Medical Sains : Jurnal Ilmiah Kefarmasian
Vol. 9 No. 3, July - September 2024
https:/ojs.stfmuhammadiyahcirebon.ac.id/index.php/iojs

REVIEW ARTICLE: NANOHERBAL AS A NATURAL SOLUTION FOR BACTERIAL DIARRHEA PROBLEMS

Dewa Ayu Embas Saraswati[1]*, Garnadi Jafar[2], Agus Sulaeman[3], Yani Mulyani[3]
1Master of Pharmacy Study Program, Faculty of Pharmacy, Bhakti Kencana University
Bhakti Kencana University, Bandung 40614, Indonesia.
2 Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, Bhakti Kencana University
Bhakti Kencana University, Bandung 40614, Indonesia.
3 Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Bhakti Kencana University
Bhakti Kencana University, Bandung 40614, Indonesia.
**Email Corresponding: embas2022@gmail.com*

Submitted: 30 April 2024 ***Revised: 10 July 2024*** ***Accepted: 24 July 2024***

ABSTRACT

Diarrhea is a global health problem that is often caused by bacterial infections, including *Escherichia coli* and *Staphylococcus aureus*. The use of conventional antibiotics in treating diarrhea often faces challenges, such as drug resistance and adverse side effects. As an alternative, current research interest is focused on the use of nanoparticles from herbal ingredients as potential antibacterial agents in the treatment of diarrhea. This review article aims to present the latest developments in the use of herbal nanoparticles as an anti-bacterial therapy for diarrhea. The literature search method was carried out via PubMed, Science Direct, and Google Scholar using relevant keywords. Selected articles must meet inclusion criteria, such as originality, language, period, and availability of full text. After the selection process, articles that meet the criteria will be reviewed to identify findings related to the use of herbal nanoparticles in treating diarrhea. Data analysis was conducted to compare the findings of each article and draw appropriate conclusions. Therefore, this review article aims to provide a comprehensive understanding of the potential use of nanoparticles from herbal ingredients as an effective and safe solution to treat diarrhea problems, while also highlighting interesting research possibilities to be carried out in the future. effectiveness and bioavailability in the treatment of diarrhea. By increasing absorption and penetration into bacterial cells, this therapy can serve as an effective and sustainable antibacterial agent. It is hoped that this nanoparticle-based alternative therapy can reduce the risk of antibiotic resistance and drug side effects in the treatment of diarrhea in the future.

Keywords: Nanoparticles, Herbal, Antibacterial, Diarrhea

INTRODUCTION

Diarrhea is a widespread health issue globally, impacting individuals of all ages and backgrounds. It is characterized by frequent loose or liquid bowel movements, that occur at least three times a day, often stemming from infections affecting the intestinal tract. This condition can persist for several days and ranks as the third leading cause of death among children under five, claiming approximately 443,832 young lives annually (World Health Organization (WHO, 2024). Infections caused by contaminated food and water remain significant contributors to morbidity and mortality worldwide, particularly in developing regions and post-natural disasters. Such diarrheal episodes pose risks to infant growth and can have enduring cognitive effects (Keely & Barrett, 2022).

Untreated acute diarrhea in children can lead to dehydration, electrolyte imbalances, and significant weight loss (Troeger et al., 2018). It is crucial to promptly and appropriately treat diarrhea to prevent serious complications and ensure optimal recovery (Shankar & Rosenbaum, 2020). Treatment options include pharmaceutical drugs available on the market as well as herbal medicines. The popularity of herbal medicines has risen due to their ability to treat various ailments with fewer side effects (Chakraborty *et al*., 2016). Herbal remedies have been used worldwide for centuries. However, challenges in the absorption and bioavailability of their active compounds have led to their integration with nanotechnology, enhancing efficacy, reducing dosage and side effects, and enabling targeted delivery of active ingredients (Silva *et al*., 2013).

While herbal medicines face challenges such as low solubility, stability, and bioavailability, nanotechnology-based formulations have garnered significant attention in recent years. This innovative approach employs nanotechnology-based delivery systems to enhance the solubility, stability, bioavailability, and pharmacological efficacy of herbal compounds (Dewi *et al*., 2022). Herbal medicines utilizing nanotechnology-based delivery systems hold immense promise and distinct advantages, effectively transforming initially poorly soluble, poorly absorbed, and unstable compounds into potent and reliable medicinal products (Sandhiya & Ubaidulla, 2020).

