Antimicrobial and Antiparasitic Efficacy of Annonamuricata: A Review on its Role in Infectious Diseases

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1. Abstract: Annona Muricata (Graviola) has a long history in tropical folk medicine as a remedy for various fevers, infections, and parasitic infestations. Given the global threat of antimicrobial resistance, its traditional use warrants scientific validation. This review confirms the plant's broad-spectrum activity, reporting potent effects against bacteria (Staphylococcus aureus), fungi (Candida albicans), and medically relevant protozoa (e.g., agents of malaria and leishmaniasis). This efficacy is linked to its complex phytochemistry, particularly the Annonaceous Acetogenins, alongside flavonoids and alkaloids, which target microbial cellular integrity and mitochondrial respiration. To transition Soursop from folk remedy to modern medicine, future work must prioritize clinical studies and rigorous safety assessments to effectively separate beneficial anti-infective compounds from potentially neurotoxic components.

2. Introduction:

In response to this global challenge, natural product screening, particularly of traditionally used medicinal plants, offers a rich pipeline for discovery. One such species is Annonamuricata Linn. (commonly known as Soursop or Graviola), a small evergreen tree indigenous to tropical regions of the Americas and widely cultivated elsewhere. In many folk medicine systems across Africa, Asia, and Latin America, various parts of the plant (leaves, bark, roots, and seeds) have been empirically used to treat a wide range of infectious and inflammatory ailments, including fevers, parasitic infections (such as against intestinal worms and protozoa), gastrointestinal illness, and topical skin ailments(**1,2**).

Despite its extensive ethno medicinal history and numerous in vitro studies reporting its bioactivity, the collective and comparative scientific evidence supporting the antimicrobial and antiparasitic properties of A. muricata remains fragmented across diverse publications. Therefore, the objective of this review is to systematically

synthesize and critically evaluate the recent scientific findings on the efficacy of Annonamuricata extracts and isolated phytochemicals against various bacteria, fungi, and parasites. This focused synthesis aims to validate its traditional use and identify its key bioactive constituents and mechanisms, thereby assessing its true potential as a viable, sustainable source for the development of novel anti-infective therapeutic agents**(1,3)**.

3. Photochemistry of Anti-infective Agents:

The diverse anti-infective and antiparasitic properties of Annonamuricata are primarily mediated by a complex mixture of secondary metabolites. The plant's efficacy is driven by several distinct classes of phytochemicals, with the Annonaceous Acetogenins standing out as the most potent group.

Annonaceous Acetogenins (ACGs)

The Annonaceousacetogenins (ACGs) are a unique class of long-chain fatty acid derivatives found exclusively within the Annonaceae plant family. These compounds are the subject of intense research due to their powerful bioactivity:

- **Antiprotozoal and Antiparasitic Power:** ACGs exhibit pronounced toxicity against various parasites, including protozoa responsible for diseases likeleishmaniasis and malaria **(1, 4).** They are considered the most significant antiparasitic agents in the plant.
- **Mechanism of Action:** Their cytotoxic and anti-infective action stems from their unique ability to potently inhibit **Complex I (NADH-ubiquinone oxidoreductase)** of the mitochondrial electron transport chain [3]. By disrupting this fundamental energy-producing process, ACGs effectively deplete ATP, leading to programmed cell death in target cells, whether they are tumor cells or rapidly dividing microbial and parasitic cells**(5)**.

Alkaloids, Flavonoids, and Phenolic Compounds

Beyond the ACGs, the broad-spectrum effects of A. muricata extracts are bolstered by the synergistic action of several other common phytochemical groups:

Alkaloids: The plant contains isoquinoline alkaloids, which are known to contribute to its **antibacterial** and **antifungal** properties **(6)**. These compounds often interfere with microbial cell division and membrane integrity.

Flavonoids and Phenolic Compounds: These are the most abundant secondary metabolites and serve as crucial **antioxidant** and radical-scavenging agents **(1)**. Their contribution to anti-infective activity lies in their ability to compromise microbial cell

membranes and inhibit key bacterial and fungal enzymes, thereby augmenting the overall **antibacterial** and **antifungal** effects of the crude extracts **(7)**.

The combined action of these phytochemicals provides A. muricata with a multi-targeted approach, which may be one reason why the crude extracts often show such potent, broad-spectrum biological activity.

4. Antimicrobial Efficacy of Annonamuricata Extracts

Antibacterial Activity

A. muricata extracts consistently show inhibitory effects on both major classes of bacteria, although the potency often depends on the extraction solvent used **(8)**.

Gram-Positive Bacteria

- **Key Targets:** Extracts are effective against clinically relevant Gram-positive pathogens, most notably **Staphylococcus aureus** and **Enterococcus faecalis(8, 9)**.
- **Activity Range:** The **Minimum Inhibitory Concentration (MIC)** against S.aureus is reported to vary widely, typically ranging from 156μg/mLto 1,024 μg/mLin various studies, highlighting the variability in extraction and testing methods **(10)**.

Gram-Negative Bacteria

- **Key Targets:** Significant activity is observed against Gram-negative bacteria such as **Escherichia coli**, **Pseudomonas aeruginosa**, and Klebsiella Pneumoniae**(8, 11)**.
- **Comparative Efficacy:** Some studies indicate that certain Gram-negative strains may be more sensitive to the extracts than Gram-positive ones **(10)**. The mechanism involves disrupting the **bacterial cell membrane** in both bacterial classes **(11)**.

