A study of Antibiotics and Neem-Chirata Extracts in clinical trials of *Salmonella typhi*

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Abstract - The purpose of this study is to provide light on the possible benefits that Neem and Chirata may have over conventional antibiotics on the market. Investigations into the length of therapy and dose selection, as well as detailed examinations of safety profiles, will be used to attain this goal. As part of the therapeutic care of Salmonella typhi infections, an investigation of the efficacy of a number of medicinal and botanical extracts, including Neem and Chirata, is described. An in-depth investigation of the efficacy and safety of a number of different drugs, with a specific emphasis on how they affect S. typhi, is the purpose of this study. After it has been carried out, mechanistic study will assist in shedding light on the particular antibacterial processes that these drugs utilize. The abstract provides a concise summary of the aims of the study, which include evaluating the overall outcomes of clinical trials, comparing these interventions to standard treatments, investigating the synergistic benefits of combination therapy, monitoring the growth of antibiotic resistance, and evaluating the efficacy of combination therapy. And last, the abstract provides a concise analysis of the objectives of the clinical research as well as the possible future contributions that these investigations might make to the treatment of infectious diseases. This is accomplished by providing a synopsis of all the significant and substantial aspects of the clinical trials that are being taken into consideration.

Keywords - Clinical trials, Antibiotics, Neem, Chirata, Salmonella typhi.

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INTRODUCTION

Research has demonstrated that herbal treatments are effective in alleviating the symptoms of several illnesses. Medical technology has come a long way in the previous several decades, yet plants play a crucial role in patient treatment even now. Medicinal plants have piqued the interest of many due to its possible preventative properties and lengthy history of use in traditional medicine, particularly in more economically developed nations. Antioxidants found in nature or in their raw extracts have chemicals that fight oxidative stress. Many people continue to think that natural remedies derived from plants are preferable to synthetic ones (Adebolu et al., 2011). Consistent evaluation of medicinal plants' susceptibility patterns is necessary for the development of suitable treatment protocols. Consistently evaluating the susceptibility pattern is key to creating effective treatment protocols. The movement of illnesses from one environment to another can be influenced by a myriad of factors, including humans and other animals. The development of microbial typing systems was a logical process for researchers. Microorganisms can be classified using a variety of methods, including antibiotic susceptibility pattern typing, bacteriocin typing, biotyping, and serotyping (Akujobi et al., 2006).

Combination Therapies Using Antibiotics and Plant Extracts

In the search to discover plants with antibacterial properties, researchers are concentrating on screening approaches. The broad use of antibiotics for the treatment of ailments throughout human history was one of the causes that led to their development. Typhoid fever is a systemic virus that may be transmitted from person to person in the community. Even in nations with a reputation for relative poverty, it poses a threat to public health (Bhan et al., 2005). The greatest prevalence of typhoid and paratyphoid fever was observed among infants and toddlers, according to a review of the literature on the subject. For both fever kinds, this was true. In humans, the estimated incidence of S. typhi was 7% and S. paratyphi was 0.9% in cases of laboratory-confirmed enteric fever. A. A multimodal strategy is required to ascertain the efficacy of antibiotics against *S. typhi* (Bharti et al., 2013).

A thorough comprehension of these factors is crucial for improving therapy efficacy and ensuring patients get the best possible results. For the treatment of both acute and chronic diseases, humans have long relied on herbal remedies. Herbal treatments presently rule the market since synthetic pharmaceuticals pose risks whereas plant-based therapies provide various advantages, including efficacy, safety, and future use (Bhutta, 2006).

Antibiotics used to treat *S. typhi*

Antibiotics can be defined in a more general sense as any chemical, whether it is generated intentionally or occurs naturally, that possesses antibacterial properties. Certain biological processes are disrupted by antibiotics, which are used to prevent the proliferation of bacteria and other organisms. The creation of proteins, DNA/RNA, and the cell wall of bacteria are all examples of these processes. Antibiotics are secondary metabolites that are produced by bacteria once they have reached the end of their exponential growth cycle (Chanda and Rakholiya 2018). In the process of an organism's development, secondary metabolites are not required in any way. Their many functions include defence, ecological interactions, the sequestration of nutrients, the transportation of metals, and the differentiation of cells, to name just a few. They are big molecules that are frequently strain-specific and have a manufacturing mechanism that is somewhat complicated. Antibiotics may have evolutionary applications that go beyond just preventing competitive interactions, according to the findings of this study (Chau et al., 2007).

