

Chapter

Acetogenins from *Annona muricata* as Antimicrobial Agents

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Abstract

Annona muricata L. is a plant belonging to the Annonaceae family and is highly appreciated for its bioactive compound content; between them are acetogenins. Acetogenins are molecules with aliphatic chains and a lactonic group, and they have been isolated from various parts of the tree (leaves, stem, and root) or fruit (peel, pulp, columella, and seeds). Also, they present different biological activities such as insecticidal, antiviral, and antitumoral. However, has it been demonstrated that acetogenins are antimicrobial. This chapter aims to show the scientific evidence of the antimicrobial effect of crude extracts or acetogenins isolated from *Annona muricata* on Gram-positive and Gram-negative bacteria and some yeasts.

Keywords: *Annona muricata*, acetogenins, bioactive compounds, mechanism of action, antimicrobial activity

1. Introduction

Annona muricata L. (*A. muricata*) is belonging to the Annonaceae family. It is mainly known in Mexico as guanabana. However, in some countries, it is also known as corossolier (French), graviola (Portuguese), zuurzak (Germany), durian belanda (Malaysian), and munolla (India) [1, 2]. Fruit is highly consumed by exquisite flavor and aroma; stems, leaves, and roots from *A. muricata* extracts have been used to combat various human ailments such as cancer, diabetes, hypertension, cardiovascular problems, anti-inflammatory, gastrointestinal disorders, and parasitic infections [3–5]. It is attributed to bioactive compounds between them, phenolic compounds, terpenes, alkaloids, and acetogenins (ACGs) [6].

ACGs are the most studied biological compounds because they are specific to the Annonaceae family. They can inhibit the mitochondria's complex I and NADH oxidase, causing cellular apoptosis [7, 8]. In addition, ACGs can affect alternative targets in cells, with possible covalent interaction, such as their ability to inhibit metalloproteins, chelate calcium, and modulate the histone H3 phosphorylation. Due to this, they exhibit essential biological activities such as insecticidal, antiviral, antitumor, and antimicrobial [5, 9–11].

This chapter aims to demonstrate the potential antimicrobial effect of crude extract, acetogenic fractions, or purified ACGs from *A. muricata* against different bacteria and yeasts, compiling recent scientific information.

2. *Annona muricata*

A. muricata L. is native to the tropical regions of Central and South America, Western Africa, and Southeast Asia [1, 5, 12]. **Figure 1** shows the *A. muricata* tree and fruit (edible fraction and seeds). The *A. muricata* tree has a height ranging from 4 to 10 m, with a diameter between 13 and 83 cm. It grows upright, and the inflorescence appears on the branches. The fruit is dark green with thorn-shaped protuberances on its pericarp, which reach average weights ranging from 300 g to 4 kg, with a diameter of 15 to 20 cm and a height of 17–25 cm. The endocarp has an abundant white fleshy part with a bittersweet flavor, an exotic smell, and abundant black seeds. The number of seeds is proportional to the size of the fruit, with around 100 or more seeds per fruit [5, 12–14]. *A. muricata* tree flourishes in altitude conditions below 1200 m above sea level, with high relative humidity (60–80%), 25–28°C temperatures, and abundant annual rainfall (greater than 1500 mm). The tree usually blooms and bears fruit throughout the year; however, there are defined seasons, which will depend on the geographical altitude of the tree [5, 13].

On the other hand, the *A. muricata* plant is rich in acetogenins. It has been demonstrated that these compounds in crude extracts, purified fractions, or purified compounds have *in vitro* and *in vivo* biological activities such as anticancer, antiviral, and antimicrobial [5, 15].

3. Acetogenins from *Annona muricata*

A. muricata has a significant content of bioactive compounds such as phenolic compounds, glucosinolates, steroids, saponins, glycosides, terpenoids, polyesterols, alkaloids, and mainly ACGs with unique chemical structures. These bioactive compounds have been extracted from the leaves [4, 16–22], stem [21], root [21], pulp [23, 24], seed [11, 21, 25–27], and peel [21].



Figure 1.
Tree and fruit (edible fraction and seeds) of Annona muricata grown in Camichin of Jauja, Tepic, Nayarit, Mexico.

