Phytochemical composition and antibacterial activities of Azadirachta indica (Neem): significance of traditional medicine in combating infectious diseases and antimicrobial resistance

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DOI: https://doi.org/10.22271/phyto.2023.v12.i5c.14733

Abstract

Traditional medicines such as Azadirachta indica (A. indica) possess medicinal properties that should be explored in drug discovery to combat infectious diseases and antimicrobial resistance. This study provided insights into the antibacterial activities of A. indica. This narrative review utilised Google Scholar and PubMed to search for articles that were published from January 2000 to September 2023 on the antibacterial activities of A. indica. The study found that A. indica has activity against Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, and other bacteria. The antibacterial activities of A. indica were reported to be due to its phytochemical content such as phenolics, tannins, saponins, flavonoids, terpenoids, fatty acids, and alkaloids. This review found that A. indica has antimicrobial activity against many Gram-negative and Gram-positive bacteria due to the presence of phytochemicals. There is a need to increase investment in drug discovery and the integration of traditional medicine into the healthcare system.

Keywords: Antibacterial activity, antimicrobial resistance, azadirachta indica, drug discovery, neem, traditional medicine

Introduction

Traditional medicines are essential in the treatment of various diseases [1-7]. There has been a rise in the burden of infectious diseases across the globe, including HIV, malaria, diarrhoea, tuberculosis, meningitis, respiratory tract infections, urinary tract infections, and soft tissue infections [8, 9]. This burden of infectious diseases has led to the overuse and misuse of antimicrobials [10-14]. Consequently, this has resulted in the emergence of antimicrobial resistance (AMR) [15-17]. AMR occurs when microorganisms stop responding to antimicrobials to which they were previously sensitive to [18]. AMR has fatal consequences as reported by many scholars [17-24], hence, the need to address it using various strategies [25-36], including the use of traditional medicine [7, 37].

The emergency of AMR demands a need to promote drug discovery and the development of newer antimicrobials and alternative therapies [2, 38-45]. This has led scientists to strengthen the isolation and discovery of novel bioactive compounds from plants to combat AMR [46-50]. Traditional medicines have the potential to cure many diseases and can be used as drug sources [1, 2, 45, 51-54]. The World Health Organization (WHO) has underscored the enduring significance of traditional medicines derived from medicinal plants in developing nations [55]. WHO states that a remarkable 80% of these developing countries continue to derive substantial benefits from the utilization of traditional medicines [55, 56]. Due to the evidence-based medicinal effects of traditional medicine, there have been many supports and recommendations to integrate it into the healthcare system, of which other countries have done so [55, 57-60].

Azadirachta indica (A. indica), also called the Neem tree, is a potential source of medicines and should be explored further in drug discovery [61-64]. This plant has been reported to have antimicrobial activity against many microorganisms [65-67]. A. indica has been found to have antibacterial activity against both Gram-positive and Gram-negative bacteria, including activity against Escherichia coli (E. coli) [68] and Enterococcus species [69]. Additionally, it has activity against drug-resistant infections, making it a potential antibiotic [70].
The active compounds (phytochemicals) present in *A. indica*, such as nimbim, nimbidin, azadirachtin, and gedunin, have been shown to exhibit remarkable bactericidal and bacteriostatic properties [71-74]. *A. indica* is also reported to possess many phytochemicals including phenolics, tannins, saponins, flavonoids, alkaloids [68], terpenoids and fatty acids [69]. Additionally, neem's antibacterial mechanism of action involves disrupting bacterial cell membranes, inhibiting crucial enzymes, and interfering with DNA replication, further enhancing its efficacy against microbial pathogens [75]. The antibacterial activities are reported at various minimum inhibitory concentration (MIC) and zones of inhibition. There are various reports on the phytochemical contents and antimicrobial activities of *A. indica*. Therefore, this study reviewed articles on the phytochemical composition and antibacterial activities of *A. indica* against bacterial isolates. The findings of this review paper can be used to promote drug discovery from natural products.