Insects and bacteria have developed resistance to antibiotics; however it is possible that these plants contain biochemicals that make medications more effective. It is worthwhile to do research on these chemicals because they have the potential to operate as agents that modify, modulate, or even reverse resistance (Crump et al., 2007). Chloramphenicol, cephalosporins, ciprofloxin, cefetoxime, and gentamicin are the four antibiotics that are capable of treating all three of the test pathogens. Cefetoxime is effective against all three strains of S. bacteria, although streptomycin is only effective against *S. paratyphi*. Ampicillin is only effective against *S. typhimurium*. An investigation that compared six different plants and antibiotics discovered that *Anacardium occidentale, Lawsonia inermis,* and *Acacia nilotica* all have antibacterial properties that were far more potent than those of Streptomycin equivalent to ampicillin, the effectiveness of these extracts against S. typhi is equivalent to that of ampicillin. For the purpose of determining whether or not antibacterial compounds were present in plant extracts, this study utilised diffusion techniques as a qualitative approach (Dolecek et al., 2008).

LITERATURE REVIEW

Fodouop et al. (2017) made the discovery of a cyanobacterium known as Fischerella sp., which, after being isolated from the bark of the Neem tree, demonstrated antibacterial capabilities. The active ingredient in a methanolic extract of the cyanobacterium Fischerella sp., which was derived from neem tree bark and cultured in a controlled environment, demonstrated activity against various bacteria in vitro, including Mycobacterium tuberculosis, Enterobacteria erogenes, Staphylococcus ureus, Pseudomonas aeruginosa, S. typhi, E. coli, and three strains of multi-drug-resistant E. coli. In order to determine the level of antibacterial activity, we utilised a modified version of the Kirby Bauer Disc Diffusion Susceptibility Method.

Gutiérrez-Alcántara et al. (2016) conducted the most common way that typhoid fever is transmitted is through the oral route of faeces contamination. This is a regular occurrence for a person who is a carrier of S. typhi but does not exhibit any symptoms after recovering from an infection, to contaminate food or water by direct contact with food, the transfer of germs by flies and other insects, or the pollution of water. Around ten percent of persons who recover from typhoid fever continue to transmit the bacterium on to their faeces for a period of three months. In the past, between two and three percent of those individuals continued to be chronic carriers of the germs.

Hannan et al. (2013) discovered that the chemical component of Swertia chirata known as 1, 5-dihydroxy-3, 8-dimethoxyxanthone has the ability to reduce inflammation in rats. When administered orally at a dose of 50 mg/kg, the chemical was able to diminish pedal edoema caused by carrageenin by 57% and caused by formalin by 58%. The chemical was able to lower the volume of exudate by 35% in turpentine-oil-induced granuloma formation when compared to the control group, which was given diclofenac.

Johny et al. (2010) found that aminoglycosides, such as streptomycin, are effective because they inhibit the body's ability to produce new proteins. When it reaches 30S ribosomes, it forms an attachment to formyl methionyl tRNA, which it then misreads in order to stop the proliferation of bacteria. strA and strB are the strains of S. typhimurium that are resistant to the antibiotic streptomycin. The primary mechanism of action of tetracycline is similar to that of streptomycin, which is to block the production of proteins. Through its interaction with the 30S subunit of ribosomes, tetracycline is able to block aminoacyl tRNA from attaching to the A site of ribosomes. There are two genes that are responsible for tetracycline resistance: tetA and tetB. In contrast to tetA, which is found on plasmids, tetB is found on chromosomes instead.

Kalia et al. (2016) that certain relatives of the Enterobactericeae family share genes that are responsible for the production of lactamase enzymes. The bacterial species Kluyvera has enzymes of the TEM, SHV, and CTX-M kinds. These enzymes are capable of hydrolyzing ceftriaxone and cefotaxime, however they are ineffective against ceftazidime. According to the most recent evidence, there were about 300 different strains of ESBL. The sequences of their amino acids made it possible to categorise them into nine different structural groupings. For the sake of epidemiological research, finding out more about TEM and SHV in ESBL isolates will be beneficial. The TEM and SHV genes are the origin of the ESBL genes that are discovered in Salmonella. It is possible to find the genes that give bla CTX-M resistance to Salmonella on either chromosomes or plasmids. In order to classify the bla CTX-M variations, seven distinct groups were constructed on the basis of the modifications made to the sequence of amino acids. In accordance with the findings of phylogenetic study, Bla CTX-M did not originate from mutant Kluyvera species but rather through the process of chromosomal transfer. Through the use of an insertion sequence known as ISEcp1, which may be found in bla CTXM, some bacteria are able to inherit resistance genes from Salmonella.