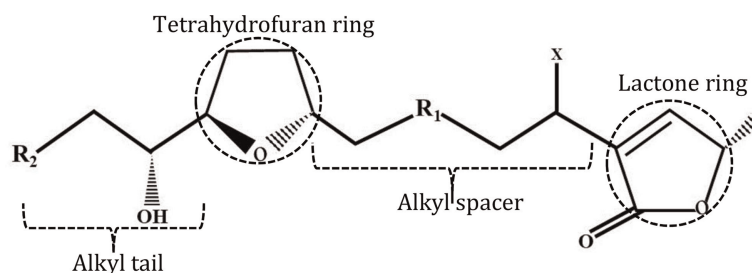


Figure 2.
 The general structure of an Annonaceous acetogenin shows the 4 segments of which it is made up (x is OH or O group, R_1 and R_2 are carbon radicals).

ACGs are molecules distinguished by a long aliphatic chain of 35 to 37 carbon atoms attached to one, two, or three tetrahydrofuran or tetrahydropyran rings in its central region. The chemical structure (Figure 2) of most acetogenins is characterized by four segments: (a) an α - β -unsaturated γ -lactone ring, (b) an alkyl spacer linking the γ -lactone, (c) one to three tetrahydrofuran (THF) rings with flanking OH groups or other groups such as ketone, epoxy and tetrahydropyran, and (d) a long alkyl tail. The presence of two OH and acetyl groups adjacent to the THF ring(s) is a common structural feature of many acetogenins. The type of ACGs (linear, epoxy, mono-, bis-, tri-, and tetrahydrofuran) is determined by the number of central oxygenated groups, mostly tetrahydrofuran (THF) traces, while the subtype is defined by the structure of the lactonic ring (the α , β -unsaturated being subtype 1) [6, 7, 28–30]. Several types of ACGs have been characterized based on the nature of the present functional groups. ACGs exhibit many biological properties such as cytotoxic, antitumoral, antiparasitic, pesticidal, and antimicrobial activities [7].

According to the literature, more than 120 ACGs are present in aqueous, methanol, ethanol, or other organic solvent extracts prepared from various parts of the *A. muricata* plant or fruit [29]. In this sense, one of the main isolated ACGs in this species is annonacin, which has been found in greater abundance in leaves [31, 32], fruit [32–34], seeds [11, 25–27, 35], peel [36], and roots [37]. Table 1 shows the main types of ACGs isolated from the various parts of the plant or fruit of *A. muricata*.

Organ	Acetogenins	Molecular formula	Type	Reference
Seeds	Diepomuricanin-A ^b	$C_{35}H_{62}O_4$	ACGs without THF (Bis-epoxy)	Leprevote et al. [38]
	Corepoxylone (CO,10)	$C_{35}H_{62}O_5$		Gromek et al. [39]
	Solamin	$C_{35}H_{64}O_5$	Mono-THF α , α' dihydroxylated	Myint et al. [40]
	15-palmitoylsolamin	$C_{51}H_{94}O_6$		Gleye et al. [41]
	15-oleylsolamin	$C_{53}H_{96}O_6$		Gleye et al. [41]
	Corossolin	$C_{35}H_{64}O_6$		Cortes et al. [42]
	Corossolone (CO,10)	$C_{35}H_{62}O_6$		Cortes et al. [42]

Organ	Acetogenins	Molecular formula	Type	Reference
	<i>Cis</i> -goniothalamicin	C ₃₅ H ₆₂ O ₇	Mono-THF α, α' dihydroxylated (Tetrahydroxylated and tri hydroxylated ketonic)	Rieser et al. [43]
	Arianacin + javoricin	C ₃₅ H ₆₂ O ₇		
	Rollinecin-A + B	C ₃₅ H ₆₄ O ₇		
	<i>Cis</i> -corossolone (CO-10)	C ₃₅ H ₆₂ O ₆		Liaw et al. [31]
	<i>Cis</i> -annonacinone (CO,10)	C ₃₅ H ₆₂ O ₇		Rieser et al. [43]
	<i>Cis</i> -annomontatacin	C ₃₇ H ₆₈ O ₇		Liaw et al. [44]
	Muricin-G (or annomocherin)	C ₃₅ H ₆₂ O ₇		Kim et al. [45, 46]
	Muricatin-C (CO,10)	C ₃₅ H ₆₂ O ₈	Mono-THF α, α' dihydroxylated (Polyhydroxylated and tetrahydroxylated ketonic)	Li et al. [47]
	Muricatatin-C (CO,10)	C ₃₅ H ₆₆ O ₈		
	Muricatalin	C ₃₅ H ₆₄ O ₈	Mono-THF α- or α' monohydroxylated (With OH at C4)	Ghi et al. [48]
	Muricatin-B	C ₃₅ H ₆₄ O ₈		Li et al. [47]
	Annopentocin-A + B	C ₃₅ H ₆₄ O ₈		Zeng et al. [49–51]
	Annopentocin-C	C ₃₅ H ₆₄ O ₈		Zeng et al. [49–51]
	Muricin-A	C ₃₅ H ₆₂ O ₇		Chang and Wu, [52]
	Muricin-Bd			
	Muricin-C			
	Muricin-D			
	Muricin-E			
	Muricin-F			
	Annocatalin	C ₃₅ H ₆₄ O ₇	Mono-THF α- or α' monohydroxylated (Without OH at C4)	Liaw et al. [31]
	Muricin-H	C ₃₅ H ₆₄ O ₆		
	Muricin-I	C ₃₅ H ₆₆ O ₆		
	Annomuricinone-D	C ₃₅ H ₆₄ O ₈	Mono-THF iso-ACGs	Zeng et al. [49–51]
	Annocatacin-A	C ₃₅ H ₆₂ O ₆	Adjacent bis-THF α-monohydroxylated γ-lactone	Chang et al. [53]
	Annocatacin-B			
	Robustecin	C ₃₅ H ₆₂ O ₅		Gleye et al. [54, 55]
	Bullatacin	C ₃₇ H ₆₆ O ₇	Adjacent bis-THF α, α' -dihydroxylated (Trihydroxylated and tetrahydroxylated)	López-Romero et al. [25]
	Squamostatin-D	C ₃₇ H ₆₆ O ₇	Non-adjacent bis-THF	
	Pseudoanonacin	C ₃₅ H ₆₇ O ₇	Mono-THF α, α' dihydroxylated (Tetrahydroxylated and trihydroxylated ketonic)	
	Annonacin	C ₃₅ H ₆₄ O ₇		

