Review Article

Antibacterial activities of seven ethnomedicinal plants from family *Annonaceae*

Diannita Harahap, Sarah Niaci[1], Vivi Mardina[2], Bintang Zaura[3], Intan Qanita[4], Agnia Purnama[1], Kana Puspita[5], Diva Rayyan Rizki[4], Muhammad Iqhrammullah[6]

Department of Biology, Faculty of Science and Technology, Universitas Islam Negeri Ar-Raniry, [1]Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Syiah Kuala, [3]Department of Mathematics Education, Faculty of Education and Teacher Training, Universitas Syiah Kuala, [4]School of Medicine, Universitas Syiah Kuala, Kopelma Darussalam, [5]Department of Chemistry Education, Faculty of Teacher Training and Education, Universitas Syiah Kuala, [6]Graduate School of Mathematics and Applied Sciences, Universitas Syiah Kuala, Banda Aceh, [2]Department of Biology, Faculty of Engineering, Universitas Samudra, Langsa, Indonesia

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Abstract

Serious threat to human health caused by bacterial infection persists as a global concern. It becomes more serious when the burden of multidrug-resistance bacteria is in the increasing trend. To overcome, researches have been conducted to develop antibacterial agents from plant-derived bioactive compounds. This review article focuses on the antibacterial activities of plant extracts from seven *Annonaceae* members, namely *Annona muricata*, *Annona reticulata*, *Annona squamosa*, *Cananga odorata*, *Annona hypoglauca*, *Polyalthia longifolia*, and *Xylopia aethiopica*. First, ethnomedical uses of the aforementioned plants are discussed and followed by the screening results of related phytochemicals. Among many secondary metabolites contained in the extracts of *Annonaceae* spp., anonaine, nornuciferine, and liriodenine are common and bioactive. The extracts were reported to have bacteriostatic and bactericidal properties against a wide spectrum of bacteria, including multidrug-resistant *Escherichia coli, Staphylococcus aureus, Bacillus cereus, Enterococcus faecalis, Enterobacter aerogenes, Enterobacter cloacae, Salmonella choleraesuis, Salmonella typhimurium,* and *Shigella dysenteriae*. We conclude that investigation on the extracts from *Annonaceae* spp. could contribute to the development of antibacterial agents that could be used against multidrug-resistant bacteria.

Key words: *Annonaceae*, antimicrobial, drug development, multidrug resistant, secondary metabolite

INTRODUCTION

Pathogenic bacteria have been recognized as the major threat to human health that intertwines with environmental factors and socioeconomic status, contributing to numerous amounts of annual death worldwide.[1] Due to the development of multidrug-resistant bacteria from the improper use of antibiotics, a higher global burden of infectious disease-related mortality is expected as well.[2] To overcome, plant-based medicines have been long utilized to cure infectious diseases, where most of the practices have been closely attached to the community and transformed into culture.[3-6] In this regard, plants from the family *Annonaceae* have been evidenced to possess prominent antibacterial properties.[7] In this present work, seven *Annonaceae* plants were reviewed for their bacteriostatic and bactericidal activities, they are *Annona muricata*,[8-10] *Annona reticulata*,[7] *Annona squamosa*,[11-13] *Cananga odorata*,[14] *Annona hypoglauca*,[15] *Polyalthia longifolia*,[16,17] and *Xylopia*

Address for correspondence:
Ms. Kana Puspita,
Department of Chemistry Education, Faculty of Education and Teacher Training, Universitas Syiah Kuala, Banda Aceh 23111, Indonesia.
E-mail: kanapuspita@unsyiah.ac.id

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aethiopica.[18,19] Medicinal benefits of *Annonaceae* plants are resulted from the bioactivities of the containing secondary metabolites. Plants biosynthesize these secondary metabolites as a means to survive from animals, bacterial and viral infection, and competition with other plants.[20] Plant-derived secondary metabolites are mostly affected by phylogenetics, where plants within the same family exclusively share similar secondary metabolites.[21] Hence, discussion in this review article is significant to inform the progress of antibacterial activities possessed by *Annonaceae*-produced secondary metabolites.