Li et al. (2005), the treatment of enteric fever may be accomplished by the use of macrolides such as erythromycin, fluoroquinolones such as ciprofloxacin, ofloxacin, and perfloxacin, and tetracyclines. Since the year 1947, when it was first discovered, chloramphenicol has been the medication of choice for treating typhoid fever. For the reason that *S. typhi* bacteria are fast becoming resistant to chloramphenicol, which is a medicine that is frequently used to treat pneumonia, there is an urgent need for new antibiotics that are both naturally active and have robust in vivo action against *S. typhi*.

RESEARCH METHODOLOGY

Plant material (Neem and Chirata)

The sample plan involves procuring specimens from nearby nurseries and marketplaces located in Sidhi. The leaves were harvested between June and July. (Because leaves that are very delicate and old have minimal principles that are bioactive) (Irshad et al., 2011). Each leaf was carefully removed off the twig after being gently cleaned with tap water. To remove extra water that had stuck to the newspaper while washing, they were equally spread out over it. After that, the leaves were stored for a week or ten days in a diffused light environment. Next, using a mortar and pestle, the completely dried leaves were gathered and ground into powder. By passing the ground-up leaf material through a sieve, a fine powder was produced (Parekh and Chanda 2006).

Sample collection

To conduct a thorough investigation on the effectiveness of Neem and Chirata in treating *Salmonella typhi* infections, carefully gathered dried plant samples will be gathered from various sources. The sample plan involves procuring specimens from nearby nurseries and marketplaces located in Sidhi. This allows for the inclusion of grown types that are easily accessible in urban and semi-urban environments. This strategy makes sure that the plants are represented that are typically available to the community, which may reflect the ways in which the plants are used there (Ochai and Kolhatkar 2008).

Study design and participants

A thorough examination of the medicinal effectiveness of antibiotics and plant extracts against infections caused by *Salmonella typhi* requires the application of a strong clinical trial design. In order to do this, a multiarm, parallel, open-label comparative study is planned that will focus on adult patients who are 60 years of age or older. The trial will take place in the District Hospital in Sidhi, an important medical facility that functions as a stand-alone government building in the Indian state of Madhya Pradesh. Sidhi's District Hospital plays a vital role in the healthcare system, especially considering that it serves a primarily rural populace from the nearby villages. Given the variety of health profiles and possible complications, this demographic diversity adds another level of difficulty to the study (Akujobi et al., 2006).

Data collection

A thorough collection of demographic data will be carried out in order to obtain a full insight of the patient cohort taking part in the clinical research. A thorough evaluation of important variables including age, gender, employment, and housing location is part of this. The main instrument for gathering data for this study will be a structured questionnaire that will delve into presenting symptoms and medical history in addition to basic demographic information. Examining these facets will help the research identify any underlying tendencies or environmental elements that might affect how the therapies are received.

Isolation and identification of *S. Typhi* from clinical specimens

Standard procedures will be utilized in order to isolate the Salmonella species that will serve as test pathogens for this investigation. According to Harley and Prescott (2002), the identity of the isolates will be verified by the use of morphological features and routine biochemical testing. According to Li et al. (2005), pure cultures were maintained at a temperature of 4 degrees Celsius on nutritional agar and Mac Conkeys agar slants.

Preparation of plant extracts

The screening program made use of two different types of extracts: methanolic and aqueous. To make the extracts, the plant material was stirred with a seven-fold solution of water and methanol overnight at room temperature. The suspension was cold-centrifuged for 15 to 20 minutes at 3000 rpm, and the supernatant was separated (Dolecek et al., 2008).

