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Exploring the Efficacy of Antibiotics and Plant Extracts (Neem & Chirata) in Clinical Trials against *Salmonella Typhi*: A Review

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Abstract- This research aims to provide insight into the potential advantages of Neem and Chirata over traditional antibiotics. This will be accomplished by comprehensive evaluations of safety profiles, investigations into therapy duration, and dose selection. An analysis of the effectiveness of several medicinal and botanical extracts, including Neem and Chirata, in the therapeutic management of Salmonella typhi infections. This study aims to meticulously examine the safety and effectiveness of various medications with a particular focus on their impact on S. typhi. Once performed, mechanistic research will provide light on the specific antimicrobial mechanisms that these medications employ. The abstract summarizes the study's objectives, which include comparing these interventions to standard treatments, looking into the synergistic effects of combination therapy, tracking the rise of antibiotic resistance, and assessing the overall outcomes of clinical trials. Lastly, the abstract gives a brief study of the goals of the clinical studies and their potential future contributions to infectious illness treatment. This is achieved by summarizing all the important and numerous facets of the clinical trials that is being considered.

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

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INTRODUCTION

Studies have shown that herbal remedies can successfully treat illness symptoms. In spite of the fact that modern medicine has advanced significantly over the last few decades, plants are still essential to patient care. Many individuals have been curious about medicinal plants because of their long history of usage in traditional medicine and their potential for prevention, especially in more economically developed nations. Natural antioxidants or raw extracts contain chemical components that can effectively counteract oxidative stress. It's still a common belief that medications made from plants are safer than those made from synthetic materials (Vongtau et al., 2005). The susceptibility pattern of therapeutic plants needs regular assessment in order to develop appropriate treatment guidelines. In order to develop appropriate treatment guidelines, it is necessary to regularly assess the susceptibility pattern. Since people and animals are among the numerous elements that might affect the spread of diseases from one habitat to another, researchers logically developed microbial typing systems. Antibiotic susceptibility pattern typing, bacteriocin typing, biotyping, and serotyping are common techniques for typing microorganisms (Doublet et al., 2003). Herbal medicine has a longer and uninterrupted history of usage in impoverished nations since medicinal plants have been an essential component of healthcare systems there since ancient times. Novel treatment techniques should target medicinal plants since they generate a wide variety of secondary metabolites, some of which have shown therapeutic promise. The discovery of new chemotherapeutic chemicals may hinge on these mostly unexplored resources. At the present time, there is no way to get *Salmonella* strains that have been identified in typhoid patients. Because antibiotics are becoming less effective and new ones are hard to come by, the goal of this study was to look into the link between metal-induced antibiotic resistance and *S. enterica serovar typhi* (Chopra and Roberts, 2001).

Antibiotics for the treatment of *S. Typhi*

In a broader sense, an antibiotic is any substance, naturally occurring or artificially produced, that has antimicrobial characteristics. To stop bacteria and other microbes from multiplying, antibiotics disrupt specific biological processes. Among these processes are the synthesis of proteins, DNA/RNA,

and the bacterial cell wall. Bacteria produce antibiotics as secondary metabolites after reaching the end of their exponential growth cycle (Muaz et al., 2018). There is no need for secondary metabolites in an organism's development. Defense, ecological interactions, nutrition sequestration, metal transport, and cellular differentiation are just a few of their various roles. They are large molecules that are often strain-specific and have a convoluted production pathway. This study's results suggest that antibiotics may have evolutionary uses beyond just stopping competitive interactions (Chokshi et al., 2019). Insects and bacteria have evolved resistance to antibiotics, yet these plants may contain biochemicals that make drugs more effective. Potentially acting as agents that alter, modulate, or even reverse resistance, these compounds are worth investigating. Screening plant extracts for direct antibacterial compounds is the only approach that has been used in the past; however, there may be ways to improve antibiotic efficacy by looking at natural resource-derived molecules that change resistance. Because they allow for the recycling of cheaper, older antibiotics that have become ineffective due to resistance, these compounds must be more attractive and effective. Several studies have proposed that novel ways to treat bacterial infections should include mixing antibiotics with compounds derived from plants due to their potential synergistic effects (Antunes et al., 2016).