### Materials and methods

This was a systematic review that was conducted from March 2023 to September 2023. The literature search was done using Google Scholar and PubMed for all articles that were published on the antibacterial properties of *A. indica*. This study employed search words including ‘Azadirachta indica’, ‘A. indica’, ‘neem’, ‘antibacterial activity’, ‘antibacterial activities’, ‘traditional medicines’, 'drug discovery', ‘phytochemical (s)’, and ‘antimicrobial resistance’. This review was conducted in line with other narrative reviews conducted in traditional and herbal medicines [76-79]. This study included original articles that were written in English and published from January 2000 to September 2023. We excluded abstracts, grey literature, thesis, narrative reviews, systematic reviews, clinical trials, opinion papers, pre-prints, and publications on non-antibacterial medicinal uses of the plant.

From these studies that were included, the following data was extracted: author, year, origin of the plant material, part of the plant extracted, method of extraction, procedure, Phytochemicals present and findings.

### Results

The phytochemical constituents and antibacterial activities of *A. indica* are shown in Table 1.

### Table 1: Phytochemical composition and antibacterial activities of Azadirachta indica

<table>
<thead>
<tr>
<th>Author names and year</th>
<th>Study Country</th>
<th>Findings on the tested pathogens</th>
<th>Tested part</th>
<th>Phytochemicals present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hikaambo <em>et al.</em>, 2022 [80]</td>
<td>Zambia</td>
<td>The extract had antibacterial activity against <em>E. coli</em> with a MIC of 10 mg/ml for the aqueous extract and 20 mg/ml for the ethanolic extract</td>
<td>Leaf extract</td>
<td>Phenolics, tannins, saponins, flavonoids, and alkaloids</td>
</tr>
<tr>
<td>Surtartono <em>et al.</em>, 2023 [69]</td>
<td>Indonesia</td>
<td>The extract had antibacterial activity against <em>E. faecalis</em> at a concentration of 12.5%</td>
<td>Leaf extract</td>
<td>Terpenoids and fatty acids</td>
</tr>
<tr>
<td>Sahrawat <em>et al.</em>, 2018 [79]</td>
<td>India</td>
<td>The extract had antibacterial activity against <em>E. coli</em> at a concentration of 58.77%</td>
<td>Leaf extract</td>
<td>Saponins, tannins, terpenoids, and alkaloids</td>
</tr>
<tr>
<td>Muhammad <em>et al.</em>, 2019 [80]</td>
<td>Nigeria</td>
<td>The extract had antibacterial activity against <em>E. coli</em> and <em>K. pneumoniae</em> at a concentration of 50 mg/ml and 75 mg/ml respectively</td>
<td>Leaf extract</td>
<td>Phenols, tannins, and alkaloids</td>
</tr>
<tr>
<td>Momoh and Olaleye, 2022 [81]</td>
<td>Nigeria</td>
<td>The extract had antibacterial activity against <em>E. coli</em> at a concentration of 100 mg/ml with a zone of inhibition of 9.33 mm, and highest activity at 500 mg/ml with a zone of inhibition of 21.36 mm</td>
<td>Root extract</td>
<td>Alkaloids, tannins, saponins, phenolics, and flavonoids</td>
</tr>
<tr>
<td>Singh, 2021 [82]</td>