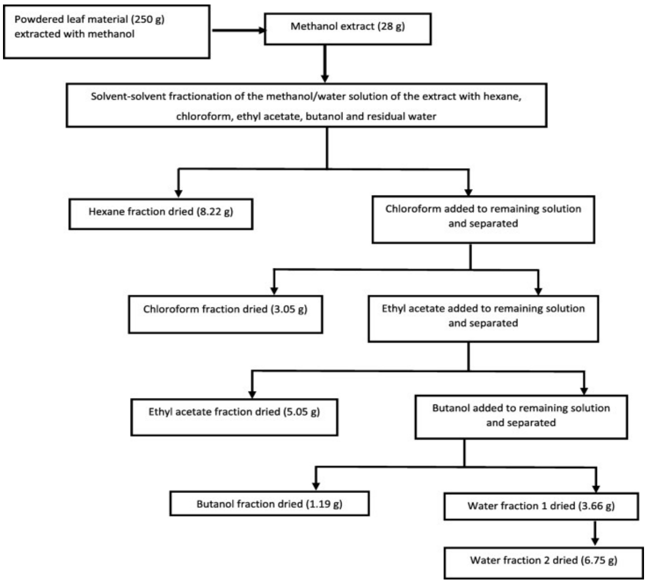


Figure 1: Extracted chemicals and plant extracts in vitro against *Salmonella typhi*

(Source: Dorcas et al., 2021)

Determination of antimicrobial activity

The conventional disc diffusion technique was applied. The bacteria were cultivated at 37°C for four hours in every experiment, and the turbidity of the culture was adjusted to meet McFarland standard No. 0.5 (National Committee of Clinical Laboratory Standards, 1993). This suspension was spread out in 100 pL on the nutrient agar test plate (Gutiérrez-Alcántara et al., 2016). The test plate was covered with sterile discs (6 mm in diameter) from Hi Media, Pvt. Ltd. in Bombay, India, which had been impregnated with 20 pL of the plant extract (methanol and aqueous).

Determination of minimum inhibitory concentration (MIC)

A microdilution broth was utilized in order to ascertain the MIC percentage. When making a stock solution of the methanolic plant extract, Mueller Hinton I was the instrument that was utilized. Furthermore, during repeated double dilutions, a range of 25.6 mg/mL was utilized as the concentration range. A microtiter aliquot of bacterial suspension of 0.5 McFarland standard was added to the wells of a microtiter aliquot of each dilution, along with Mueller Hinton broth (both positive and negative controls) (Mandal et al., 2010). The aliquots were each hundred microliters in volume.

Analysis of phytoconstituents in the plant extracts

The phytoconstituents found in the plant extracts that had notable antibacterial action were examined. Plant methanol extracts were treated to a battery of biochemical assays and High performance liquid chromatography (HPLC) in order to identify the distinct phytoconstituents (Friedman, 2015). Two extracts that demonstrated exceptional antibacterial activity were chosen for in-depth phytoconstituent investigation using liquid chromatography mass spectrometry (LC MS) (Sultana et al., 2021).

Antibacterial activity

In order to test the antibacterial activity of the aqueous extracts, the cup diffusion method will be applied on nutrient agar medium (Anon 1996). Inoculums containing 106 colony-forming units per milliliter of bacterial suspension will be disseminated on the solid plates using a sterile swab that has been dampened with the bacterial suspension (Vasantharaj et al., 2013).

Evaluation of anti-Salmonella activity

The antibacterial activity of the extract was evaluated by the use of the agar diffusion experiment (Reeves, 1989). Following an incubation period of four hours at 37 degrees Celsius in Mueller Hinton broth (MHB) with shaking conditions, 0.1 milliliters of the test organism inoculum was evenly distributed on Mueller Hinton Agar (MHA) plates using a glass spreader that had been sterilized. After the seeded plates had been allowed to dry in the incubator at 37 degrees Celsius, a sterile cork borer measuring 6 millimeters was used to produce wells in the infected MHA plate. Two hundred microliters of the extracts, which had been re-suspended in the appropriate solvents, as well as negative controls with a ratio of one solvent to one water, were introduced to the wells. The stock extracts had a concentration of 200 milligrams per milliliter. The plates that were infected were kept in an incubator at 37 degrees Celsius for a period of twenty-four hours (Noel et al., 2022).