There are four antibiotics that can treat all three test pathogens: chloramphenicol, cephalosporins, ciprofloxin, cefetoxime, and gentamicin. Streptomycin only works against *S. paratyphi* A, ampicillin only works against *S. typhimurium,* and cefetoxime works against all three. A study comparing six plants and antibiotics found that *Anacardium occidentale, Lawsonia inermis*, and *Acacia nilotica* all had much stronger antibacterial effects than Streptomycin. The anti-S. *typhi* efficacy of these extracts is comparable to that of ampicillin. As a qualitative approach, this study used diffusion methods to determine the presence or absence of antibacterial chemicals in plant extracts (Alikwe et al., 2013). The dilution processes used to establish the least inhibitory concentration are nevertheless considered quantitative tests, nevertheless. Some research has connected hydrogen peroxide, free radicals, and reactive oxygen species (ROS) to cancer and age-related diseases such as arthritis, atherosclerosis, and neurological disorders. Antioxidants found in food and drink have an important role in chemoprevention, making their identification and characterization a top priority (Cadmus et al., 2010).

The discovery of a new antibiotic, though, reduced the chances of finding a new chemical. This method yielded several antibiotics, including the broad-spectrum phosphonate fosfomycin, cephamycin C, thienamycin, and various carbapenems. Fujisawa, a Japanese company, discovered the first monobactam molecule, nocardicin, while screening a mutant strain of *E. coli* that was highly susceptible to beta-lactams (Mehdi et al., 2018). Globally, the development and dissemination of drug-resistant microorganisms is a major cause of the problem. Therefore, an effective and safe way to combat microbial resistance to pharmaceuticals may be found in the area of phytomedicines. Even though pharmaceutical companies release a slew of new antibiotic brands every year, the worldwide problem of MDR bacteria is reducing the efficacy of these drugs. A multidrug-resistant strain of *S. typhi* showed no response to first-line antibiotics like ampicillin, chloramphenicol, and trimethioprim-sulfamethoxazole. Because of these problems, scientists are trying to figure out how to use the phytotherapeutic characteristics of medicinal plants like neem *(Azadirachta indica)* instead of the more expensive and dangerous conventional antibiotics (Bowdish et al., 2005). The selective expansion of organisms brought about by the extensive antibiotic insult and the adaptive capabilities of microorganisms led to the emergence of both the terms "antibiotic resistance" and "multidrug resistance (MDR)". As a result, the availability of antibiotics is increasingly limited in treating illnesses caused by bacteria that are resistant to multiple medications (Singh and Prasad, 2014).

Antibiotic-Plant Extract Combination Therapies

Researchers are focusing their attention on screening methods in order to identify plants that have the potential to inhibit the growth of bacteria. One of the factors that contributed to the development of antibiotics was the widespread application of antibiotics for the treatment of illnesses over the course of human history. Members of the community can transmit typhoid fever, which is a systemic virus. It continues to be a problem for public health, particularly in countries that are considered to be poor (Das et al., 2014). A higher frequency of this can be seen in places that are overcrowded, unclean, lacking in resources, and not provided with enough access to sanitation. The fact that the sickness is more prevalent among youngsters, despite the fact that it may affect persons of any age, is evidence that the viruses are being aggressively spread across the population in India. A meta-analysis on the burden of typhoid and paratyphoid fever found that the highest incidence was recorded among young children. This was the case for both types of fever. For *S. typhi*, the estimated prevalence of laboratory-confirmed enteric fever among individuals was 7%, while for *S. paratyphi*, the prevalence averaged 0.9%. A. In order to determine whether or not antibiotics are effective against *S. typhi*, it is necessary to employ a multimodal approach (Chanda and Dave, 2007).

In order to ensure that patients receive the best possible outcomes and to enhance the efficacy of treatment methods, it is essential to have a full understanding of these components. Since the dawn of time, people have depended on plant medicines for the treatment of infectious illnesses and chronic conditions. Due to the dangers associated with synthetic medications and the numerous benefits of plant-based therapy, such as

effectiveness, safety, and potential for future use, herbal remedies currently dominate the industry (Zengin et al., 2011).

Complementary and alternative medicine (CAM) dermatologists use a broader set of knowledge that includes both traditional dermatological procedures and CAM methods in addition to modern scientific findings to help with diagnosis and treatment. CAM's holistic approach is believed to improve dermatological care (Gianfaldoni et al., 2018). *S. typhi* has been identified as a high-priority pathogen by the World Health Organization (WHO), which indicates that there is an immediate need for novel approaches to treatment choices. According to the World Health Organization (WHO), over eighty percent of the world's population makes use of traditional healing methods that use plants. Estimates suggest that traditional remedies all over the world utilize between 40,000 and 70,000 different kinds of medicinal plants (Khan and Salah, 2018).