Organ	Acetogenins	Molecular formula	Type	Reference	
	Squamocin	C ₃₇ H ₆₆ O ₇	Adjacent bis-THF α , α' - dihydroxylated (Trihydroxylated, dihydroxylated ketonic, tetrahydroxylated and pentahydroxylated)		
	Isodesacetylvaricin	C ₃₇ H ₆₆ O ₆	Adjacent bis-THF α , α' - dihydroxylated (dehydroxylated)		
	Desacetylvaricin	C ₃₇ H ₆₆ O ₆			
Leaves	Annomutacin	C ₃₇ H ₆₈ O ₇	Mono-THF α , α' -dihydroxylated (Tetrahydroxylated and trihydroxylated ketonic)	Wu et al. [56]	
	Cis-corosolone (CO-10)	C ₃₅ H ₆₂ O ₆		Liaw et al. [31]	
	Annomuricin-A	C ₃₅ H ₆₄ O ₈	Mono-THF α , α' -dihydroxylated (Polyhydroxylated and tetrahydroxylated ketonic)	Wu et al. [57]	
	Annomuricin-B	C ₃₅ H ₆₄ O ₈			
	Muricatocin-A	C ₃₇ H ₆₆ O ₇		Wu et al. [58]	
	Muricatocin-B	C ₃₅ H ₆₇ O ₇			
	Muricatocin-C	C ₃₅ H ₆₄ O ₇		Wu et al. [59]	
	Annomuricin-C	C ₃₇ H ₆₆ O ₇			
	Annohexocin	C ₃₇ H ₆₆ O ₇		Zeng et al. [60]	
	Annomuricin-E	C ₃₅ H ₆₄ O ₈		Kim et al. [61, 62]	
	Muricapentocin	C ₃₅ H ₆₄ O ₈			
	Murihexocin-A + B	C ₃₅ H ₆₄ O ₉	Mono-THF α - or α' - monohydroxylated (THF α - monodihydroxylated)	Zeng et al. [49–51]	
	Annopentocin - A + B	C ₃₅ H ₆₄ O ₈			
	Annopentocin-C	C ₃₅ H ₆₄ O ₈			
	Annomuricinone-D	C ₃₅ H ₆₇ O ₇	Mono-THF (Mono-THF iso)		
	Muricoreacin	C ₃₅ H ₆₄ O ₉	Mono-THF α - or α' - monohydroxylated (THF α - monodihydroxylated)	Kim et al. [61, 62]	
	Murihexocin-C	C ₃₅ H ₆₄ O ₇			
	Muricatalicin	C ₃₅ H ₆₄ O ₈	Mono-THF α , α' -dihydroxylated (Polyhydroxylated and tetrahydroxylated ketonic)	Gui and Yu [63]	
	Annonacinone-A	C ₃₅ H ₆₄ O ₇	Mono-THF (Mono-THF-iso)	Wu et al. [56–59]	
	Root	Montecristin	C ₃₇ H ₆₆ O ₄	Vicinal dihydroxylated and olefinic linear	Gleye et al. [64, 65]
		Cohibin-A	C ₃₅ H ₆₆ O ₆		
		Cohibin-B	C ₃₅ H ₆₄ O ₄		
Muriedienin-1		C ₃₅ H ₆₂ O ₂	Olefinic and acetylenic linear	Gleye et al. [66, 67]	
Muriedienin-2		C ₃₇ H ₆₆ O ₂			
Chatenaytrienin-1 + 2		C ₃₅ H ₆₀ O ₂			
Chatenaytrienin-3 + 4		C ₃₇ H ₆₄ O ₂			
Muricadienin		C ₃₅ H ₆₂ O ₂			
Muricadienin-3 + 4		C ₃₇ H ₆₆ O ₂			