IDENTITY AND ETHNOMEDICINAL USES

Annonaceae is a family generally found in lowland forests in tropical and subtropical areas consisting of about 130 genera and 2200 species.[22] *Annonaceae* is a flowering plant of the ordo *Magnoliales* which belongs to the class *Magnoliids*. Most of the *Annonaceae* family have been used as traditionally alternative medicines to treat multiple diseases.[23] All details pertaining to the ethnomedicinal use of the *Annona* family have been presented in Figure 1.

SECONDARY METABOLITES OF *ANNONACEAE* PLANTS

Annonaceae plants contain secondary metabolites that have been summarized in Table 1. Among the identified secondary metabolites, alkaloids are consistently reported in all the cited works.[7,8,14-16] Alkaloids have been associated with their pharmacological properties that include antibacterial, anti-insect, anticancer, analgesic, antimalarial, and neuroprotective activities.[24,25]

Further identification of alkaloid constituents led to the findings of anonaine, asimilobine, liriodenine, nornuciferine, xylopine, reticuline, and corypalmine from *A. muricata* leaves.[8] Anonaine and nornuciferine were also identified in the extract of *A. hypoglauca* stem barks, along with isoboldine and actinodaphne.[15] Anonaine and its related alkaloid structures are ubiquitous in *Annonaceae* spp.,[26] associated with potent pharmacological activity in terminating microbes.[27] Another secondary metabolite is liriodenine, reported to play a significant role in the early defense system of *Annonaceae* spp.[28,29] The presence of isoboldine along with its antibacterial potential was also reported in extracts from *Annona cherimolia* stem barks – a member of *Annonaceae*.[30]

ANTIBACTERIAL ACTIVITY

Antibacterial activities of various extracts from *Annonaceae* plant samples have been summarized in Table 1. Most of the published literatures reported antibacterial activities of *Annonaceae* plant extracts against *Escherichia coli* and *Staphylococcus aureus*.[7,8,11,15,16,18] Both *E. coli* and *S. aureus* are among the common multidrug-resistant pathogenic microbes.[31] A study using multifarious bacteria revealed the effective bacteriostatic and bactericidal of methanolic extract from *A. muricata* leaves against