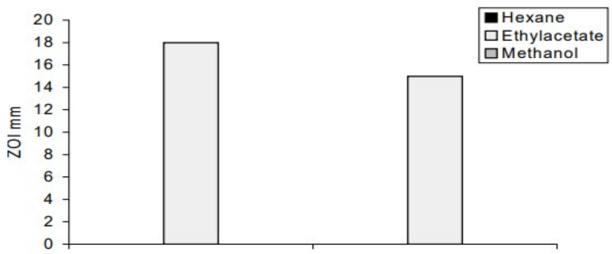
RESULTS

Spectrophotometric analysis of phytochemicals

The spectrophotometric (FTIR) examination indicated the presence of ketones, phenolic compounds, carboxylic acids, aromatic compounds, amides, proteins, aldehydes, and aliphatic compounds. All of these chemicals are applied in a number of therapies as a means of combating S. typhi. The bark extracts from Azadirachta indica were subjected to spectrophotometric and qualitative phytochemical analysis, which revealed the presence of flavonoids, glycosides, tannins, alkaloids, and phenolic compounds, in addition to saponins. These bioactive components were derived from the phytochemical screening that was performed on the bark (Alzohairy et al., 2016).

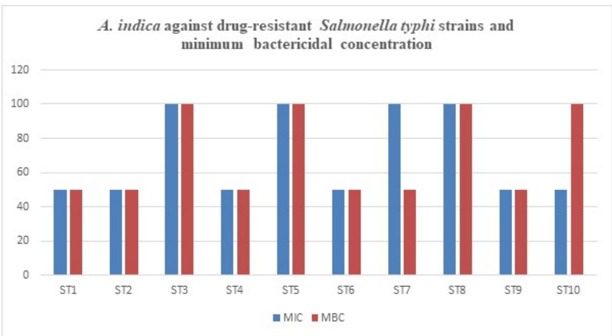
Antimicrobial efficacy of plant extracts and antibiotics against *Salmonella typhi*

In the instance of S. typhi, the leafy sections of plant extracts shown a greater capacity to suppress bacterial growth, with zones of inhibition measuring 8 mm and 10.5 mm respectively. A study was conducted, and the results showed that the plant extracts had the highest zones of inhibition against *S. typhi.* Study conducted in a variety of other areas of antibacterial study has shown that A. indica is effective against a number of key human infections. In general, a significant amount of research has been written about this topic over the course of the previous 10 years, particularly in relation to the growing number of organisms that are resistant to certain antibiotics. As a similar point of interest, the vast list of threats that are resistant to antibiotics may contain a number of bacterial species that are responsible for wound infections (Olasupo et al., 2003).



A. indica ***Swertia chirata***

Figure 2: ZOI exhibited by different plant extract against *Salmonella typhi*



Antimicrobial Resistance Mechanisms of *Salmonella Typhi*

The resistances to trimethoprim, ampicillin, chloramphenicol, tetracycline, sulfamethoxazole, and streptomycin in *S. Typhi* isolates were mediated by the genes that correspond to these include blaTEM-1, catA1, tetA/tetB, sul1 and/or sul2, dfrA7/dfrA15, and strA-strB/aadA1. Twenty-three MDR strains had the tetB gene, while four non-MDR strains had the tetA gene. Every MDR strain has both sul1 and sul2 genes for resistance to sulfonamide, while the non-MDR bacteria only had sul1 genes. With the exception of isolates with the AMPR-STRR-NALR-DCS profile, every MDR and non-MDR isolate possessed the class 1 integron with the characteristic 3'-CS of the qacEΔ1 and sul1 genes. Except for the isolates, sequencing of the 750 bp gene cassettes of class 1 integrons revealed the existence of the trimethoprim-resistant dfrA7 gene (Indu et al., 2006).

Due to the presence of a wide variety of phytochemicals, the crude extracts of these plants, at varying quantities, have the potential to be utilized for medicinal reasons as powerful antioxidants and antimicrobials. These particular medicines and plant extracts have a significant amount of promise as antimicrobial agents against bacteria, and they have the potential to be utilized in the treatment of infectious disorders that are brought on by pathogens that are resistant to therapy. It is possible that some medicines and plant material will have greater efficacy against bacterial strains than the other extracts if they are selected specifically. In the current status of Ayurveda, traditional medicine, and Geographical Indications (GI) of the Vindhya eco-region, the data of the proposed research work will be added more.