Nanoparticles are solid particles typically sized between 100 and 500 nanometers (Rizvi & Saleh, 2018). Advanced nanoparticle development enhances general drug delivery effectiveness and allows tailored designs for specific applications, thereby improving overall patient outcomes (Mitchell et al., 2021). Operating at the nanoscale, nanoparticle technology offers several advantages, including increased surface area, enhanced stability, and optimized drug delivery capabilities (Rizvi & Saleh, 2018). Nanoparticles provide a safe and well-tolerated treatment approach, minimizing side effects (Srinivasan & Elumalai, 2023). Their application in herbal extracts aims to address common issues such as low water solubility, poor bioavailability, instability, and limited absorption rates. Thus, integrating nanoparticle technology can significantly enhance the efficacy of herbal medicines (Sutoyo S., et al., 2022).

Herbal nanoparticle diarrhea drug therapy represents an innovative approach that integrates the therapeutic benefits of medicinal plants with nanoparticle technology to enhance the effectiveness of diarrhea treatment. This method involves transforming herbal extracts, known for their antimicrobial or anti-inflammatory properties, into nano-sized particles. These nanoparticles can be formulated into suspensions, capsules, or solutions, facilitating improved bioavailability and enhanced absorption of the active substances within the body. This approach holds promise for optimizing the delivery and efficacy of herbal medicines in treating diarrhea.

In this context, the advancement of herbal drug delivery systems holds significant importance. These systems are designed to enhance the bioavailability and stability of active ingredients found in medicinal plants, while also ensuring their timely and targeted delivery within the body. This article aims to review recent developments in herbal drug delivery systems, specifically for antidiarrheal therapy. It will delve into key discoveries, challenges encountered, and emerging opportunities within this field. Moreover, the review will underscore the potential future clinical applications of herbal nanoparticles in managing diarrhea. This comprehensive review seeks to deepen understanding of the potential benefits of utilizing herbal nanoparticles in combating diarrhea and suggest areas for further research exploration in this promising area of study.

RESEARCH METHODS

Literature Search Strategy:

Search Sources: A literature search was conducted through three main sources, namely PubMed, Science Direct, Mendeley, and Google Scholar, to collect information on herbal nanoparticles that act as antibacterials in diarrhea. Keywords: the keywords used include

"Nanoparticles or Nanoemulsion"; "Plant or Herbal Extracts"; "Novel Drug Delivery System"; "Antibacterial"; and "Diarrhea.". Search filters: the search focused on original articles, in Indonesian or English, published within the last 10 years (2014-2024), and available in full text.

Literature Criteria:

To ensure the quality and relevance of the studies included in this review, we established specific inclusion and exclusion criteria. Inclusion criteria encompassed originality, language (English or Indonesian), publication within 2014-2024, availability of full text, relevance to the topic, clear methodology, adequate sample size, appropriate statistical analysis, and acknowledgment of potential bias. Exclusion criteria comprised duplicated or plagiarized content, inappropriate language, publication outside the last 10 years, incomplete full-text access, lack of relevance, unclear or inadequate methodology, insufficient sample size, inappropriate statistical analysis, and the absence of acknowledgment of potential bias. These criteria were applied rigorously to ensure that the selected studies met the standards necessary to contribute to the validity and reliability of the review findings.

Literature Selection Phase:

In the initial phase of this study, we conducted a literature review to identify relevant articles on the use of herbal nanoparticles for antidiarrheal therapy. The selection process commenced with the analysis of titles, abstracts, and keywords from various scientific databases, yielding 45 potential articles. Utilizing Mendeley reference management software facilitated efficient organization and screening of articles based on predefined inclusion and exclusion criteria. From the initial pool of 45 articles, 20 were selected based on the initial criteria for further evaluation. Following additional screening, 6 articles were identified as the most pertinent and of high quality for detailed review. The final step involved rigorous verification of the accuracy and relevance of the selected articles to the research topic, ensuring no data duplication. This systematic approach ensured alignment of the literature with the study's objectives and criteria, thereby enhancing the validity and quality of our findings.

