora* showed an anti-inflammatory and chemo-preventive therapeutic potential. Oral treatment (100 and 300 mg/kg) of the extract significantly inhibited the carrageenan-induced ooedema formation and the myeloperoxidase enzyme (MPO) activity in rats. In addition, the total leukocytes in the pleurisy model were significantly reduced (Rocha, 2015).

Another study showed the anti-inflammatory activity of a crude methanol extract of *A. dioica* leaves. From 30 to 300 mg/kg this extract manifested in rats an anti-oedematogenic effect in carrageenan-induced paw ooedema, in a time- and dose-dependent manner. In addition, 6 h after the induction of paw oedema, a decrease of the MPO activity was exhibited at all doses of extract tested (Formagio et al., 2013b).

Even more, Carballo and collaborators undertook a study on the ethanolic extract of *A.diversifolia* leaves which supported its traditional use for the treatment of spasmodic and arthritic pain. They showed that this medicinal species possesses antinociceptive activity in rats and mice and they suggest that 5-HT(1A) receptors and endogenous opioids seem to be involved in the mechanism of action (Carballo et al., 2010).

Another study carried out with petroleum ether, ethyl acetate and methanol extracts of *A. reticulata* bark showed significant analgesic activity and CNS depressant activity. Extract at a dose of 100 mg/kg was used for both studies. The phytochemical study showed the presence of terpenes and steroids in the petroleum ether extract, alkaloids and flavonoids in the ethyl acetate extract while tannins, flavonoids and glycosides were observed in the methanol extract. Significant central analgesic activity was exhibited by the extracts in the hot plate method in mice. All extracts exhibited mild to moderate central nervous system depressant activity which might be due to increased concentration of GABA in the brain (Jamkhande and Wattamwar, 2015).

A study, that provides a scientific validation of the use of *A. senegalensis* against asthma and cough in the Ivorian pharmacopoeia, demonstrated that the ethanol extract of its leaves produced an important reduction in the number of inflammatory cells. The author attributed this activity to the presence of tannins and phenolic compounds in the extract (Yeo et al., 2011).

In a search for phytochemicals with anti-inflammatory activity, the cyclooxygenase-2 (COX-2) inhibitory activity of 15 typical Annonaceous acetogenins was examined in human epidermoid carcinoma cells and in Raw mouse leukemic monocyte-macrophages cells. Isodesacetyluvaricin, from the Formosan tropical fruit tree of *A. glabra,* exhibited the most potent activity (total inhibition at 5 μM) (Wu et al., 2012).

Other authors tested three cyclopeptides (cyclomontanins A, C and D) from the seeds of *A.montana* that revealed anti-inflammatory activity *in vitro* using the murine macrophage J774A.1 cell line (Chuang et al., 2008).

On the other hand, a 14-kDa lectin from *A. coriacea* seeds was able to induce leukocyte migration into the mice peritoneal cavity by mechanisms involving interactions of the lectin with cell-specific mannose recognition, leading to the release of cyclooxigenase 2 (COX-2) derived mediators and platelet activating factor (PAF) (Coelho et al., 2006).

From the bark of *A. reticulata* kaur-16-en-19-oic was isolated, and demonstrated a significant ($p < 0.05$) analgesic and anti-inflammatory activity similar to the control. The sesquiterpene fraction and the

unsaponified petroleum ether extract from this bark also manifested a significant peripheral and central analgesic and anti-inflammatory effects (Chavan et al., 2012a; 2012b).

The essential oil of *A. sylvatica* leaves, at doses of 20 and 200 mg/kg administered orally caused an important inhibition in carrageenan-and complete Freund's adjuvant-induced mouse paw oedema. The main compounds identified by gas chromatography-mass spectrometry in the essential oil were sesquiterpenes. The same investigation also showed an inhibitory effect on all cell cancer line tested. These results could reveal opportunities for the discovery of drugs with both anti-inflammatory and anticancer activities (Formagio et al., 2013b).

Two compounds isolated from petroleum ether extract of the bark of *A. squamosa,* caryophyllene oxide and 18-Acetoxy-ent-kaur-16-ene, similarly to the employee control, manifested significantly peripheral and central analgesic in addition to anti-inflammatory effect (Chavan et al., 2010, 2011). In other assay, 16β, 17-dihydroxy-ent-kauran-19-oic acid from the stems of *A. squamosa* showed inhibitory effects on respiratory burst and degranulation of human neutrophils through the inhibition of cytosolic calcium mobilization (Yeh et al., 2005).