CONCLUSIONS

In conclusion, the entire review of clinical research that explored the efficacy of antibiotics and plant extracts, especially Neem and Chirata, against *S. Typhi* reveals promising insights into possible therapeutic options. Neem and Chirata were especially targeted for their effectiveness against *S. Typhi.* Underscoring the multimodal character of the battle against *S. typhi* infections is the vast diversity of studies that was investigated. The continuous use of antibiotics in clinical practice is backed by the fact that they have regularly proven efficacy. Additionally, the use of plant extracts, in particular those produced from Neem and Chirata, demonstrates a promising field for the development of alternative and complementary treatment. It is clear that these plant extracts have the potential to be employed as adjunct medications due to the antibacterial activity that have been found in them, which are validated by evidence from rigorous clinical trials. While antibiotics continue to play an essential role in the treatment of bacterial infections, the inclusion of compounds derived from plants adds to the development of a more holistic approach to therapy. The development of innovative therapy techniques to treat *S. typhi* infections may be helped by additional study and investigation of the synergistic effects that occur between antibiotics and plant extracts. For the objective of establishing treatment methods that are both more successful and more sustainable, this study underscores the significance of continual research, cooperation, and awareness of the connection between traditional medicine and current medicine.

REFERENCES

1. Adebolu, T. T., Adeoye, O. O., & Oyetayo, V. O. (2011). Effect of garlic (Allium sativum) on Salmonella typhi infection, gastrointestinal flora and hematological parameters of albino rats. *African journal of biotechnology*, *10*(35), 6804-6808.
2. Akujobi, C. O., Ogbulie, J. N., & Uchegbu, U. N. (2006). Antibacterial activities and preliminary phytochemical screening of Vernonia amygdalina and Citrus aurantifolia. Nig. *J. Microbiol*, *20*(1), 649-654.
3. Behera, B., & Mathur, P. (2011). High levels of antimicrobial resistance at a tertiary trauma care centre of India. *The Indian Journal of Medical Research*, *133*(3), 343.
4. Bhan, M. K., Bahl, R., & Bhatnagar, S. (2005). Typhoid and paratyphoid fever. *The Lancet*, *366*(9487), 749-762.
5. Bharti, V., Vasudeva, N., Sharma, S., & Duhan, J. S. (2013). Antibacterial activities of Origanum vulgare alone and in combination with different antimicrobials against clinical isolates of Salmonella typhi. *Ancient science of life*, *32*(4), 212.
6. Bhutta, Z. A. (2006). Current concepts in the diagnosis and treatment of typhoid fever. *Bmj*, *333*(7558), 78-82.
7. Chanda, S., & Rakholiya, K. (2011). Combination therapy: Synergism between natural plant extracts and antibiotics against infectious diseases. *Microbiol Book Series*, *1*, 520-529.
8. Chau, T. T., Campbell, J. I., Galindo, C. M., Van Minh Hoang, N., Diep, T. S., Nga, T. T. T., ... & Dolecek, C. (2007). Antimicrobial drug resistance of Salmonella enterica serovar Typhi in Asia and molecular mechanism of reduced susceptibility to the fluoroquinolones. *Antimicrobial agents and chemotherapy*, *51*(12), 4315-4323.
9. Crump, J. A., Luby, S. P., & Mintz, E. D. (2004). The global burden of typhoid fever. *Bulletin of the World Health Organization*, *82*(5), 346-353.
10. Dolecek, C., Phi La, T. T., Rang, N. N., Phuong, L. T., Vinh, H., Tuan, P. Q., ... & Farrar, J. (2008). A multi-center randomised controlled trial of gatifloxacin versus azithromycin for the treatment of uncomplicated typhoid fever in children and adults in Vietnam. *PLoS One*, *3*(5), e2188.
11. Fodouop, S. P. C., Tala, S. D., Keilah, L. P., Kodjio, N., Yemele, M. D., kamdje Nwabo, A. H., ... & Gatsing, D. (2017). Effects of Vitellaria paradoxa (CF Gaertn.) aqueous leaf extract administration on Salmonella typhimurium-infected rats. *BMC complementary and alternative medicine*, *17*, 1-11.
12. Gutiérrez-Alcántara, E. J., Rangel-Vargas, E., Gómez-Aldapa, C. A., Falfan-Cortes, R. N., Rodríguez-Marín, M. L., Godínez-Oviedo, A., ... & Castro-Rosas, J. (2016). Antibacterial effect of roselle extracts (Hibiscus sabadariffa), sodium hypochlorite and acetic acid against multidrug-resistant Salmonella strains isolated from tomatoes. *Letters in applied microbiology*, *62*(2), 177-184.
13. Hannan, A., Asghar, S., Naeem, T., Ullah, M. I., Ahmed, I., Aneela, S., & Hussain, S. (2013). Antibacterial effect of mango (Mangifera indica Linn.) leaf extract against antibiotic sensitive and multi-drug resistant Salmonella typhi. *Pak J Pharm Sci*, *26*(4), 715-719.
14. Johny, A. K., Hoagland, T., & Venkitanarayanan, K. (2010). Effect of subinhibitory concentrations of plant-derived molecules in increasing the sensitivity of multidrug-resistant Salmonella enterica serovar Typhimurium DT104 to antibiotics. *Foodborne Pathogens and Disease*, *7*(10), 1165-1170.
15. Kalia, P., Kumar, N. R., & Harjai, K. (2016). Studies on the therapeutic effect of propolis along with standard antibacterial drug in Salmonella enterica serovar Typhimurium infected BALB/c mice. *BMC complementary and alternative medicine*, *16*, 1-15.
16. Li, Y., Xu, C., Zhang, Q., Liu, J. Y., & Tan, R. X. (2005). In vitro anti-Helicobacter pylori action of 30 Chinese herbal medicines used to treat ulcer diseases. *Journal of ethnopharmacology*, *98*(3), 329-333.
17. Mandal, S., DebMandal, M., Pal, N. K., & Saha, K. (2010). Antibacterial activity of honey against clinical isolates of Escherichia coli, Pseudomonas aeruginosa and Salmonella enterica serovar Typhi. *Asian Pacific Journal of Tropical Medicine*, *3*(12), 961-964.
18. Maskey, A. P., Day, J. N., Tuan, P. Q., Thwaites, G. E., Campbell, J. I., Zimmerman, M., ... & Basnyat, B. (2006). Salmonella enterica serovar Paratyphi A and S. enterica serovar Typhi cause indistinguishable clinical syndromes in Kathmandu, Nepal. *Clinical infectious diseases*, *42*(9), 1247-1253.
19. Mbatchou, V. C., Ayebila, A. J., & Apea, O. B. (2011). Salmonella typhi. *Journal of Animal & Plant Sciences*, *10*(1), 1248-1258.
20. McMurray, R. L., Ball, M. E. E., Tunney, M. M., Corcionivoschi, N., & Situ, C. (2020). Antibacterial activity of four plant extracts extracted from traditional Chinese medicinal plants against Listeria monocytogenes, Escherichia coli, and Salmonella enterica subsp. enterica serovar Enteritidis. *Microorganisms*, *8*(6), 962.