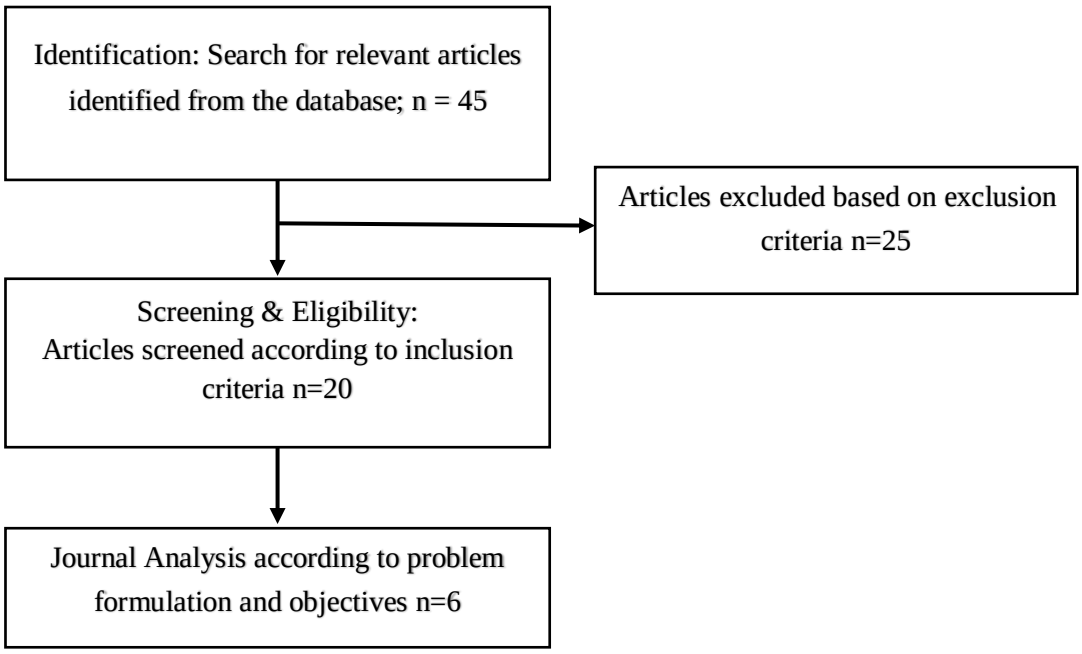

Figure 1. Flow of Article Search

RESULTS AND DISCUSSION

Before going into a more detailed discussion, **Table I** below presents a summary of studies that investigated the antibacterial activity of various nanoherbal formulations. Each section in the table includes the preparation method, findings, type of bacteria inhibited, and relevant references. Nanoherbals, as listed in the table, show potential as an alternative in the treatment of bacterial infections by using various formulation approaches to enhance antibacterial effectiveness against different types of pathogens. This reflects the ongoing efforts in research to develop new strategies that can overcome the challenges of antibiotic resistance and expand safe and effective therapeutic options for patients.

Table I. Nano herbals have antibacterial activity

Article Title	Preparation Method	Results	Inhibited Bacteria	References
Synthesis of Cobalt Ferrite Nanoparticles ($CoFe_2O_4$) Using *Binahong* (*Anredera cordifolia* (Ten) Steenis) Leaf Extract and Its Application as an Antibacterial	Magnetic nanoparticles Cobalt Ferrite ($CoFe_2O_4$)	*Binahong* Leaf Extract $CoFe_2O_4$ Nanoparticles can inhibit bacterial growth.	*Escherichia coli* and *Staphylococcus aureus.*	(Luntung et al., 2020)
Effectiveness of *binahong* extract nanoemulsion against *Staphylococcus aureus*, *Salmonella typhi*, and *Escherichia coli*	Nano Emulsion	*Binahong* extract nanoemulsion shows antibacterial activity by inhibiting bacterial growth.	*Staphylococcus aureus*, *Salmonella typhi*, and *Escherichia coli*	(Wijanarko et al., 2022)
Antibacterial Activity Test of Ethanol Extract Nanoparticles of Matoa Leaves (*Pometia Pinnata* JR Forst & G. Forst) Against *Escherichia coli* Bacteria	Chitosan nanoparticles	Nanoparticles from matoa leaf ethanol extract show antibacterial activity, where a 2.5% concentration of extract nanoparticles has an effect equivalent to half the dose of a 25% concentration of	*Escherichia coli*	(Siregar et al., 2023)