Organ	Acetogenins	Molecular formula	Type	Reference
	Sabadelin	C ₃₅ H ₆₂ O ₃	ACGs without THF rings; epoxy ACGs	Gleye et al. [68]
	Coronin	C ₃₇ H ₆₄ O ₄	ACGs without THF rings (Bis-epoxy ACGs)	Gleye et al. [69]
	Cis-solamin	C ₃₅ H ₆₄ O ₅	Mono-THF α, α' dihydroxylated (Dihydroxylated)	Gleye et al. [67]
	Cis panatellin	C ₃₅ H ₆₄ O ₅		
	Cis-uvariamicin-IV	C ₃₇ H ₆₈ O ₅		
	Cis-uvariamicin-I	C ₃₇ H ₆₈ O ₅	Mono-THF α, α' dihydroxylated (Trihydroxylated and dihydroxylated ketonic)	
	Cis-reticulacin	C ₃₅ H ₆₂ O ₅		
	Cis-reticulatacin-10-one	C ₃₇ H ₆₈ O ₆		
Ripe Fruit	Epomurinin-A	C ₃₅ H ₆₂ O ₃	ACGs without THF rings; epoxy ACGs	Melot et al. [70]
	Epomurinin-B	C ₃₅ H ₆₂ O ₃		
Stem bark	Epoxymurin-A	C ₃₅ H ₆₂ O ₃		Hisham et al. [71]
	Epoxymurin-B	C ₃₅ H ₆₂ O ₃		Roblot et al. [72]
	Epomuricenin-A	C ₃₅ H ₆₂ O ₃		Hisham et al. [71]
	Epomuricenin-A	C ₃₅ H ₆₂ O ₃		Roblot et al. [72]
Pulp	Annonamuricin-B	C ₃₅ H ₆₄ O ₇	Mono-THF α, α'-dihydroxylated (Tetrahydroxylated and trihydroxylated ketonic with OH at C4)	Sun et al. [73]
	Annonamuricin-C	C ₃₅ H ₆₄ O ₇		
	Annonamuricin-D	C ₃₅ H ₆₄ O ₇		
	Muricin-N	C ₃₅ H ₆₄ O ₇		Sun et al. [74]
	muricenin	C ₃₅ H ₆₆ O ₃		
	Muricin-J	C ₃₅ H ₆₄ O ₇		
	Muricin-K	C ₃₅ H ₆₄ O ₇	Mono-THF α- or α'-monohydroxylated (with OH at C4)	Sun et al. [75]
	Annonamuricin-A	C ₃₅ H ₆₄ O ₇		
	Muricin-M	C ₃₅ H ₆₄ O ₇		
	Muricin-O	C ₃₅ H ₆₄ O ₇		Sun et al. [75]
Peel	Annonacin	C ₃₅ H ₆₄ O ₇	Mono-THF α, α' dihydroxylated (Tetrahydroxylated and trihydroxylated ketonic)	Jaramillo et al. [36]
	Annonacin A	C ₃₅ H ₆₄ O ₇		
	Annomuricin A	C ₃₅ H ₆₄ O ₈	Mono-THF α, α'-dihydroxylated (Polyhydroxylated and tetrahydroxylated ketonic)	

THF: Tetrahydrofuranic; ACGs: acetogenins.

Table 1.
Main acetogenins isolated from the different parts of the plant or fruit of *A. muricata*.

The most isolated ACGs are from the *A. muricata* seeds, leaves, and roots. Also, this table shows that the primary type of ACGs reported in this genus are mono-THF type. Thus, the following section will address the mechanism of action of ACGs as antimicrobials.