<td>India</td>
<td>The extract had antibacterial activity against <em>E. coli</em> at a concentration of 1 mg/ml with a zone of inhibition of 0.1 mm</td>
<td>Leaf extract</td>
<td>Flavonoids, resin, and phlobatannins</td>
</tr>
<tr>
<td>Ogidi <em>et al.</em>, 2021 [83]</td>
<td>Nigeria</td>
<td>The extract had antibacterial activity against <em>Staphylococcus</em> spp, <em>Shigella</em> spp, <em>Vibrio</em> spp, and <em>E. coli</em> with zones of inhibition of 10mm and 7.0 mm, 7.0 mm and 26.0 mm, 7.0 mm and 10.6 mm, and 9.3 mm and 10 mm, respectively</td>
<td>Leaf extract</td>
<td>Saponins, tannins, steroids, glycosides, terpenoids, flavonoids, and alkaloids</td>
</tr>
<tr>
<td>Meressa, 2017 [84]</td>
<td>Ethiopia</td>
<td>The extract had antibacterial activity against <em>S. typhi</em> and <em>E. coli</em> with zones of inhibition of 20 mm and 16mm respectively</td>
<td>Stem bark extract</td>
<td>Tannins, saponins, phlobatannins, flavonoids, cardiac glycosides and alkaloids</td>
</tr>
<tr>
<td>Kulkarni, Pandey and Patil, 2017 [85]</td>
<td>India</td>
<td>The extract had antibacterial activity against <em>E. coli</em>, <em>S. aureus</em>, <em>K. pneumoniae</em>, <em>E. aerogenes</em>, <em>P. aeruginosa</em>, <em>S. typhi</em>, <em>S. epidermidis</em> and <em>P. vulgaris</em></td>
<td>Leaf extract</td>
<td>Alkaloids, glycosides, and tannins</td>
</tr>
<tr>
<td>Mohammed, Stephens and Sadiq, 2022 [86]</td>
<td>Nigeria</td>
<td>The extract had antibacterial activity against <em>E. coli</em> and <em>S. aureus</em> at a concentration of 200 mg/ml</td>
<td>Leaf extract</td>
<td>Glycosides, carbohydrates, phenols, alkaloids, and flavonoids</td>
</tr>
<tr>
<td>Fatima, 2020 [87]</td>
<td>Pakistan</td>
<td>The extract had antibacterial activity against <em>E. coli</em>, <em>S. aureus</em>, and <em>P. aeruginosa</em> with zones of inhibition of 25 mm, 26mm and 23mm respectively</td>
<td>Leaf extract</td>
<td>Tannins, glycosides, alkaloids, and saponins</td>
</tr>
<tr>
<td>Beniskeikh, 2019 [88]</td>
<td>Nigeria</td>
<td>The extract had antibacterial activity against <em>S. aureus</em> with a zone of inhibition of 10 mm</td>
<td>Seed extract</td>
<td>Terpenoids</td>
</tr>
<tr>
<td>Mustafa, 2016 [89]</td>
<td>Saudi Arabia</td>
<td>The extract had antibacterial activity against <em>E. faecalis</em> a zone of inhibition of 17.70 mm</td>
<td>Leaf extract</td>
<td>Tannins</td>
</tr>
<tr>
<td>Faujdar, Bisht and Sharma, 2020 [90]</td>
<td>India</td>
<td>The extract had antibacterial activity against <em>E. coli</em>, <em>K. pneumoniae</em>, <em>Citrobacter</em> spp, <em>Proteus</em> spp, <em>Acinetobacter baumannii</em>, <em>P. aeruginosa</em>, and <em>Enterobacter</em> spp</td>
<td>Leaf extract</td>
<td>-</td>
</tr>
<tr>
<td>Maleki <em>et al.</em>, 2017 [80]</td>
<td>Iran</td>
<td>The extract had antibacterial activity against <em>P. aeruginosa</em> at a concentration of 300 mg/ml. The extract also had activity against <em>S. aureus</em> and <em>E. faecalis</em></td>
<td>Leaf extract</td>
<td>-</td>
</tr>
</tbody>
</table>
**Table:**