		matoa leaf ethanol extract.		
Antibacterial Activity of Nanoemulsion Stem Fraction of Pucuk *Idat* (*Cratoxylum glaucum*)	homogenized particles	Nanoemulsion of the MeOH: water fraction from idate shoot stems had a droplet size of 101.6 nm with a PI value of 0.274. The transmittance percentage reached 80.33%, indicating that this nanoemulsion can be considered as a nanoemulsion with good stability when compared with ethyl acetate and n-hexane nanoemulsions. In addition, MeOH: water nanoemulsion also showed strong antibacterial activity against *S. aureus* with an inhibition zone diameter of 10.42 cm.	*Staphylococcus aureus*	(Pratama et al., 2021)
Antibacterial Activity of *Pandan Wangi* Leaf Extract Nano-Particles (*Pandanus Amaryllifolius* Roxb) Against *Escherichia coli* and *Staphylococcus aureus*	Chitosan nanoparticles	The findings show that in one milliliter of fragrant pandan leaf extract nano-particles with a concentration of 60%, the greatest inhibitory power is 11 mm and 7 mm against	*Staphylococcus aureus* and *Escherichia coli*	(Puspitasari et al., 2023)

		Staphylococcus aureus and *Escherichia coli.*		
Nanoherbal Synthesis from Ethanol Extract of Indonesian Fern Selaginella plana and Antibacterial Activity Test	Chitosan Nanoparticle Ionic Glass	Nanoherbal showed strong antibacterial ability against *E. coli* and *S. dysentriae*, while antibacterial activity against *S. aureus* and *B. subtilis* was moderate. The antibacterial activity of nanoherbal F-1 against *E. coli* and *S. dysentriae* exceeds tetracycline, while against *S. aureus* and *B. subtilis* it is lower than tetracycline.	*Escherichia coli, Shigella dysenteriae, Staphylococcus aureus*, and *Bacillus subtilis.*	(Sutoyo S et al., 2022)

Diarrhea poses a significant global health challenge, particularly affecting developing regions and communities lacking access to clean water, proper sanitation, and adequate healthcare. Bacterial infections, such as *Escherichia coli* and *Staphylococcus aureus*, are common causes of diarrhea. Immediate treatment is crucial to prevent dehydration, which can lead to severe complications and even death. Current treatments often entail side effects, and the rise of antibiotic resistance underscores the need for safe and effective alternatives. Herbal therapies offer promising, affordable alternatives; however, enhancing the bioavailability and efficacy of these herbal ingredients remains a key challenge. Advances in nanotechnology, particularly the development of nanoparticles, present opportunities to address these challenges and improve the treatment of diarrhea.

This review article discusses the development of nanoparticles from herbal ingredients as antidiarrheal therapy, which has attracted attention in the scientific world. By utilizing advances in the field of nanotechnology, this research explores the potential for using nanoparticles to increase the effectiveness and bioavailability of herbal ingredients that have long been known in traditional medicine. Research cited in this article reveals that herbal nanoparticles can enhance antimicrobial effects that can help reduce and treat diarrhea symptoms efficiently.

Based on the results of antibacterial activity tests on *binahong* leaf extract, it was found that it has the ability to inhibit bacterial growth naturally, with an inhibitory power value of 8.25 for *Escherichia coli* and 10.25 for *Staphylococcus aureus*. However, with the addition of $CoFe_2O_4$ nanoparticles to the extract, there was a significant increase in the inhibitory power against both types of bacteria. The inhibitory power value reached 15 mm for *Escherichia coli* and 20 mm for *Staphylococcus aureus*, indicating a strong effect in inhibiting the growth of Gram-negative (*E. coli*) and Gram-positive (*S. aureus*) bacteria. The

cause of this increase is the ability of $CoFe_2O_4$ nanoparticles to attach to bacterial cell walls and penetrate their cell membranes. This results in damage to the bacterial cell structure and, ultimately, cell death. Apart from that, $CoFe_2O_4$ nanoparticles can also release ions that cause oxidative stress in bacterial cells, thereby damaging bacterial DNA. It should be noted that the antibacterial activity of $CoFe_2O_4$ nanoparticles is stronger against *Staphylococcus aureus* than *Escherichia coli*, due to the differences in structural and biological characteristics between the two types of bacteria. Thus, $CoFe_2O_4$ nanoparticles show potential as an effective antibacterial agent, capable of inhibiting the growth of Gram-negative and Gram-positive bacteria, and increasing their effectiveness when used with *binahong* leaf extract. (Luntung *et al*., 2020).

