Antibacterial activities of seven ethnomedicinal plants from family Annonaceae

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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., annonaine, normuciferine, and liroidenine 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,[6,10] Annona reticulata,[7] Annona squamosa,[11-13] Cananga odorata,[14] Annona hypoglauca,[15] Polyalthia longifolia,[16,17] and Xylopia

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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. Plant-derived secondary metabolites are mostly affected by phylogenetics, where plants within the same family exclusively share similar secondary metabolites. 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. Annonaceae is a flowering plant of theordo Magnoliales which belongs to the class Magnoliids. Most of the Annonaceae family have been used as traditionally alternative medicines to treat multiple diseases. All details pertaining to the ethnomedicinal use of the Annona family have been presented in Table 1. Among the identified secondary metabolites, alkaloids are consistently reported in all the cited works. Alkaloids have been associated with their pharmacological properties that include antibacterial, anti-insect, anticancer, analgesic, antimalarial, and neuroprotective activities.

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

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. Alkaloids have been associated with their pharmacological properties that include antibacterial, anti-insect, anticancer, analgesic, antimalarial, and neuroprotective activities.

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. Both E. coli and S. aureus are among the common multidrug-resistant pathogenic microbes. A study using multifarious bacteria revealed the effective bacteriostatic and bactericidal of methanolic extract from A. muricata leaves against...
Table 1: Antibacterial activities and secondary metabolites of Annonaceae-derived extracts

| Sample          | Reference | Solvent                  | Identified phytoconstituents                  | Antibacterial activities | Main findings                                                                 |
|-----------------|-----------|--------------------------|-----------------------------------------------|--------------------------|--------------------------------------------------------------------------------|
| A. muricata     | [8]       | Methanol                 | Anonaine, asimilobine, liriodenine, normuciferine, xylopine, reticuline, corylpalmine<sup>a</sup> | B. cereus, E. faecalis, S. aureus | The lowest values for MIC and MBC against P. aeruginosa were 39 and 625 µg/mL, respectively |
| A. cereus, E. faecalis, S. aureus | E. aerogenes, E. cloaca, E. coli, P. aeruginosa, S. typhimurium, S. choleraesuis, S. dysenteriae | Active against multidrug-resistant bacteria isolated from HIV/AIDS patients, such as K. pneumonia, E. coli, C. diversus, and so on |
| A. cereus       | [9]       | Distilled water          | Flavonoids, phenols, saponins, tannins, terpenoids<sup>b</sup> | S. aureus                | Active against multidrug-resistant bacteria isolated from HIV/AIDS patients, such as K. pneumonia, P. mirabilis, P. aeruginosa and so on |
| A. cereus       | [9]       | Ethanol 95%              | Alkaloids, flavonoids, phenols, quinones, saponins, steroids, tannins, terpenoids<sup>b</sup> | S. aureus                | As suggested by the inhibition zone, ethyl acetate extract from A. muricata aerial part is higher than the methanol extract |
| A. reticulate  | [10]      | Methanol                 | Tannins, glycosides, resins, flavonoids, sterols, phenols, carbohydrate<sup>b</sup> | S. aureus, B. subtilis   | The methanol extract and chloroform fraction were the most active |
| A. reticulate  | [10]      | Ethyl acetate            | Tannins, resins, phlobatannins, flavonoids, phenols<sup>b</sup> | S. aureus, B. subtilis   | The methanol extract and chloroform fraction were the most active |
| A. reticulate  | [10]      | n-butanol                | -                                             | S. aureus, P. vulgaris, B. subtilis | K. pneumonia, Salmonella typhi |
| A. retelecule   | [10]      | Chloroform               | -                                             | S. epidermidis, S. aureus, P. vulgaris, B. subtilis | E. coli, P. aeruginosa, K. pneumonia, Salmonella typhi |
| A. reticulate   | [10]      | Acetone                  | -                                             | S. epidermidis, S. aureus, B. subtilis | E. coli, K. pneumonia, Salmonella typhi |
| A. squamosal    | [11]      | Methanol: distilled water (8:2) | -                                             | B. subtilis, S. aureus, S. faecalis | E. coli, N. gonorrhoeae, P. aeruginosa |
| A. squamosal    | [11]      | Aceton: distilled water (1:1) | -                                             | B. subtilis, S. aureus, S. faecalis | E. coli, N. gonorrhoeae, P. aeruginosa |
| A. squamosal    | [11]      | Water (boiling)          | -                                             | S. faecalis              | E. coli |
| A. squamosal    | [11]      | Ethanol: water (1:1)     | -                                             | B. subtilis, S. aureus, S. faecalis | E. coli, N. gonorrhoeae, P. aeruginosa |
| A. squamosal    | [13]      | Methanol                 | -                                             | S. mutans, S. sobrinus   | 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 |

Contd...
Table 1: Contd...

| Sample/Reference | Solvent | Identified phytoconstituents | Antibacterial activities | Main findings |
|------------------|---------|------------------------------|--------------------------|--------------|
| A. squamosal leaves[12] | Methanol | Gemcadiene-D, trans-caryophyllene, palmintone, bicyclogermacrene, phyto[α-copaene] | B. subtilis, S. aureus, E. faecalis | 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) |
| C. odorata stem barks[14] | Acetone | B. subtilis, E. faecalis | E. coli, P. aeruginosa, K. pneumonia | 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) |
| C. odorata stem barks[14] | Distilled Water | E. faecalis | E. coli, P. aeruginosa, K. pneumonia | |
| C. odorata stem barks[14] | Ethyl acetate | P. acnes | - | |
| C. odorata stem barks[14] | Ethanol | P. acnes | - | |
| A. hypoglauca stem barks[15] | Dichloromethane: methanol (1:1) | Isoboldine, anonaine, nonuciferine, actinodaphnine | S. aureus | 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) |
| P. longifolia stem bark[17] | Methanol: distilled water (1:1) | 3-O-methyl ellagic acid | S. pneumonia, S. pyogenes, S. viridans, S. aureus, MRSA | 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. catarrhalis 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[19] | 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 H37Rv and H37Ra 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. Pseudomonas aeruginosa, an encapsulated bacterium that could cause multiple infection to human, was reported to be effectively inhibited by leaf extracts from A. muricata, A. reticulata, A. squamosa, and P. longifolia. Effective inhibitions of Streptococcus faecalis and Neisseria gonorrhoeae were revealed by a study employing acetone extract from A. squamosa leaves. 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. 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 and A. squamosa. Moreover, a study suggested the ability of an extract from X. aethiopica stem barks to inhibit the growth of immunosuppressor bacteria – Moraxella catarrhalis, Moraxella catarrhalis.

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. Methanolic extracts from A. reticulata leaves and bark were reported unable in inhibiting mutans Streptococci bacteria isolated from patients with dental caries. 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. The authors of cited studies did not clearly prove reasons regarding the impotent antibacterial activities of the Annonaceae plant extracts. However, inactive or inert phytoconstituents in the extract could reduce the antibacterial activities.

**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. 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. 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.

**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...
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 Annonaceae spp. need carried out.

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Conflicts of interest
There are no conflicts of interest.

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