Critical Synthesis (Extract Effectiveness)

- **Most Effective Extracts: Methanolic** and **ethanolic** extracts, predominantly from the leaves, are generally the most potent, as these solvents efficiently dissolve a high concentration of the active **alkaloids** and **phenolic compounds (8,12)**.
- **Parameters:** The efficacy is measured using the **Zone of Inhibition (ZOI)** and **MIC**. Extracts showing the lowest MIC values are considered the most effective antibacterial agents.

Antifungal Activity

A. muricata is highly effective against opportunistic fungal pathogens, making it a promising source for new antifungal agents **(13)**.

Key Target: Activity is most pronounced against the common human pathogen **Candida albicans**, including multi-drug resistant (MDR) strains and those forming

biofilms **(13,14)**. Activity has also been confirmed against **C.krusei** and **C. parapsilosis (14)**.

- **Active Compounds:** The antifungal power is attributed to the presence of multiple synergistic compounds, including **alkaloids**, **flavonoids (e.g., rutin)**, and **Annonaceous Acetogenins(1,13)**.
- **Mechanism of Action:** The primary elucidated mechanism involves targeting the **fungal cell envelope(13)**:
  - **Mitochondrial Disruption:** Extracts cause **depolarization of the fungal mitochondrial membrane**, disrupting the energy supply (ATP synthesis).
  - **Cell Envelope Damage:** Integrity of both the plasma membrane and the cell wall is compromised, leading to leakage of cellular material and fungal cell death.

5. Antiprotozoal Efficacy of Annonamuricata Extracts

The antiparasitic and antiprotozoal efficacy of Annonamuricata is a significant area of research, primarily validating its extensive traditional use against various internal and external parasites.

Antiprotozoal Efficacy

The plant's activity against protozoal parasites, which cause major tropical diseases, is largely attributed to the presence of **Annonaceous Acetogenins** and other compounds **(1)**.

Activity against Plasmodium species (Malaria)

- **In Vivo Efficacy:** Studies using A. muricata aqueous leaf extracts in murine models infected with **Plasmodium berghei** have demonstrated significant dose-dependent **Antimalarial activity (15)**.
- **Inhibition:** Aqueous extracts at doses up to 1000 mg/kg have shown substantial **parasitemia inhibition** (up to over 85% in one study) and prolonged the survival time of the infected mice **(15)**.
- **Active Compounds:** While the crude extract shows activity, the effect is linked to the plant's diverse phytochemical profile, including **alkaloids** and **acetogenins**, which are known to interfere with ATP production in parasites **(1,8)**.

Activity against Leishmania species (Leishmaniasis)

- **Key Compounds:** Antileishmanial activity is strongly correlated with the presence of **acetogenins** and **alkaloids (8, 16)**.
- **Specific Acetogenins:** Isolated acetogenins like **annonacinone** and **corossolone** from A. muricata have demonstrated potent **leishmanicidal activity**in vitro against promastigote forms of several species, including **L.donovani, Lmexicana**, and **L. major(17)**.

- **Potency:**Annonacinone exhibited high activity with EC_{50} values ranging from approximately **6.7 to 8.0** µg /mL against the tested Leishmania species, establishing the plant as a promising source for new leishmanicidal agents **(17)**.
- **Mechanism (Proposed):** The mechanism of acetogenins involves inhibition of the **mitochondrial complex I (NADH-ubiquinone oxidoreductase)**, a critical enzyme for ATP production in the parasite **(8)**.

Anthelmintic and Insecticidal/Larvicidal Activity

The traditional use of A. muricata seeds and leaves against intestinal worms and external pests has been scientifically validated, primarily utilizing the high concentration of acetogenins in the seeds **(8)**.

Anthelmintic Activity (Internal Parasites)

- **Traditional Use:** The seeds and fruits have been traditionally employed in folk medicine, particularly in African and South American regions, to treat **internal and external parasitic infections** and are specifically cited for their **anthelmintic** properties **(8, 18).**
- **Tested Use:** Although less frequently quantified than the antiprotozoal activity, the overall antiparasitic classification confirms its use against various internal worms and flukes **(8)**.

Insecticidal/Larvicidal Activity (External Pests)

- **Key Compounds:** This activity is largely attributed to the **acetogenins**, such as **annonacin**, which are highly concentrated in the seeds **(2,19)**.
- **Larvicidal Action:** Extracts, particularly from the seeds and leaves, exhibit strong **larvicidal efficacy** against vectors of human diseases and agricultural pests:
  - **Mosquitoes:** Seed extracts and the isolated acetogenin**annonacin** are highly effective against the larvae of **Aedesaegypti** and **Aedesalbopictus** (vectors of Dengue, Zika, and Chikungunya). The acetogenin-rich fraction often shows low LC_{50} values, confirming its potential as a natural mosquitocide**(16)**.
  - **Agricultural Pests:**Ethanolic leaf extracts show potent toxicity and mortality against larvae of agricultural pests like the **diamondback moth Plutellaxylostella(20)**.
- **Mechanism:** The insecticidal action of acetogenins is also linked to the inhibition of mitochondrial respiration, which rapidly leads to paralysis and death in insects (1).

6. Conclusion

The comprehensive review confirms that **Annonamuricata** (soursop) is a potent source of natural anti-infective agents, validating many of its traditional uses. The extracts exhibit **broad-spectrum antimicrobial efficacy** against Gram-positive bacteria (S.aureus), Gram-negative bacteria (E.coli), and opportunistic fungi (C. albicans) **(1, 8)**. Crucially, the plant displays significant **antiprotozoal activity** against major pathogens, including **Plasmodium** (malaria) and **Leishmania**species **(15, 17)**. This versatile biological profile is largely driven by its unique phytochemical composition, with **Annonaceous Acetogenins** identified as the principal class of bioactive compounds responsible for cytotoxicity and enzyme inhibition across various microbial and parasitic targets **(8)**.

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