The antibacterial activity test results of the *binahong* extract nanoemulsion showed that the P1 formulation showed strong antibacterial activity against *Staphylococcus aureus*, *Salmonella typhi*, and *Escherichia coli*, with inhibition zones reaching 8.1 mm, 8 mm, and 8.1 mm, respectively. In formula P2, nanoemulsions of *binahong* extract exhibited moderate antibacterial activity against *Staphylococcus aureus* (5.1 mm), but demonstrated weaker activity against *Salmonella typhi* (0.8 mm) and *Escherichia coli* (1.6 mm). This study confirms that nanoemulsion technology enhances the efficiency of extract utilization, achieving comparable or superior antibacterial activity at lower concentrations. The size of the inhibition zone correlates with the potency of the active compound in restraining bacterial growth. The significant antibacterial effectiveness of formulation P1 against all three tested bacteria underscores the potential of *binahong* extract nanoemulsion as a viable alternative to antibiotics across a range of bacterial types (Wijanarko *et al*., 2022).

The difference in antibacterial activity between ethanol extract and ethanol extract nanoparticles from matoa leaves was investigated, showing that the concentration of 75% matoa leaf ethanol extract and 7.5% matoa leaf ethanol extract nanoparticles showed the greatest inhibitory power. The higher the concentration of matoa leaf ethanol extract and extract nanoparticles, the greater the inhibitory power. Concentrations of plant extracts that have a higher antibacterial effect tend to produce greater inhibitory power and inhibitory zone diameters, depending on the type of plant and bacteria tested. Research shows that the metabolite compounds contained in plants affect the inhibitory power of the extract. The research results show that ethanol extract from matoa leaves can be converted into nanoparticles with an average particle size of around 324.97 nm. There was a difference in antibacterial effectiveness between ethanol extract and nanoparticle extract against *Escherichia coli*, as measured by the zone of inhibition. The zone of inhibition for the ethanol extract was 13.9 mm (25% concentration), 14.6 mm (50% concentration), and 18 mm (75% concentration), while for the nanoparticle extract it was 6.6 mm (2.5% concentration), 7.2 mm (5% concentration), and 7.7 mm (7.5% concentration), while the zone of inhibition of tetracycline 30µg was 22.4 mm. According to the Clinical Laboratory Standards Institute, the interpretation standards for the diameter of the inhibition zone of *E. coli* against Tetracycline antibiotics are less than or equal to 11 mm (resistant), between 12 and 14 mm (intermediate), and 15 mm or more (sensitive). Even though the 2.5% nanoparticle extract concentration showed antibacterial activity equivalent to half the dose of the 25% ethanol extract concentration, it had a category of resistance to the control antibiotic, tetracycline 30µg. The small particle size of nanoparticles has special characteristics in terms of a larger surface area and increased reactivity. This allows more intense interactions between the charges on the bacterial surface, which can result in stronger antimicrobial effects. With a large surface area, nanoparticles can stick to the surface of bacterial cells in greater numbers, which can cause instability in the cell membrane and result in leakage of intracellular substances, which ultimately induces cell death. (Tandiono, 2018).

The results of the antibacterial test showed that the response pattern of the nanoemulsion shoot stem fraction of idate against *E. coli* and *S. aureus* bacteria was different. Against *E. coli*, there was a decrease in the zone of inhibition in the nanoemulsion compared to the fraction, but against *S. aureus*, there was an increase in the zone of

inhibition in the nanoemulsion. In addition, the MeOH: water fraction nanoemulsion was more effective in dealing with *S. aureus* (inhibition zone 10.42 mm) than *E. coli* (inhibition zone 7.88 mm), due to differences in the cell wall structure of the gram-positive bacteria *S. aureus* has a single layer, which allows the nanoemulsion to penetrate the membrane more easily, while *E. coli* has a more complex cell wall structure with three layers, which makes it difficult for antibacterial agents to penetrate. The antibacterial mechanism of phenolic derivative compounds such as anthraquinones and xanthones involves disruption of the peptidoglycan component in the bacterial cell wall which has hydrogen bonds. The hydroxyl group (OH) in phenol compounds plays a role in antibacterial activity by causing protein denaturation through an adsorption process that disrupts hydrogen bonds. Research shows that nanoemulsion fractions of idate shoot extract have the potential to increase antibacterial activity, especially against *E. Coli* bacteria, when compared with extracts that are not in nanoemulsion form. (Pratama *et al*., 2021).