4. Mechanism of action of acetogenins as antimicrobials

It has been demonstrated that the biological activities are dependent on the ACGS chemical structure, the presence of either of the two OH groups adjacent to the THF ring is sufficient to maintain potent activity, and only when the γ -lactone and THF ring molecules are directly linked by an alkyl spacer (the optimal length of which is about 13 carbon atoms), ACGs act as a potent inhibitor [76, 77]. Shimada et al. [78, 79] demonstrated that a robust interaction could occur between the THF rings and the polar terminals of phospholipids within liposome membranes. They proposed that these THF rings serve as a hydrophilic anchor to the membrane, enhancing the alignment and configuration of the functional groups of ACG. The terminal lactone is considered a component of the domain spacer, which is the segment of the molecule expected to directly engage with the active site of the enzyme in mitochondrial complex I. This interaction is facilitated through lateral diffusion within the inner mitochondrial membrane.

There are different proposed mechanisms of ACGs as antimicrobials. The established first (Figure 3A) was that they are the most potent inhibitors of NADH ubiquinone oxide reductase (located in complex I) of the mitochondrial respiratory chain in eucaryotic and procaryotic cells, and NADH oxidase located in the

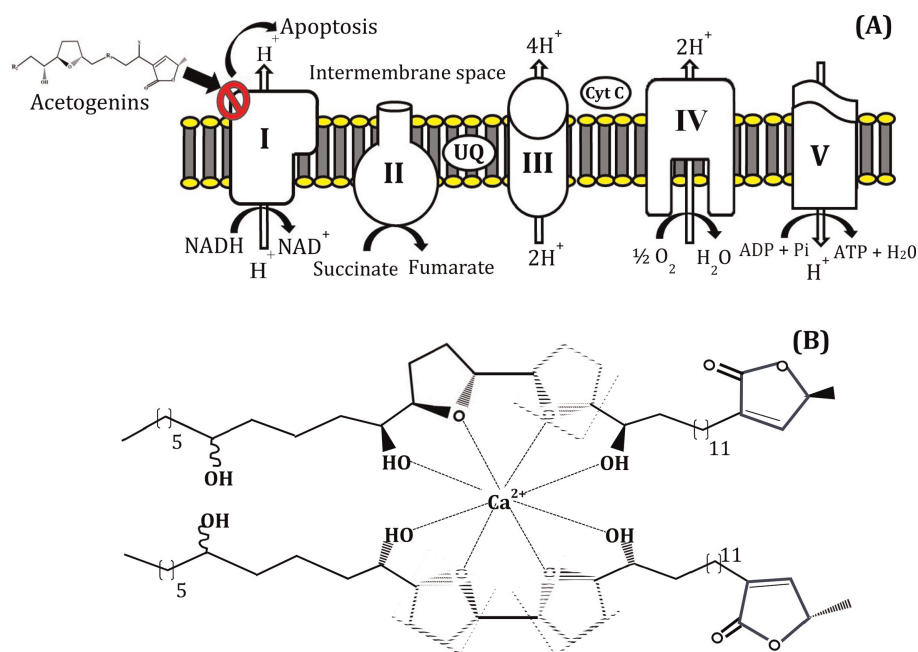


Figure 3. (A) Mechanism of action of acetogenins and their effect on mitochondrial complex I (NADH ubiquinone oxidoreductase). (B) Interaction of acetogenins with calcium ions forming a chelating complex (adapted of Bermejo et al. [7] and Liaw et al. [80]).

plasma membrane of bacteria, which reduces the production of ATP in the cells causing apoptosis [7]. By inhibiting these enzymes, ACGs modify the transit of negatively charged ions through the respiratory chain and inhibiting proton cascades that affect cellular respiration and directly inducing apoptosis, autophagy, or cell cycle interruption, causing cell death [4, 77].

Another mechanism that involves the THF segments of ACG and their adjacent hydroxy groups is the independent interactions with bivalent cations, such as Ca^{2+} and Mg^{2+} . Individual ACG molecules can assume novel secondary structures distinct from their free counterparts. Bivalent cations can form complexes with multiple ACG molecules, allowing THF nuclei and neighboring hydroxy groups to engage with ions and form chelating complexes. The creation of chelating complexes involving ACG and Ca^{2+} can potentially disrupt intracellular calcium balance by sequestering these ions within the ACG- Ca^{2+} complexes (**Figure 3B**). This process facilitates the movement of ions across the mitochondrial membrane, driven by the hydrophobic nature of the complexes. Consequently, this leads to elevated calcium levels within the cell, specifically within the mitochondria, resulting in a decrease in mitochondrial membrane potential and the initiation of proapoptotic signal [80, 81].