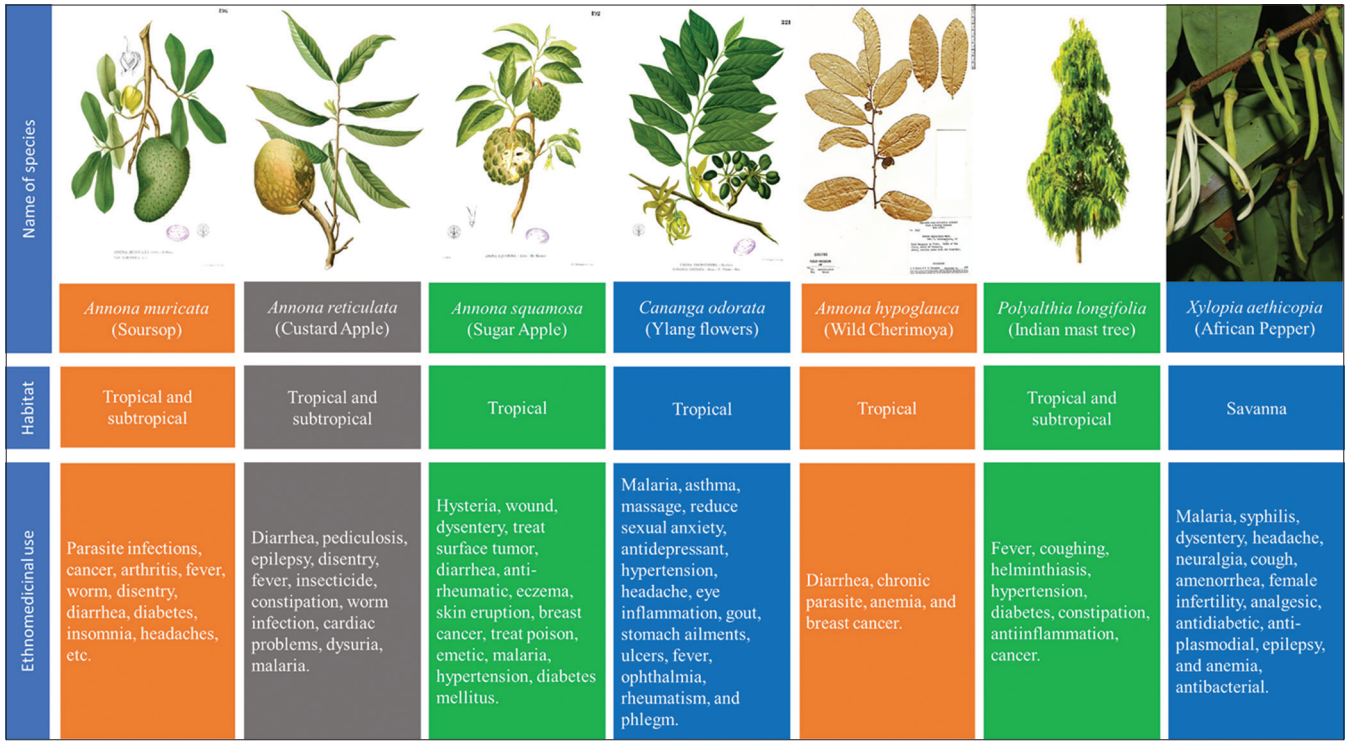

Figure 1: Illustrations of the *Annonaceae* plants along with their habitats and enthnomedicinal uses

Table 1: Antibacterial activities and secondary metabolites of Annonaceae-derived extracts

Sample[Reference]	Solvent	Identified phytoconstituents	Antibacterial activities		Main findings
			Gram-positive	Gram-negative	
A. muricata leaves[8]	Methanol	Anonaine, asimilobine, liriodenine, nornuciferine, xylopine, reticuline, corypalmine[a]	*B. cereus, E. faecalis, S. aureus*	*E. aerogenes, E. cloacae, E. coli, P. aeruginosa, S. typhimurium, S. choleraesuis, S. dysenteriae*	The lowest values for MIC and MBC against *P. aeruginosa* were 39 and 625 μg/mL, respectively
A. muricata leaves[9]	Distilled water	Flavonoids, phenols, saponins, tannins, terpenoids[b]	*S. aureus*	*K. pneumonia, P. aeruginosa*	Active against multidrug-resistant bacteria isolated from HIV/AIDS patients, such as *K. pneumonia, E. coli, C. diversus,* and so on
A. muricata fruit-skin[9]	Ethanol 95%	Alkaloids, flavonoids, phenols, quinones, saponins, steroids, tannins, terpenoids[b]	*S. aureus*	*K. pneumonia, P. aeruginosa*	Active against multidrug-resistant bacteria isolated from HIV/AIDS patients, such as *K. pneumonia, P. mirabilis, P. aeruginosa* and so on
A. muricata aerial part[10]	Methanol	Tannins, glycosides, resins, flavonoids, sterols, phenols, carbohydrate[b]	*S. aureus, B. subtilis*	*E. coli, P. aeruginosa,* Salmonella typhi, *K. pneumonia*	As suggested by the inhibition zone, ethyl acetate extract from *A. muricata* aerial part is higher than the methanol extract
	Ethyl acetate	Tannins, resins, phlobatannins, flavonoids, phenols[b]	*S. aureus, B. subtilis*	*E. coli, P. aeruginosa,* Salmonella typhi, *K. pneumonia*	
A. reticulate leaves[7]	Methanol	Alkaloids, flavonoids, phenols, steroids, triterpenoids[b]	*S. aureus, P. vulgaris, B. subtilis*	*E. coli, P. aeruginosa, K. pneumonia,* Salmonella typhi	The methanol extract and chloroform fraction were the most active
	n-butanol	-	*S. aureus, P. vulgaris, B. subtilis*	*K. pneumonia,* Salmonella typhi	
	Chloroform	-	*S. epidermidis, S. aureus, P. vulgaris, B. subtilis*	*E. coli, P. aeruginosa, K. pneumonia,* Salmonella typhi	
	Acetone	-	*S. epidermidis, S. aureus, B. subtilis*	*E. coli, K. pneumonia,* Salmonella typhi	
A. squamosal leaves[11]	Methanol: distilled water (8:2)	-	*B. subtilis, S. aureus, S. faecalis*	*E. coli, N. gonorrhoeae, P. aeruginosa*	Acetone has the highest total phenolic contents (395 mg GAE/g). The acetone extract was the most active, especially against *S. aureus* and *S. faecalis* with an inhibition zone of 15 mm. The inhibition of Gram-negative or Gram-positive bacteria is strongly correlated with the total phenolic content of the extract
	Acetone: distilled water (1:1)	-	*B. subtilis, S. aureus, S. faecalis*	*E. coli, N. gonorrhoeae, P. aeruginosa*	
	Water (boiling)	-	*S. faecalis*	*E. coli*	
	Ethanol: water (1:1)	-	*B. subtilis, S. aureus, S. faecalis*	*E. coli, N. gonorrhoeae, P. aeruginosa*	
A. squamosal stem bark[13]	Methanol	-	*S. mutans, S. sobrinus*	-	Highest inhibition zone against *S. sobrinus* KP975179 isolated from patients with dental caries (17 mm) at 50 mg/mL extract