Based on the results of the nanoherbal synthesis of the ethanol extract of the Indonesian Fern *Selaginella plana* and the antibacterial activity test, it was found that the ethanol extract from the fern *Selaginella plana* showed strong antibacterial activity against *Escherichia coli* and *Shigella dysenteriae*, as well as moderate antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis*. Tetracycline also shows significant antibacterial activity against *Escherichia coli*, *Shigella dysenteriae*, and *Bacillus subtilis*, as well as very strong antibacterial activity against *Staphylococcus aureus*. Furthermore, the antibacterial activity of nanoherbal F-1 against *Escherichia coli* and *Shigella dysenteriae* was higher than tetracycline, while the antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis* was lower than tetracycline. Similarly, the antibacterial activity of Selaginella plana ethanol extract shows varying effectiveness compared to tetracycline. It exhibits lower activity against *Shigella dysenteriae* and *Staphylococcus aureus*, but comparable activity against *Escherichia coli*. Specifically, its effectiveness against *Bacillus subtilis* is also noted, although it varies compared to tetracycline. The potential for developing F-1 nanoherbal as an antibacterial agent is supported by the content of phenolic compounds, especially flavonoids, in the ethanol extract from the *S. plana* fern. Flavonoid compounds possess properties that inhibit bacterial growth by damaging cell membranes, inactivating enzymes, binding to adhesins, and inhibiting nucleic acid synthesis. The hydroxyl groups in flavonoids also influence their antibacterial activity, where the position of the hydroxyl groups at C-5, C-6, and C-7 in the A ring of flavonoids can increase their antibacterial activity. The ethanol extract of *S. plana* produced from nanoherbal F-1 showed increased antibacterial activity against *E. coli, S. dysentriae, B. subtilis,* and *B. subtilis*. In nano form, the amount of isolated active substance increases due to the larger particle surface contact area, so the antibacterial activity is stronger. Nano-sized particles also have the ability to penetrate intercellular spaces, either through diffusion or opsonification. Apart from that, the presence of chitosan polymer in nanoherbal F-1 also supports its antibacterial activity by inhibiting bacterial growth. Chitosan can form a polymer membrane on the surface of bacterial cells, preventing nutrients from entering the cells so that they will die. The positive charge of chitosan will interact with the negative charge on the surface of the bacteria, causing damage to cell membrane permeability, cell leakage, and ultimately cell death. (Sutoyo S. *et al*., 2022).

Nanoparticles play a very important role in enhancing the antibacterial effectiveness of herbal extracts through several well-documented mechanisms. First, nanoparticles have a larger surface area compared to conventional particles, allowing for more intense interactions with bacterial cell membranes. This strengthens the ability of nanoparticles to adhere to the bacterial cell wall, which can lead to membrane damage and leakage of intracellular substances. In addition, the better penetration ability of the nanoparticles allows them to reach targets within the bacteria more effectively. During this process, nanoparticles can also generate reactive oxygen species (ROS) such as hydroxyl and superoxide radicals, which effectively damage bacterial cellular components such as DNA, proteins, and lipids, ultimately resulting in efficient bacterial cell death (Saravanan *et al*., 2021). Nanoparticles have the capability to interact with bacterial cell membranes, triggering the production of

reactive oxygen species (ROS). These ROS can disrupt essential components within bacterial cells, including DNA and proteins, ultimately leading to cell death (Saravanan *et al*., 2021). The significant surface area-to-volume ratio of nanoparticles, combined with their highly charged surfaces, facilitates effective interaction with bacterial cell walls, enhancing the generation of ROS that disrupt bacterial membranes, proteins, and DNA (Abolarinwa *et al*., 2022).

When compared to conventional antibiotics, herbal nanoparticles demonstrate several potential advantages. While conventional antibiotics remain the primary treatment for bacterial infections, they are frequently linked to drug resistance and significant side effects. In contrast, herbal nanoparticles provide a safer alternative with robust antimicrobial properties. Research indicates that herbal nanoparticles can effectively combat a variety of pathogenic bacteria, sometimes achieving equivalent or superior effectiveness, while mitigating the risks of drug resistance and adverse health effects (Wijanarko *et al*., 2022).