Recent studies validated the ethno-medicinal use against pain and inflammation of the ethanol extract from *A. muricata* leaves in experimental animal models (De Sousa et al., 2010) (Chang and Roslida, 2012) (Roslida et al., 2012). In the same line, our research group has evaluated the antiinflammatory action of an aqueous extract of *Annona muricata* leaves (Dominican soursop) *in vivo* and *in vitro*. This extract exhibited a significant effect in the carrageenan inflammation, with an oedema decrease of 52 % at 500 mg/kg and in the topical TPA-induced oedema with a reduction of 78% at doses of 5 mg/ear in mice. This last effect was highly mediated by the reduction in the myeloperoxidase enzyme activity in the ear homogenates (92.5%). Besides, the aqueous extract of *A. muricata* exerted a dose-dependent reduction in the release of nitrite by LPS-stimulated murine macrophages, reaching at 500 µg/mL the highest inhibition (73 %) (Quilez et al., 2015).

In relation to the mechanism of action of the anti-inflammatory and analgesic activity manifested by *A. muricata* fruit extract, a recent study has shown that the inhibition of chemical mediators of inflammation and the interaction with the opioidergic pathway were implicated (Ishola et al., 2014).

3.6. Circulatory system diseases

3.6.1. Hypotensive: *A. muricata* L.

We only found a study of an aqueous extract of *A. muricata* leaves that showed a significant ($p<0.05$) dose-dependent decrease in blood pressure without changing the heart rates in rats. Researchers observed that the lowering effect of the blood pressure was mediated by peripheral

mechanisms involving antagonism of Ca^{2+}, without the intervention of muscarinic, histaminergic, adrenergic and nitric oxide pathways (Nwokocha et al., 2012).

3.7. Central nervous system disorders

3.7.1. Antidepressant, anxiolytic, anticonvulsivant: *A. cherimolia* Mill.*, A. diversifolia S*aff.*, A. muricata* L.*, A. purpurea* Moc. & Sessé ex Dunal*, A. senegalensis* Pers.

The alkaloid extract of the aerial parts of *A. cherimolia* showed that repeated treatment to mice with this extract produces a generalized increase in monominergic turnover (dopamine and 5-HT). This activity manifested synergism with antidepressant drugs, such as imipramine and clomipramine without cause a rise in locomotor activity (Martinez-Vazquez et al., 2012). According to the author, this study supports the use in the traditional Mexican medicine of *A. cherimolia* and strongly suggests its therapeutic potency as an antidepressant agent.

Anxiolytic-like actions, probably related with the GABA/ benzodiazepine receptor complex, have been shown by the hexane extract of *A. cherimola* and the alkaloid annomontine, isolated from *A. purpurea* (Rejón-Orantes et al., 2011; Lopez-Rubalcava et al., 2006). Palmitone, a secondary metabolite of polyketide origin identified from *A. diversifolia,* demonstrates an anxiolytic-like activity too, but behavioural studies suggest that this metabolite has a neuropharmacological profile different from the benzodiazepines such as diazepam (González-Trujano et al., 2006).

In others researches the anticonvulsant and neuroprotective activity of ethanol extract of leaves of *A. diversifolia* and palmitone has been manifested. Both of them did not induce a sedative-hypnotic effect and reduced, in rats, the severity of behavioural and EEG seizures caused by penicillin. This fact suggests that the decrease in the paroxystic effect by *A. diversifolia* is probably induced by palmitone through GABAergic neurotransmission (González-Trujano et al., 2001, 2006). Palmitone also prevents the pentylenetetrazole (PTZ)-caused neuronal damage in the CA3 hippocampal region (Cano-Europa et al., 2010). These studies justified and reinforce of the traditional use of this plant in epilepsy.

The fruit and the leaves of *A. muricata* are used in traditional medicine for their tranquillizing and sedative properties (Gupta, 1995, *Hasrat et al., 1997a*). Isoquinoline alkaloids (annonain, nornuciferine and asimilobine) isolated from the fruit were found to exhibit anti-depressive effects on test animals (Hasrat et al., 1997b). Studies in Nigeria demonstrated that the ethanol extract of graviola leaves significantly reduced the incidence of tonic pentylenetetrazol (PTZ) seizures and mortality (N'gouemo et al., 1997). Another study in albino rats found that administration of an ethanol extract of the stem bark of this plant significantly inhibited cold immobilization stress-induced, increase in lipid peroxidation in the liver and brain of albino rats (Padma et al., 1997).