On the other hand, other studies suggest that the bioactivity of ACG mixtures also depends on their structure, purity, concentration, and the type of microorganism evaluated [26, 82]. Therefore, in the following section, we will discuss the effect of these compounds as antimicrobials.

5. Antimicrobial activity of acetogenins

The antimicrobial effect of ACGs has been little explored; however, this review shows all the studies on the antimicrobial effect of ACGs on various Gram-positive and Gram-negative bacteria, some yeasts, and their advantages compared with antibiotics (see **Table 2**).

The study developed by Oyedeji et al. [16] demonstrated that an extract from *A. muricata* leaves (1000 $\mu\text{g}/\text{disc}$) presented similar inhibition to the antibiotic tested (streptomycin at 10 $\mu\text{g}/\text{disc}$) when they were tested against *S. Typhi* and *E. faecalis* with inhibition of 28.3 mm and 26.3 mm, respectively. Similarly, streptomycin presented inhibition of 27.3 mm and 28.6 mm, respectively. In addition, these authors found a bactericidal minimum concentration (BMC) of 0.125 $\mu\text{g}/\text{mL}$ against *S. Typhi* and 0.0625 $\mu\text{g}/\text{mL}$ for *E. faecalis*. Another study development by Pinto et al. [4] demonstrated that an *A. muricata* leaf extract at concentrations of 0.0025–5 mg/mL showed bactericidal effect (MIC = 78–625 $\mu\text{g}/\text{mL}$) against *Salmonella Typhimurium*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* and a bacteriostatic significant impact (MIC = 39–1250 $\mu\text{g}/\text{mL}$) against *Bacillus cereus*, *Enterococcus faecalis*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Salmonella choleraesuis*, and *Shigella dysenteriae*. These authors concluded that the antibacterial action of *A. muricata* leaf extract varied depending on the type of microorganism. Still, it was effective against both Gram-positive and Gram-negative bacteria. The results could be explained by bioactive compounds that damage the bacterial membrane by increasing membrane permeability and the leakage of nucleotides that inhibit bacterial growth and induce cell death. The authors also mention that damage to the membranes of Gram-negative bacteria may be more significant than in Gram-positive bacteria because Gram-positive bacteria consist of a thick cell wall surrounded by several layers of peptidoglycan and surface glycopolymers, such as teichoic acids; in contrast,

Sample type	Part of plant or fruit	Concentration (mg/mL)	Microorganism	Results	References
Aqueous-methanol Extract	Leaves	0.00125–0.4	<i>S. aureus</i> , <i>E. faecalis</i> , <i>B. subtilis</i> , <i>C. sporogenes</i> , <i>P. aeruginosa</i> , <i>K. pneumonia</i> , <i>E. coli</i> , and <i>S. marcescens</i>	The MIC values ranged between 0.0313–0.0625 µg/mL. It was most inhibitory against <i>S. typhi</i> , <i>S. aureus</i> , <i>E. faecalis</i> , <i>K. pneumonia</i> , and <i>S. marcescens</i>	Oyedepi et al. [16]
Aqueous extracts	Leaves	0.01–0.2	<i>S. mutans</i> , <i>S. mitis</i> , <i>P. gingivalis</i> , <i>P. intermedia</i> , and <i>C. albicans</i>	Shows a bacterial inhibition of 20.8% against <i>S. mutans</i>	Pai et al. [17]
Aqueous-ethanol-methanol extract	Leaves	0.0015–2	<i>hydrophila</i> , <i>B. subtilis</i> , <i>A. niger</i> , and <i>S. aureus</i>	A MIC of 500–1000 µg/mL was determined against <i>B. subtilis</i> , <i>S. aureus</i> , <i>A. hydrophila</i> and <i>A. niger</i> .	Ulusola et al. [18]
Methanolic Extract	Leaves	0.0025–5	<i>B. cereus</i> , <i>E. faecalis</i> , <i>S. aureus</i> , <i>E. aerogenes</i> , <i>E. cloacae</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. Typhimurium</i> , <i>S. Choleraesuis</i> , and <i>S. dysenteriae</i>	Bactericidal effect for <i>S. typhimurium</i> , <i>S. aureus</i> , and <i>P. aeruginosa</i> (MIC = 78–625 µg/mL) and bacteriostatic for the other bacteria tested (MIC = 39–1250 µg/mL)	Pinto et al. [4]
Fractionated extracts	Fresh pulp	2	<i>S. Typhimurium</i> , <i>E. aerogenes</i> , <i>E. faecalis</i> , <i>B. subtilis</i> , <i>R. stolonifer</i> , and <i>C. gloeosporioides</i>	Higher antimicrobial activity of all fractions was observed for <i>E. aerogenes</i> (25.95–41.15%) and <i>C. gloeosporioides</i> (10–59.90%).	León-Fernández et al. [23]
Ethanollic extracts	Leaves	50–400	<i>S. mutans</i>	Antibacterial activity was observed at all concentrations tested with 10–80% inhibition.	Rodriguez-Perez and Millones-Gomez [19]
Ethanollic extracts	Leaves	100	<i>C. albicans</i>	An inhibition percentage of 96.9% against <i>C. albicans</i> was observed.	Rustanti and Fatmawati [20]
Aqueous-ethanol extract	Leaf, stem, seed, peel, and root	0.25–32	Methicillin-resistant <i>S. aureus</i>	A synergistic effect of streptomycin and tetracycline was observed with <i>A. muricata</i> extracts, with a 32-fold increase in antibacterial activity against <i>S. aureus</i> (methicillin-resistant).	Neglo et al. [21]