Nanoparticles derived from herbs are emerging as a promising alternative to conventional antibiotics for treating bacterial infections. They have demonstrated effectiveness against a range of pathogens, including *Escherichia coli* and *Staphylococcus aureus*, occasionally outperforming conventional antibiotics. Key advantages of herbal nanoparticles include their potential to mitigate drug resistance, the utilization of safer natural ingredients, and their adaptability to diverse clinical formulations as needed. However, extensive research is necessary to ascertain their long-term safety, comparative efficacy, and suitability for widespread clinical application before they can be widely adopted in medical practice.

While the reviewed studies present promising results, several limitations should be noted. Variations in sample sizes among different studies can impact the reliability of the results. Additionally, differences in experimental conditions such as extraction methods, nanoparticle formulation, and assay parameters may influence result interpretation. Biases in the selection of in vitro or in vivo models should also be considered, as they can affect the generalizability of findings to clinical settings. These factors underscore the need for cautious interpretation and further research to validate and refine the outcomes of herbal nanoparticle studies.

For future research directions, several areas warrant exploration. Firstly, investigating different types of nanoparticles to assess their efficacy against diverse bacterial pathogens could yield valuable insights. Additionally, exploring variations in nanoparticle dosage is crucial to determining the optimal microbiological response. Longitudinal studies are essential to understand the prolonged effects of herbal nanoparticles on normal microbiota and to monitor the potential development of resistance over time. Advancements in these areas could lead to innovative strategies for tackling global challenges in the treatment of bacterial infections.

CONCLUSION

Nanoparticles hold promise for enhancing the effectiveness and bioavailability of herbal ingredients in diarrhea treatment. Antibacterial activity tests have demonstrated that nanoparticles derived from herbal extracts can enhance antimicrobial effects. Utilizing nanoparticles in herbal therapy has the potential to improve efficacy through increased absorption and penetration into bacterial cells. Consequently, this nanoparticle-based alternative therapy could serve as an effective and sustainable antibacterial agent for diarrhea treatment, while also mitigating the risks of antibiotic resistance and drug-related side effects.

REFERENCES

Abolarinwa, TO, Ajose, DJ, Oluwarinde, BO, Fri, J., Montso, KP, Fayemi, OE, Aremu, AO, & Ateba, CN (2022). Plant-derived Nanoparticles as Alternative Therapy Against Diarrheal Pathogens In The Era of Antimicrobial Resistance: A review. *Frontiers in Microbiology*, 13. https://doi.org/10.3389/fmicb.2022.1007115

Chakraborty, K., Shivakumar, A., & Ramachandran, S. (2016). Nano-technology In Herbal Medicines: A review. *International Journal of Herbal Medicine*, 4(3), 21–27. https://doi.org/10.22271/flora.2016.v4.i3.05

Dewi, MK, Chaerunisaa, AY, Muhaimin, M., & Joni, IM (2022). Improved Activity of Herbal Medicines through Nanotechnology. *Nanomaterials*, 12(22), 4073. https://doi.org/10.3390/nano12224073

Keely, S. J., & Barrett, K. E. (2022). Intestinal Secretory Mechanisms and Diarrhea. *American Journal of Physiology*. *Gastrointestinal and Liver Physiology*, 322(4), G405–G420. https://doi.org/10.1152/ajpgi.00316.2021

Luntung, CL, Aritonang, HF, & Kamu, VS (2020). Synthesis of Cobalt Ferrite Nanoparticles ($CoFe_2O_4$) Using *Binahong* (*Anredera cordifolia* (Ten) Steenis) Leaf Extract And Its Application As An Antibacterial. *Chemistry Progress*, 12(1). https://doi.org/10.35799/cp.12.1.2019.27919

Mitchell, MJ, Billingsley, MM, Haley, RM, Wechsler, ME, Peppas, N.A., & Langer, R. (2021). Engineering Precision Nanoparticles for Drug Delivery. *Nature Reviews Drug Discovery*, 20(2), 101–124. https://doi.org/10.1038/s41573-020-0090-8

Pratama, Y., Mahardika, RG, & Adisyahputra, A. (2021). Antibacterial Activity of Nanoemulsion Stem Fraction of Idat Shoots (*Cratoxylum glaucum*). *EduChemia (Journal of Chemistry and Education)*, 6(2), 208. https://doi.org/10.30870/educhemia.v6i2.10242