Contd...

Table 1: Contd...

Sample[Reference]	Solvent	Identified phytoconstituents	Antibacterial activities		Main findings
			Gram-positive	Gram-negative	
A. squamosal leaves[12]	Methanol	Germacrene-D, trans-caryophyllene, palmitone, bicyclogermacrene, phytol, α -copaene[c]	*B. subtilis, S. aureus, E. faecalis*	*E. coli, P. aeruginosa, K. pneumonia*	Methanolic extract has the highest total phenolic content (282.1 mg GAE/g). Highest antibacterial activities obtained from methanolic extract with inhibition zone (16.5 mm) more than that of commercial tetracycline for *S. aureus* (14.8 mm)
	Acetone	-	*B. subtilis, E. faecalis*	*E. coli, P. aeruginosa, K. pneumonia*	
	Distilled Water	-	*E. faecalis*	*E. coli, P. aeruginosa, K. pneumonia*	
C. odorata stem barks[14]	n-hexane	-	*P. acnes*	-	At 200 μg/well extracts, the n-hexane extract was the most active with an inhibition zone of 17 mm, followed by ethyl acetate (16 mm) and ethanol (13 mm)
	Ethyl acetate	-	*P. acnes*	-	
	Ethanol	-	*P. acnes*	-	
A. hypoglauca stem barks[15]	Dichloromethane: methanol (1:1)	Isoboldine, anonaine, nonuciferine, actinodaphine[c]	*S. aureus*	*E. coli*	The highest inhibition against *E. faecalis* and *S. aureus* with MICs of 40 and 70 g/mL, respectively
P. longifolia leaves[16]	Distilled water	-	*S. aureus*	Not active (*E. coli* and *P. aeruginosa*)	The chloroform: methanol (1:1) and petroleum ether extracts were the most active with 13 mm inhibition zone diameter. The petroleum ether extract showed synergistic activity with commercial antibiotics lincomycin against *S. aureus* (inhibition zone of 37 mm)
	Ethanol	-	*S. aureus*		
	Petroleum ether	Steroids, saponins, tannins, terpenoids, alkaloids[b]	*S. aureus*	Not active (*E. coli* and *P. aeruginosa)*	
	Chloroform: methanol (1:1)	-	*S. aureus*	Not active (*E. coli* and *P. aeruginosa)*	
P. longifolia stem bark[17]	Methanol: distilled water (1:1)	3-O-methyl ellagic acid[d]	*S. pneumonia, S. pyogenes, S. viridans, S. aureus*, MRSA	*P. aeruginosa, E. coli, A. baumannii*	The isolated compound had MIC reaching 80 μg/mL for *S. pyogenes, S. viridans,* and *S. aureus.* Meanwhile, for *S. pneumonia* and MRSA, the MICs were 160 μg/mL
X. aethiopica stem barks[18]	Dichloromethane: methanol (1:1)	-	*S. aureus, M. smegmatis, M. aurum*	*K. pneumonia, M. catarrhalis*	The highest inhibitions against *M. catarrhalis* (MIC=250 g/mL) and *M. aurum* (MIC=130 g/mL)
X. aethiopica leaves[18]	Dichloromethane: methanol (1:1)	-	*M. smegmatis, M. aurum*	*K. pneumonia, M. catarrhalis*	The highest inhibitions against *M. smegmatis* (MIC=25 g/mL) and *M. aurum* (MIC=500 g/mL)
X. aethiopica fruit[19]	Methanol	-	*M. tuberculosis*	-	MICs and MBCs for *M. tuberculosis* H_{37}Rv and H_{37}Ra reached 512 μg/mL and 1024 μg/mL, respectively