<table>
<thead>
<tr>
<th>Author</th>
<th>Region</th>
<th>Description</th>
<th>Antibacterial Activity</th>
<th>Seed and Bark Extractions</th>
<th>Phytochemicals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melese et al., 2016 [92]</td>
<td>India</td>
<td>The extract had antibacterial activity against <em>S. aureus</em>, <em>P. aeruginosa</em>, and <em>E. coli</em> at the concentration of 400 mcg/ml</td>
<td>Seed and bark extracts</td>
<td>Alkaloids, carotenoids, saponins, anthraquinones, and cardiac glycosides</td>
<td></td>
</tr>
<tr>
<td>Sharma et al., 2014 [93]</td>
<td>India</td>
<td>The extract had antibacterial activities against <em>E. coli</em> and <em>Bacillus amyloliquefaciens</em> at the different MICs</td>
<td>Leaves, roots, seed and bark extracts</td>
<td>Tannin, saponins, alkaloids, phenolics, and flavonoids</td>
<td></td>
</tr>
<tr>
<td>Saleem et al., 2022 [98]</td>
<td>Pakistan</td>
<td>The extract had antibacterial activities against <em>S. aureus</em> and <em>E. coli</em> at the zone of inhibition of zone of 10 mm</td>
<td>Leaves extract</td>
<td>Saponins, tannins, reducing sugars, glycosides, alkaloids, and flavonoids</td>
<td></td>
</tr>
<tr>
<td>Dereje et al., 2021 [95]</td>
<td>Ethiopia</td>
<td>The extract had antibacterial activities against <em>Streptococcus pyogenes</em> at the concentration of 100 mg/ml</td>
<td>Leaves extract</td>
<td>Alkaloids, terpenoids, saponins, flavonoids, phenols, tannins, and steroids</td>
<td></td>
</tr>
<tr>
<td>Kumari et al., 2019 [96]</td>
<td>India</td>
<td>The extract had antibacterial activities against <em>Streptococcus mutans</em> with a zone of inhibition of 1.18 mm</td>
<td>Barks, leaves and twig pieces were the extracts</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Mohammed, 2017 [97]</td>
<td>Sudan</td>
<td>The extract had antibacterial activities against <em>E. coli</em>, <em>P. aeruginosa</em>, <em>Proteus mirabilis</em>, <em>Klebsiella pneumoniae</em>, <em>S. aureus</em>, and <em>E. faecalis</em> with the highest inhibition against <em>Proteus mirabilis</em> and <em>E. faecalis</em> at the concentration of 6.25 mg/ml and 12.5 mg/ml respectively</td>
<td>Leaf extract</td>
<td>Alkaloids, terpenoids, saponins, flavonoids, and phenols,</td>
<td></td>
</tr>
<tr>
<td>Altayb et al., 2022 [98]</td>
<td>Saudi Arabia</td>
<td>The extract had antibacterial activities against <em>S. aureus</em>, <em>P. aeruginosa</em>, <em>E. coli</em>, <em>Proteus spp.</em>, <em>S. epidermidis</em>, <em>Citrobacter spp.</em>, <em>K. pneumoniae</em>, <em>E. faecalis</em>, <em>S. aureus</em> at the different zones of inhibition with the highest recorded with <em>P. aeruginosa</em> with 13 mm</td>
<td>Leaves extract</td>
<td>Fatty acids, hydrocarbons, pyridine derivatives, aldehydes, phenol group, aromatic substances, coumarins, monoterpenes and beta. d- Mannocturanoside O-geranyl</td>
<td></td>
</tr>
<tr>
<td>Ibrahim and Kebede, 2020 [99]</td>
<td>Ethiopia</td>
<td>The extract had antibacterial activities against <em>S. aureus</em>, <em>S. typhi</em>, <em>Streptococcus agalactiae</em>, and <em>Shigella boydii</em> with the methanol extract showing the highest inhibition zone at the concentrations of 125 mg/ml and 150 mg/ml</td>
<td>Leaves extract</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Senthilkumar et al., 2018 [100]</td>
<td>India</td>
<td>The extract had antibacterial activities against <em>P. aeruginosa</em> at concentrations ranging from 2 to 16 µg/ml</td>
<td>Leaves extract</td>
<td>Silver nanoparticle</td>
<td></td>
</tr>
<tr>
<td>Singh et al., 2017 [101]</td>
<td>India</td>
<td>The extract had antibacterial activities against <em>S. aureus</em>, <em>Streptococcus pyogenes</em>, <em>E. coli</em>, <em>S. typhi</em>, and <em>K. pneumonia</em></td>
<td>Leaves extract</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Pandey, Verma and Singh, 2014 [102]</td>
<td>India</td>
<td>The extract had antibacterial activities against <em>E. coli</em> and <em>S. aureus</em> with the inhibition zone 13.23 ± 3.26 and 16.52 ± 3.28 at the concentration of 1.50 mg/ml respectively.</td>
<td>Leaves extract</td>
<td>Alkaloids, terpenoids, saponins, flavonoids, phenols, tannins, steroids, and aldehydes</td>
<td></td>
</tr>
<tr>
<td>Ali et al., 2021 [103]</td>
<td>Bangladesh</td>
<td>The extract had antibacterial activity against multidrug-resistant <em>E. coli</em> and <em>Salmonella spp.</em></td>
<td>Leaf extract</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