Puspitasari, D., Hanafi, M., & Wahyudi, D. (2023). Testing The Antibacterial Activity of Nano-Particles of *Pandan Wangi* Leaf Extract (*Pandanus amaryllifolius* Roxb) Against *Escherichia coli* and *Staphylococcus* aureus. *Simplicia Pharmaceutical Journal*, 3(1), 98–108. https://doi.org/10.30867/jifs.v3i1.340

Rizvi, SAA, & Saleh, AM (2018). Applications of Nanoparticle Systems in Drug Delivery Technology. *Saudi Pharmaceutical Journal*, 26(1), 64–70. https://doi.org/10.1016/j.jsps.2017.10.012

Sandhiya, V., & Ubaidulla, U. (2020). A Review on Herbal Drugs Loaded Into Pharmaceutical Carrier Techniques and its Evaluation Process. *Future Journal of Pharmaceutical Sciences*, 6(1), 51. https://doi.org/10.1186/s43094-020-00050-0

Saravanan, A., Maruthapandi, M., Das, P., Luong, JHT, & Gedanken, A. (2021). Green Synthesis of Multifunctional Carbon Dots with Antibacterial Activities. *Nanomaterials*, 11(2), 369. https://doi.org/10.3390/nano11020369

Shankar, S., & Rosenbaum, J. (2020). Chronic diarrhea in children: A Practical Algorithm-based Approach. *Journal of Pediatrics and Child Health*, 56(7), 1029–1038. https://doi.org/10.1111/jpc.14986

Silva, P., Bonifácio, B., Ramos, M., Negri, K., Maria Bauab, T., & Chorilli, M. (2013). Nanotechnology-based Drug Delivery Systems and Herbal Medicines: A Review. *International Journal of Nanomedicine*, 1. https://doi.org/10.2147/IJN.S52634

Siregar, HN, Rahayu, YP, Nasution, HM, & Nasution, MP (2023). Testing The Antibacterial Activity of Matoa Leaf (*Pometia pinnata* JR Forst & G. Forst) Ethanol Extract Nanoparticles Against *Escherichia coli* Bacteria. *Indonesian Pharmaceutical Research Journal*, 5(1), 24–41. https://doi.org/10.33759/jrki.v5i1.329

Srinivasan, S., & Elumalai, K. (2023). The New Frontier of Drug Delivery Through Nanotechnology. *Intelligent Pharmacy*, 1(4), 169–174. https://doi.org/10.1016/j.ipha.2023.08.002

Sutoyo S, Amaria A, Sanjaya I, Hidayah R, Sari D, Dwitarani N, Oktavia F, & Fadzlillah N. (2022). Synthesis of Nanoherbal from Ethanol Extract of Indonesian Fern Selaginella plana and Antibacterial Activity Assay. *Tropical Journal of Natural Products Research*, 6(1), 44–49. https://doi.org/10.26538/tjnpr/v6i1.9

Tandiono, S. (2018). Preparation and Evaluation of Chitosan-Sodium Tripolyphosphate Nanoparticle Suspension as an Antibacterial. University of Northern Sumatra.

Troeger, C., Blacker, B., Khalil, IA, Rao, PC, Cao, J., Zimsen, SRM, Albertson, SB, Deshpande, A., Farag, T., Abebe, Z., Adetifa, IMO, Adhikari, TB, Akibu, M., Al

Lami, FH, Al-Eyadhy, A., Alvis-Guzman, N., Amare, AT, Amoako, YA, Antonio, CAT, … Reiner, RC (2018). Estimates of The Global, Regional, and National Morbidity, Mortality, and Aetiologies of Lower Respiratory Infections in 195 Countries, 1990–2016: A Systematic Analysis For The Global Burden of Disease Study 2016. *The Lancet Infectious Diseases*, 18(11), 1191 –1210. https://doi.org/10.1016/S1473-3099(18)30310-4

Wijanarko, FR, Krismaputri, ME, Purnamasari, L., Khasanah, H., Yulianto, R., & Widianingrum, DC (2022). Effectiveness of Binahong Extract Nanoemulsion Against *Staphylococcus aureus, Salmonella typhi,* and *Escherichia coli*. *Conference of Applied Animal Science Proceeding Series*, 3(3), 1–7.

World Health Organization (WHO). (2024, March 7). Diarrhoeal Disease. Https://Www.Who.Int/News-Room/Fact-Sheets/Detail/Diarrhoeal-Disease. https://www.who.int/news-room/fact-sheets/detail/diarrhoeal-disease