Neem and Chirata Plant Extracts for the Treatment of *S. Typhi*

It has become a naturalized plant in the majority of tropical or subtropical countries. India was the country of origin for it. Neem is widely dispersed over the entire planet and offers a wealth of medicinal benefits. The chemical components of neem contain a wide range of physiologically active substances. Some examples of these chemicals include alkaloids, flavonoids, triterpenoids, phenolic compounds, carotenoids, steroids, and ketones. Among the seven isomeric molecules (named A–G) that comprise the complex, azadirachtin E is the one that exhibits the highest level of physiological activity at the present time. It has medicinal use in the treatment and prevention of ailments. However, there is a lack of complete comprehension of the precise molecular process involved in the prevention of pathogenesis (Tetali et al., 2009). Meliantriol and volatile oils are two examples of additional compounds that have the ability to exert a biological effect, in addition to salannin and nimbin. Research has already documented and published that the substance is becoming more advanced due to its absence of harmful effects and increasing safety. Currently, people worldwide are using phytomedicines, which are cures derived from plants or their components. Phytomedicines have a long history of use in medicine, and their popularity continues to this day. People from all over the world have utilized herbal remedies for thousands of years due to their medicinal capabilities. Due to the fact that it is easily accessible, inexpensive, and does not cause any ill effects or toxicity, herbal medicine has garnered an enormous amount of popularity (Ejaz et al., 2023).

Neem is revered in India as a "village dispensary" or a tree with the ability to tackle global issues. Seeds of neem have yielded more than 135 distinct compounds due to the plant's incredible structural and chemical diversity. Isoprenoids are a group of molecules that includes limonoids, azadirone, gedunin, compounds of the vilasinin type, and C-secomeliacins like nimbin, salanin, and an azadirachtin, among others. They contain protomeliacin. Nonisoprenoids are in the second group, which also includes proteins, amino acids, carbohydrates, sulfur compounds, polyphenolics (such as flavonoids and their glycosides), dihydrochalcone, coumarin, tannins, aliphatic chemicals, and many more. There is a perennial plant known as *A. indica* that is extremely valuable and grows throughout the entire year over the Indian subcontinent (Arnison et al., 2013). Aromatic ginseng has a long and storied history of use in traditional Indian medicine, dating back thousands of years. The neem tree is a rich source of medicinal compounds that can alleviate a wide range of symptoms and illnesses. These compounds include oil, bark extracts, and leaves, among many others. *Azadirachta indica*, a tree belonging to the Meliaceae family, is an exemplary multi-use tree. The bark of *A. indica* has long been used in traditional medicine due to its medicinal characteristics. This method has been used for a long period. In addition, the stem bark aqueous extract served as a stimulant and tonic, effectively treating various skin problems. Since there are no negative effects associated with using this natural component, it is a multipurpose product with a wide range of uses (Karmakar et al., 2011).

The Effectiveness of Antibiotics: Findings from Clinical Studies

The plant's high concentration of antioxidants and other beneficial active compounds leads many to believe it has therapeutic properties. Some of the components include salannin, quercetin, azadirachtin, nimbolinin, nimbin, nimbidin, and nimbidol. Plant and natural product antioxidant activity, bacterial growth suppression, and genetic pathway regulation all play key roles in disease prevention and therapy. Because of their low cost and lack of side effects, a variety of plants are still the subject of vigorous study into their potential therapeutic function in disease management (Arora et al., 2010). It is well known that allopathy-based medications are not only costly but also harmful to normal tissues and a wide range of biological processes. Most people agree that medicinal plants and other natural resources are the source of many pharmacologically active medications. Other sacred texts, including the Quran and the Bible, also endorse the healing and preventative properties of plants. Ayurveda, Unani, homeopathy, and contemporary medicine all make use of neem components to treat a wide range of infectious, metabolic, and cancer-related illnesses (Andersson and Hughes 2010). Many nations' disease control programs make extensive use of various preparations derived from plants or their components. In 2012, researchers conducted a study on the antimicrobial properties of neem leaf extract. Based on the results, the methanol extract reduced the growth of *Bacillus pumillas*,

Staphylococcus aureus, Pseudomonas aeruginosa, and *Staphylococcus aureus*, in that order. In addition to azadirone and its derivatives, neem leaves contain isoprenoids, terpenoids (including limonoids), and other useful components. Several researchers looked into the plant's medical qualities, including its effects on the central nervous system, cardiovascular system, wound healing, antidiabetic, anti-fertility, and anti-malaria effects. Several investigations have demonstrated that *A. indica* has anti-microbial effects. The seed oil exhibited antibacterial properties against many microbes. It is demonstrated that the oils derived from the leaves, seeds, and bark exhibit an antibacterial effect against certain microorganisms (Jayaprakasan et al., 2014).