**Discussion:**

This study reviewed publications on the phytochemical composition and antibacterial activities of *A. indica* against various bacterial species. In reviewing the literature, our study found that the leaf, stem, root, and bark extract of *A. indica* has antibacterial activity due to the presence of phytochemicals including phenolics, tannins, saponins, flavonoids, alkaloids, terpenoids, fatty acids, glycosides, etc. Additionally, we found that *A. indica* has antibacterial activity against Gram-negative and Gram-positive bacteria including *E. coli*, *Enterococcus* species, *S. aureus*, *S. typhi*, *K. pneumoniae*, *Streptococcus pyogenes*, *Enterobacter* spp., and other bacteria.

This study revealed that the part of the plant that has antibacterial activities includes the leaf, stem, root, and bark extract, as reported by many publications [68, 79, 81, 82, 84, 86-88, 90, 91, 99, 96, 98, 102, 103]. The antibacterial activity of *A. indica* leaves is attributed to its bioactive compounds such as nimbins, nimbibin, and nimbibidin, which act by disrupting the bacterial cell membrane and interfering with their metabolic processes [70]. The stem contains compounds like gedunin and mahmoodin, which have been identified as active antibacterial agents [104]. These compounds inhibit the growth and proliferation of bacteria by disrupting their cellular functions [105]. *A. indica* root extracts have been less studied compared to other parts of the plant, but evidence shows its antibacterial efficacy [106]. Roots contain azadirachtin, a prominent bioactive compound responsible for many of *A. indica*’s medicinal properties, including its antibacterial activity. Azadirachtin has been found effective against bacterial strains like *Bacillus subtilis* and *K. pneumoniae* [106]. *A. indica* bark extract is another part of the plant that possesses antibacterial potential [106]. Some studies have shown that the bark extracts contain compounds such as quercetin and beta-sitosterol, which exhibit antibacterial activity against various pathogenic bacteria [107]. It’s important to note that while *A. indica* extracts have shown promising antibacterial properties in vitro, further research is required to explore their efficacy *in vivo* and their potential use in clinical settings. Furthermore, it’s important to note that the levels of active compounds within these extracts can exhibit significant variations, contingent upon factors such as geographical location, prevailing climatic conditions, and the maturity of the plant from which they are derived. These variables can exert a profound impact on the collective antibacterial potential of the extracts, thereby necessitating a comprehensive understanding of the intricate interplay between environmental factors and the phytochemical composition of these natural remedies. Such insight is crucial for optimizing the antibacterial efficacy of these extracts and harnessing their therapeutic potential to combat microbial infections effectively.

The findings of this review provide compelling evidence for the antibacterial potential of *A. indica* against *E. coli*, *S.
and other bacteria. The review, which encompassed a comprehensive analysis of literature from multiple studies, consistently demonstrated that An. indica exhibits significant antibacterial activity against this pathogenic bacterium. The consistent outcomes across these studies reinforce the validity and reliability of the observed antibacterial effects of An. indica against the various bacteria. However, the limited number of studies included in this review underscores the need for further research to strengthen the evidence base. The inclusion of more studies from diverse geographical locations and experimental setups would enhance the generalizability and robustness of the findings. Finally, the findings of this review demonstrated the importance of integrating traditional medicine into the modern healthcare system.

Conclusion
Azadirachta indica has antibacterial activities due to its rich composition of phytochemicals. These findings are critical and may be utilised in drug discovery. Therefore, there is a need for more investment in drug discovery, especially with the growing resistance of pathogens to conventional antimicrobials. There is a need to promote further research in traditional medicine that can inform policy and support the incorporation of traditional medicine in the healthcare system to be used together with conventional medicines.

Acknowledgements
We acknowledge the University of Zambia e-library for providing us with access to all the publications used in this article.

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