Sample type	Part of plant or fruit	Concentration (mg/mL)	Microorganism	Results	References
Crude extract and isolated ACGs	Seeds	0.0125–4	<i>C. albicans</i> , <i>C. glabrata</i> , <i>C. tropicalis</i> , and <i>C. krusei</i>	The highest inhibition was observed with ACGs isolated at 400 µg/mL against <i>C. albicans</i> (15.50 mm), <i>C. tropicalis</i> (14 mm), and <i>C. krusei</i> (13.50 mm).	López-Romero et al. [25]
Crude extract and isolated ACGs	Seeds	0.0125–4	<i>S. mitis</i> , <i>L. monocytogenes</i> , <i>S. aureus</i> , <i>E. faecalis</i> , <i>S. mutans</i> , <i>S. salivaris</i> , <i>A. hydrophila</i> , <i>E. coli</i> , <i>S. choleraesuis</i> , <i>B. cenocepacia</i> , <i>S. paratyphi</i> , and <i>K. pneumoniae</i>	The isolated ACGs show the highest antibacterial effect against <i>E. faecalis</i> (11–15.67 mm), <i>L. monocytogenes</i> (12–18 mm), <i>A. hydrophila</i> (10.33–11.67 mm), <i>B. cenocepacia</i> (11–12 mm), and <i>S. paratyphi</i> (11–15.67 mm) at all concentrations tested, and a MIC 0.009–12.50 µg/mL.	Aguilar-Hernández et al. [26]
ACGs-Nanosuspensions	Seeds	0.0987, 0.177 and 0.32	<i>E. faecalis</i> and <i>Listeria monocytogenes</i>	The highest inhibition for <i>E. faecalis</i> (87%) and <i>L. monocytogenes</i> (75%) was observed with up to 12 h of exposure to 320 µg/mL	López-Romero et al. [27]
ACGs-Nanosuspensions	Seeds	0.0987, 0.177 and 0.32	<i>E. faecalis</i> and <i>Listeria monocytogenes</i>	The highest inhibition for <i>E. faecalis</i> (83%) and <i>L. monocytogenes</i> (86%) was observed with up to 12 h of exposure to 320 µg/mL	Montalvo-González et al. [11]

MBC = Minimum bactericidal concentration; MIC = Minimum bactericidal concentration; ACGs: acetogenins.

Table 2.

Antimicrobial effect of extracts from different parts of the plant or fruit *A. muricata* against various microorganisms studied.

Gram-negative bacteria have an outer membrane, lipoproteins, lipopolysaccharides, and a single layer of peptidoglycan. The bacterial membrane limits the entry of drugs or chemicals and serves as an essential barrier to keep intracellular proteins intact. Therefore, Gram-positive bacteria may have reduced permeability to bioactive compounds from *A. muricata* extracts [4].

On the other hand, the same authors mentioned that the extract inhibited the bacteria more rapidly and with greater potency compared to antibacterial agents with slow elimination kinetics. Thus, another study showed that the *A. muricata* extract (9.75, 19.5, and 39 µg/mL) had a similar action to chloramphenicol (6.25 and 12.5 µg/mL) in the initial stages of growth of *S. aureus*, *S. Typhimurium*, and *E. faecalis*. However, the extract had better inhibition after the bacterial latency phase, with greater efficacy than chloramphenicol, a bacteriostatic drug [4].