An Investigation on Chirata Plant Extracts

Chirata, a flowering herbaceous plant that may grow to a height of three to four feet, is native to the northern hill regions of Bhutan and India. In addition to mentioning this plant, the ancient Vedic text Charaka Samhita lists the many health benefits it gives. In the mouth, it melds flavors of heat, pungentness, and bitterness. In scientific terms, it is known as *Swertia chirata*. The beneficial qualities of chirata are due to its abundance of various components. This plant contains antioxidants, glycosides, and alkaloids, all of which have positive effects on health. An assortment of glycosides and a number of acids (palmitic, stearic, oleic, chiratanin, xanthone, swertiamarin, amarogentin, chiratol, gentiopicrin, swertanone, swerchirin, and a few more) are contained in this compound. Numerous bioactive compounds found in *Swertia* are responsible for its bitter taste. (Bretón et al., 2018). The temperate Himalayas in northern India are home to the vast majority of chirata. Felwort is another name for *Swertia.* Its possible uses include treating a wide range of illnesses, including those involving the liver, as well as inflammation, hypoglycemia, hepatoprotection, infection, wound healing, and related problems. Many different herbal remedies incorporate the herbaceous plant as an ingredient (Dubey et al., 2011).

Chirata is the name of a medicinal herb that originates in the Himalayas. A typical chirata is an erect stem that is two or three feet long. Half of the stem is round in the middle, while the other half is four-angled with a distinct decurrent line at each of the angles. The stems display various shades of brown, purple, orange, and red. The short, simple, tapered, and powerful root is over seven centimeters long. The Chirayita inflorescence is two feet long and consists of a profusion of small, loosely coiled cymes arranged in axillary clusters and spread out along short branches (Eloff, 2019). Despite chirata's amazing effects on lowering blood sugar levels, it's crucial to remember that the sugar level does not go below the target level. This will lead to hypoglycemia, which is dangerous for health. Researchers tested the antioxidant components to determine the antioxidant potential of three distinct plant extracts using the DPPH free radical scavenging method (Ferrazzano et al., 2013). Chiratanin, alkaloids, amarogentin, swertiamarin, xanthones, and other bioactive chemicals are found in chirata preparations. According to figures given by the World Health Organization (WHO), almost 80% of the global population uses traditional remedies that mostly include the intake of plant extracts. While *Swertia* is typically employed as a flavoring element, the bitter taste of *S. chirata* made the same patient throw up (Kar et al., 2013).

Researchers found that when mixed with divi-divi plant seeds, it effectively treated malaria. Sotha, daha, jvara, krmiroga, kandu, kushta, meha, trsna, and vrana are some of the other favorite combinations. There are some surprising health benefits and some bad repercussions for the traditional medicinal plant *S. chirata*, which is in danger of extinction. Due to claims that it is safe for human consumption, people have been exploiting *Swertia* to an unhealthy degree. A need for conservation efforts has arisen because of the species' imminent extinction (Kareru et al., 2010). There are no negative effects when used as directed; nevertheless, side effects include vomiting and nausea, as well as hypoglycemic problems such as disorientation and tingling in the extremities, which can occur with excessive use. Use it as an antipyretic, to cure constipation, gastrointestinal issues, anorexia, intestinal worms, and skin problems; it has many more potential uses. Some people have also used it as a bitter tonic (Kazmi et al., 2015).

CONCLUSION

In conclusion, the complete evaluation of clinical studies that investigated the efficiency of antibiotics and plant extracts, notably Neem and Chirata, against *S. Typhi* gives exciting insights into prospective treatment possibilities. Neem and Chirata were specifically targeted for their effectiveness against *S. Typhi*. Underscoring the multidimensional nature of the fight against *S. typhi* infections is the wide variety of research that was explored. The sustained use of antibiotics in clinical practice is supported by the fact that they have consistently shown effectiveness. Additionally, the use of plant extracts, in particular those derived from neem and chirata, demonstrates a promising area for the development of alternative and complementary care. It is clear that these plant extracts have the potential to be used as adjunct medicines due to the antibacterial activities that have been identified in them, which are backed by data from rigorous clinical trials. While antibiotics continue to play an important role in the treatment of bacterial infections, the incorporation of chemicals derived from plants contributes to the development of a more holistic approach to therapy. The development of novel treatment approaches to treat *S. typhi* infections may be facilitated by more study and investigation of the synergistic effects that occur between antibiotics and plant extracts. For the purpose of developing treatment methods that are both more successful and more sustainable, this study highlights the importance of continual

research, cooperation, and knowledge of the interaction between traditional medicine and contemporary medicine.

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