Okoye and collaborators have validated the ethno-pharmacological use of *A. senegalensis* root bark to treat epilepsy and febrile seizures in Nigeria (Okoye et al., 2013). The bioactive-guided fractionation of the methanol-methylene chloride extract afforded an ethyl-acetate fraction and a diterpenoid (kaur-16-en-19-oic acid). These three samples to have potent anticonvulsant activity and significantly delayed, ($p<0.05$) in a dose-dependent manner, the onset of myoclonic spasms and tonic-clonic phases of seizures induced by PTZ and maximal electroshock seizures. The anticonvulsant effect is most likely being mediated through central inhibitory mechanisms.

4. Toxicity and interactions

The safety of a natural medicine is assessed in terms of its side effects and toxicity, as well as by any interactions when it is consumed together with other drugs. It is common for patients that are self-medicating with herbal medicines to be taking more than one drug and to be unaware of the potential interactions (Quílez et al., 2012).

Epidemiological studies linked the consumption of fruits and infusions or decoctions of *Annonaceas* to a prevalence of atypical Parkinsonism in Guadeloupe and in other tropical areas (Caparros-Lefebvre et al., 2006; Caparros-Lefebvre and Elbaz, 1999). This has been associated with the presence of acetogenins in this plant family. Champy et al. determined the concentration of annonacin in extracts of the fruit and leaves by mass spectrometry techniques. These authors state that, on average: a single fruit is estimated to contain about 15 mg of annonacin; a can of commercial nectar 36 mg; and a cup of infusion or decoction contains 140 µg. According to this data, if an adult, over the course of a year, consumes a daily intake of one fruit or can of nectar, then this adult will be eating proportionately the same amount of annonacin as that which induced brain lesions in rats receiving purified annonacin by intravenous infusion (Champy et al., 2005). The possible toxicity is related to the capacity of the tetrahydrofuran ring of acetogenins to chelate calcium ions. These formed complexes that help calcium cations in trespassing through cell membranes and in increasing intracellular calcium levels (Tundis et al., 2017).

The neurotoxicity of acetogenins included in the composition of the fruit and leaves of the *Annona* species have aroused the interest of several research groups. The fruit of *A. squamosa* from different batches has recently been analyzed for its quantity of squamocin by HPLC-MS, whereby evidence of a content of 13.5-36.4 mg/fruit was found. The authors suggest that the long-term consumption of this fruit should be considered a possible risk factor for neurodegenerative disorders (Bonneau et al., 2017). Moreover, dietary supplements containing extracts of *A. muricata* freely available in USA have been found to exert neurotoxicity in human neuron cultures (Höllerhage et al., 2015).

On the other hand, it is essential to determine the existence of synergies and antagonisms and the degree of interference with other drugs

in order to make the right choice from the range of phytomedicines available. The most appropriate professional advice (once the patient's situation has been studied) does not necessarily have to be that of halting the intake of the medicinal plant when it is compatible with the patient's medication (Williamson et al., 2013).

In our case, the information available on the interaction of *Annona* species is related to the treatment of diabetes. A study of the safety and potential for interaction with other drugs of an antidiabetic herbal formulation (ADD-199) that included *A. senegalensis* (used by some Ghanaian diabetic patients), found that the aqueous extract of ADD-199 had no overt organ-specific toxicity and demonstrated no potential for drug interactions via CYP-mediated metabolism on rats on subchronic administration (Nyarko et al., 2005). Moreover, as mentioned above, the coadjuvant administration of capsules of *A. muricata* leaves to glibenclamide improved the glycaemia control compared to patients treated solely with glibenclamide (Arroyo et al., 2009). Another study undertaken on an aqueous leaf extract of custard apple with glipizide, in the treatment of type-2 diabetes and its complications in rats, showed that this combination could reduce the dose of glipizide by up to 50%, thereby decreasing the risk of the need for insulin therapy (Kaur et al., 2012). These findings support important applications of *Annona* species in the therapy with antidiabetic drugs, in order to reduce the side effects and increase the effectiveness of these drugs.