A. muricata: Annona muricata, A. reticulate: Annona reticulate, A. squamosal: Annona squamosal, C. odorata: Cananga odorata, A. hypoglauca: Annona hypoglauca, P. longifolia: Polyalthia longifolia, X. aethiopica: Xylopia aethiopica, B. cereus: Bacillus cereus, E. faecalis: Enterococcus faecalis, S. aureus: Staphylococcus aureus, B. subtilis: Bacillus subtilis, P. vulgaris: Proteus vulgaris, S. epidermidis: Staphylococcus epidermidis, S. faecalis: Streptococcus faecalis, S. mutans: Streptococcus mutans, S. sobrinus: Streptococcus sobrinus, P. acnes: Propionibacterium acnes, S. pneumonia: Streptococcus pneumonia, S. pyogenes: Streptococcus pyogenes, S. viridans: Streptococcus viridans, M. smegmatis: Mycobacterium smegmatis, M. aurum: Mycobacterium aurum, M. tuberculosis: Mycobacterium tuberculosis, E. aerogenes: Enterobacter aerogenes, E. cloacae: Enterobacter cloacae, E. coli: Escherichia coli, P. aeruginosa: Pseudomonas aeruginosa, S. typhimurium: Salmonella typhimurium, S. choleraesuis: Salmonella choleraesuis, S. dysenteriae: Shigella dysenteriae, K. pneumonia: Klebsiella pneumonia, N. gonorrhoeae: Neisseria gonorrhoeae, A. baumannii: Acinetobacter baumannii, M. catarrhalis: Moraxella catarrhalis, C. diversus: Citrobacter diversus, P. mirabilis: Proteus mirabilis, MRSA: Methicillin-resistant *S. aureus*, MBC: Minimum bactericidal concentration, MIC: Minimum inhibitory concentration

multidrug-resistant and pathogenic *Bacillus cereus, Enterococcus faecalis, Enterobacter aerogenes, Enterobacter cloacae, Salmonella choleraesuis, Salmonella typhimurium,* and *Shigella dysenteriae*.[17] *Pseudomonas aeruginosa,* an encapsulated bacterium that could cause multiple infection to human, was reported to be effectively inhibited by leaf extracts from *A. muricata,*[8] *A. reticulata,*[7] *A. squamosa,*[11] and *P. longifolia*.[16] Effective inhibitions of *Streptococcus faecalis* and *Neisseria gonorrhoeae* were revealed by a study employing acetone extract from *A. squamosa* leaves.[11] The World Health Organization published a list of antibiotic-resistant so-called "priority pathogens" due to its growing threat in multidrug resistance and the need for new antimicrobial medicines. These Gram-negative bacteria include Carbapenem-resistant *P. aeruginosa* and fluoroquinolone-resistant bacteria – Salmonellae and *N. gonorrhoeae*.[32] Other than the aforementioned, bacteria that are responsible for critical diseases in human have been reported as well. *Salmonella typhi* that could cause typhoid fever were reported inhibitable by leaf extracts of *A. reticulata*[7] and *A. squamosa*.[11] Moreover, a study suggested the ability of an extract from *X. aethiopica* stem barks to inhibit the growth of immunosuppressor bacteria – *Moraxella smegmatis* and *Moraxellacatarrhalis*.[18]