21. Mehta, J., Rolta, R., & Dev, K. (2022). Role of medicinal plants from North Western Himalayas as an efflux pump inhibitor against MDR AcrAB-TolC Salmonella enterica serovar typhimurium: In vitro and In silico studies. *Journal of Ethnopharmacology*, *282*, 114589.
22. Olowosulu, A. K., & Ibrahim, Y. K. E. (2006). Studies on the antimicrobial screening of aqueous extracts of five plants used in Folk medicine in Nigeria. *West Afr J Boil Sci*, *3*(5), 21-6.
23. Orsi, R. D. O., Sforcin, J. M., Funari, S. R. C., Fernandes Junior, A., & Bankova, V. (2006). Synergistic effect of propolis and antibiotics on the Salmonella typhi. *Brazilian Journal of Microbiology*, *37*, 108-112.
24. Pandit, A., Arjyal, A., Day, J. N., Paudyal, B., Dangol, S., Zimmerman, M. D., ... & Basnyat, B. (2007). An open randomized comparison of gatifloxacin versus cefixime for the treatment of uncomplicated enteric fever. *PLoS One*, *2*(6), e542.
25. Parry, C. M., Ho, V. A., Phuong, L. T., Bay, P. V. B., Lanh, M. N., Tung, L. T., ... & Farrar, J. J. (2007). Randomized controlled comparison of ofloxacin, azithromycin, and an ofloxacin-azithromycin combination for treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever. *Antimicrobial agents and chemotherapy*, *51*(3), 819-825.
26. Sadiq, M. B., Tarning, J., Aye Cho, T. Z., & Anal, A. K. (2017). Antibacterial activities and possible modes of action of Acacia nilotica (L.) Del. against multidrug-resistant Escherichia coli and Salmonella. *Molecules*, *22*(1), 47.

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