5. Conclusions and future perspectives

From among the 27 revised species, four species are highlighted for their important pharmacological activities in most of the groups of illnesses: *A.muricata, A. squamosa, A. senegalensis,* and *A. cherimola*. Many experimental investigations have been performed with extracts from the leaves, bark, fruit, and seeds and have shown a wide range of pharmacological activities, such as antiprotozoal, antitumoural, antidiabetic, hepatoprotective, anti-inflammatory, analgesic, anxiolytic, and anticonvulsant activities. The experimental results from the pharmacological research enable the validation of their traditional uses in several of the groups of diseases mentioned above (Table 6) and reveal these plants to be a valuable source for therapeutic molecules. The number of investigations carried out with *A. muricata* and *A. squamosa* is noteworthy. These two species are extensively used in their countries of origin. Thus, the effective results from the research developed on the leishmanial, trypanocidal and antimalarial actions shown by these and another Brazilian *Annona* species support the uses of these plants in South American countries. Moreover, these species exerted insecticidal and larvicidal actions against *Plasmodium falciparum*, and constitute a good remedy for the control of vectors of malaria in aquatic habitats close to human settlements. On the other hand, several *in vivo* experiments can support the use of *A. senegalensis* against trypanosomiasis in Nigeria. The methods employed for testing the antiprotozoal activity are those validated by the WHO.

Although different parts of the species are used, the aqueous and ethanolic extracts of the leaves are those most frequently consumed in popular medicine. However, it should be noted that although some of the extracts have been subjected to a phytochemical screening, most of pharmacological work has been carried out on uncharacterized crude extracts and there are few studies on the chemical profile of the mayor components. In this respect, detailed chemical analysis studies would be necessary to obtain standardized extracts. Besides, decoctions and infusions are fundamental in traditional medicinal systems and therefore their active compounds and pharmacological activities should be investigated in depth.

Most of the revised articles meet the quality criteria demanded in pharmacological studies; however, we have observed great variability in the dosage range, especially when the samples are tested in experimental animals and in only some of the *in vivo* studies, the amount of the extract used in terms of the equivalent concentration of the active ingredient, was extrapolated from the amount traditionally consumed. This does not occur in studies carried out *in vitro* or in cell cultures where more homogeneous doses are tested. In the most investigated pharmacological activities, possible mechanisms of actions have been determined but however further investigations should be carried out along this line in order to accurately elucidate the action of the different active components.

Moreover, there are no studies on the bioavailability of the phytochemicals, upon which health benefits depend. More extensive *in vivo* studies are required on the absorption and bioavailability of the extracts and on their fractions in order to better understand the amount of active metabolites responsible for the pharmacological actions.

The main classes of constituents of the *Annona* species are acetogenins, alkaloids, ent-kaurene diterpenoids, phenols, and essential oils. The acetogenins are mainly contained in the seeds, although they have also been detected in smaller quantities in the leaves and in the pulp of the fruit. The chemistry of the Annonaceous acetogenins (ACGs) has been extensively investigated since these compounds possess very potent antitumoural activity. Many of the assays were carried out with the isolated acetogenins in various lines of tumour culture cells and were found to be effective at very low doses even in multidrug-resistant tumours, and hence constitute promising compounds in the treatment of different types of cancers. However, there are a few experimental assays in different *in vivo* models of cancers.

Four of the *Anonna* species have a recognized traditional use in tumour processes: *A. muricata (*soursop), *A. squamosa* (custard apple), *A. senegalensis* (wild custard apple), and *A. cherimola* (cherimola). Among these, *A. muricata* is reported with the highest number of studies and has provided several patents and commercial products. Nevertheless, the popular use of these plants, without having been clinically tested, constitutes a major cause for concern. To the best of our knowledge, there are no studies with extracts rich in acetogenins in the clinical field. In this respect, further clinical investigations would be necessary to establish

optimal and safe doses of consumption on the application of these medicinal plants.

Moreover, it would be necessary to ascertain the total content of acetogenins present in the extracts of their seeds, fruits, and leaves due to their associated to neurological damages as Parkinsonism after a long comsumption. In addition, further detailed investigation into acute and chronic toxicities on animals would be recommended. This could provide a better understanding of the potential side effects of these *Annona* extracts and identify the responsible compounds.

The present review provides a comprehensive understanding of the pharmacology of main species of Annonas and support their ethnomedicinal uses. Other species of Annonas, lesser-used in popular medicine, remain to be investigated.

Conflict of interest

The authors have no conflict of interest with the context of this report.

7. Author contributions

All authors equally participated in the search for information. All authors collected and analyzed data from the multiple articles to be included in the tables and in the manuscript. Quilez and De la Puerta drafted the manuscript. All authors read, critically revised and gave the final approval to the version to be submitted for publication.

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