Furthermore, a study conducted by López-Romero et al. [25] found that the crude extract and isolated ACGs from *A. muricata* seeds showed a significant antifungal

effect against *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, and *Candida krusei* at concentrations of 0.0125–4 mg/mL. However, the most significant impact as an inhibition zone was found when isolated ACGs at concentrations of 0.8 mg/mL against *C. albicans* (15.50 mm), *C. tropicalis* (14 mm), *C. krusei* (13.50 mm), and *C. glabrata* (8.50 mm). These authors demonstrated that crude and isolated ACGs at all concentrations showed more significant inhibition against *C. albicans*, *C. krusei*, and *C. tropicalis* compared to ketoconazole (500 mg/mL), which only showed inhibition against *C. albicans* (14.75 mm). It demonstrated the potential of ACGs against this type of yeast. Yeasts and fungi contain NADH dehydrogenase or NADH-ubiquinone-6-oxidoreductase type II enzymes. Because of this, ACGs can block the activity of these enzymes and, as a result, promote cell death; however, this depends on the type of microorganism. Furthermore, isolated or purified bioactive compounds cause microbial inhibition by adherence to the cell surface or diffusion into the fungal cells. The antifungal compounds in an extract can prevent the formation of nucleic acids (DNA and RNA), thus inactivating the ability of the genetic material to function [83].

Recently, Aguilar-Hernández et al. [26] concluded that isolated ACGs (0.0125–4 mg/mL) from *A. muricata* seeds exhibited a significant inhibitory effect (7–18 mm of inhibition zone) against Gram-negative (*Streptococcus mitis*, *Listeria monocytogenes*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus mutans*, and *Streptococcus salivaris*), and Gram-positive bacteria (*Aeromonas hydrophila*, *Escherichia coli*, *Salmonella choleraesuis*, *Burkholderia cenocepacia*, *Salmonella paratyphi*, and *Klebsiella pneumoniae*). In this study, it was demonstrated that the isolated ACGs showed a similar effect to ampicillin (500 mg/mL) against *L. monocytogenes* and *S. aureus*; however, for Gram-negative bacteria (except *E. coli* and *S. paratyphi*), this inhibition was more remarkable when compared to ampicillin, which did not show any inhibition against the rest of the bacteria.

On the other hand, although ACGs have a broad antimicrobial spectrum, their high hydrophobicity restricts *in vitro* and *in vivo* applications. Therefore, López-Romero et al. [27] and Montalvo-González et al. [11] developed nanosuspensions to carrier isolated ACGs from *A. muricata* seeds in aqueous media. These nanosuspensions were tested at concentrations of 0.0987, 0.177, and 0.32 mg/mL against *Enterococcus faecalis* and *Listeria monocytogenes*. Both authors coincided that the highest bacterial inhibition was observed against *E. faecalis* (83–87%) and *L. monocytogenes* (75–86%) at 320 µg/mL. Furthermore, it has been noted that the quantity of unsaturations in the aliphatic chain of ACGs is a structural characteristic that significantly affects their antibacterial action. Additionally, a process of insertion into the cell membrane similar to that of fatty acids affects the viability and functionality of bacteria [84]. Finally, with the studies described in this section, it was possible to demonstrate that ACGs can be potent inhibitors against Gram-positive and Gram-negative bacteria and some yeasts, even under the same conditions as the antibiotics used or at lower doses, and in some cases inhibit antibiotic-resistant microorganisms, such as *B. cenocepacia* and *C. tropicalis*.

6. Conclusions

The fight against pathogenic microorganisms has always been relevant because they cause millions of deaths yearly in humans and food animals worldwide. The studies analyzed in this chapter demonstrated that crude extracts, fractions, and acetogenins isolated from the pulp, leaves, and seeds of *A. muricata* have a vital

potential with a broad spectrum of antimicrobial applications against Gram-positive bacteria (*S. aureus*, *S. mutans*, *S. mitis*, *L. monocytogenes*, *E. faecalis*, *S. salivaris*, *S. mitis*, and *B. subtilis*) and Gram-negative bacteria (*E. cloacae*, *V. cholerae*, *E. coli*, *P. gingivalis*, *A. hydrophila*, *K. pneumoniae*, *S. paratyphi*, *S. abatetuba*, *S. cholerasius*, *S. Typhimurium*, *B. cenocepacia*, and *E. aerogenes*), and some yeasts (*C. albicans*, *C. glabrata*, *C. tropicalis*, *C. krusei*, *R. stolonifera*, and *C. glaucosporioides*); therefore, although many studies are needed to investigate other types of pathogens, we can suggest that ACGs are very promising bioactive compounds that could be used as a potential alternative against others bacteria (including more enterococci) using *in vivo* models.

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Conflict of interest

The authors declare that they have no financial interests or personal relationships that could influence the work presented in this research.

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