Despite growing evidence of its antibacterial activities, several studies on extracts from *Annonaceae* spp. reported the otherwise. Extracts of *P. longifolia* leaves were not active in inhibiting Gram-negative *E. coli* and *P. aeruginosa*, and only active against Gram-positive *S. aureus*.[16] Methanolic extracts from *A. reticulata* leaves and bark were reported unable in inhibiting mutans Streptococci bacteria isolated from patients with dental caries.[13] Moreover, alkaloid extracts obtained from Indonesian *A. muricata* also did not have inhibiting properties against various bacteria including *E. coli*, Klebsiella *pneumonia*, *Acinetobacter baumannii*, and *P. aeruginosa*.[10] The authors of cited studies did not clearly provide reasons regarding the impotent antibacterial activities of the *Annonaceae* plant extracts. However, inactive or inert phytoconstituents in the extract could reduce the antibacterial activities.[25]

SYNERGISM WITH ANTIBIOTICS

At least, there are two reports studying the synergism of extracts of *Annonaceae* plants with commercial antibiotics. One study revealed the synergism between *A. muricata* leaves extract and erythromycin against *S. typhimurium* resulting in the induction of bacterial membrane permeability.[8] Another study reported that petroleum ether extract from *P. longifolia* leave had a synergistic activity with commercial antibiotics lincomycin against *S. aureus*, evidenced by increased inhibition zone diameter.[16] Several proposed mechanisms were associated with the synergism effect including the loss of membrane integrity, induction of pores, and structure or function modification of the membrane phospholipid bilayer. It is still exactly unknown how the phytocompounds interact with the antibiotics resulting in the synergism. However, several phytoconstituents, such as tannins, have been attributed to such synergism.[9]

CONCLUSIONS AND IMPLICATIONS

Annonaceae spp plants have been reported to have high activity against various strains of bacteria; Gram-positive and Gram-negative bacteria. The activity could be associated to the presence of secondary metabolites such as alkaloids, flavonoids, steroids, tannins, and terpenoids. Anonaine is the most ubiquitous alkaloid found in *Annonaceae* spp. that has antibacterial potentials. The secondary metabolites may work synergistically with antibiotics by inhibiting the multidrug resistance mechanisms of the bacteria. *Annonaceae* spp. has been proven important in antibacterial drug development. The overall discussion of this article has been summarized in Figure 2.

It is still unclear, why extracts of several *Annonaceae* plants are impotent against bacterial growth or only work against

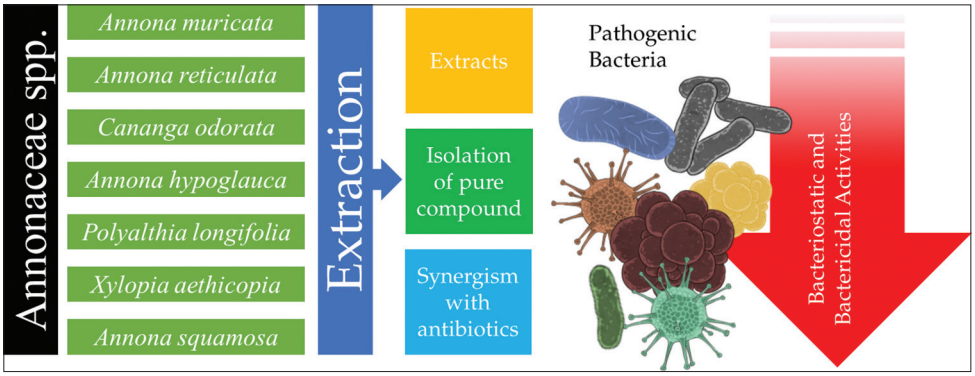

Figure 2: Schematic summary of this review article. *Annonaceae* spp. plants have been used for ethnomedicinal used, namely *Annona muricata, Annona reticulata, Cananga odorata*, *Annona hypoglauca*, *Polyalthia longifolia, Xylopia aethiopica,* and *Annona squamosa*. After the extraction, the extracts, isolates, and combination with antibiotics were tested against pathogenic bacteria, in which the growth of the bacteria could be inhibited

certain bacterial species. Despite their potential, studies on antibacterial activities of *Annonaceae* spp. are still scarce along with inconclusive results as stated above. Hence, more investigations on secondary metabolites of *A*nnonaceae spp. need carried out.

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Conflicts of interest

There are no conflicts of interest.

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