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Review Article

Search for Natural Remedies for the Treatment of *Salmonella Typhi* Infections

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Abstract

Typhoid is a major public health threat, particularly in areas lacking access to clean water, proper nutrition, and hygienic practices. The emergence of antibiotic resistance, inaccessibility of vaccines to the global south, and asymptomatic carriers of *Salmonella typhi* (*S. typhi*) have made tackling the scourge of typhoid a major challenge. Plant-based antimicrobial compounds have opened a new avenue for effectively managing typhoid by minimizing drug-related side effects and targeting the resistant strains of typhoidal *salmonella* cost-effectively. This review article contains many such candidates, who can potentially modify the typhoid treatment guidelines like *Azadirachta indica, Canarium schweinfurthii*-derived scopoletin, and *Punic granatum,* and those that target the resistant strains of *S. typhi*, like *Amaranthus hybridus,* and *Quercus infectoria and Phyllanthus emblica*. The article will also shed light on the challenges and promises associated with phytocompound extraction and standardization as the researchers navigate the uncharted waters of alternative medicinal sources.

Keywords: Anti-typhoid phytocompound, *Salmonella typhi*, phytoextarcts, AMR-typhoid, typhoid management

1. Introduction

Typhoid is among the most prevalent bacterial infections in developing countries caused by *Salmonella typhi (S. typhi).* It is endemic in areas where sanitary conditions are lacking and access to clean water is limited. William Budd, in 1873, established the contagious nature of typhoid and identified fecal-contaminated water as its transmission source. Over time, the organism had different names, including *Bacillus typhosus, Erbethella typhosa, Salmonella typhosa*, and *S. typhi* (Parry 2006).

S. typhi, particularly its multidrug-resistant (MDR) form, is prevalent in countries like Pakistan. This is increasing the healthcare burden. Factors like poor sanitation, the collapsing economy, and limited access to clean drinking water provide a favorable breeding ground for these pathogens, posing multifaceted challenges to the governments in containing them. The COVID-19 pandemic shifted the focus away from typhoid, which is why it is becoming a formidable threat like other infectious diseases. Socioeconomic disparities, geographical, and demographic barriers will further limit access to appropriate typhoid management. Lastly, illiteracy and self-medication with antibiotics may make Pakistan vulnerable to typhoid outbreaks (Tharwani et al. 2022).

Looking back, typhoid control has been achieved with water and sanitation interventions. However, just like its name, *S. typhi* evolved as well. Currently, with the emergence of antimicrobial resistance (AMR), two World Health Organization-prequalified vaccines are available to address the situation in the short term. However, antibiotic resistance continues to pose a major challenge in the treatment of typhoid fever, as portended by the rise of azithromycin and third-generation cephalosporin-resistant *S. typhi* strains (Carey, McCann, and Gibani 2022). A proactive approach is required before it turns into a public health disaster. Antimicrobial agents from alternative sources, like plants, can be instrumental in this case. Additionally, in the longer term, water and sanitation interventions could be implemented to sustainably prevent typhoid in low- and middle-income countries (Vanderslott et al. 2023).

2. Epidemiology of Typhoid

Astoundingly, the global burden of typhoid fever currently stands at 9 million cases, with 110,000 deaths annually(IHME 2020). The largest portion of the typhoid-afflicted population resides in Africa, South and Southeast Asia, mostly among children. However, there are regional differences both within and between countries (Radhakrishnan et al. 2018), due to the reasons mentioned in the introduction of this article. Therefore, knowing the updated burden of typhoid fever at the global, national, and regional levels is essential to successfully eradicate typhoid, as emphasized by (DeRoeck et al. 2005)

Prolonged or persistent infection of *S. typhi* in macrophages and the gallbladder is known to be a key feature among these healthy chronic carriers(Monack, Mueller, and Falkow 2004). While lacking symptoms themselves, the carriers shed *S. typhi* in their stool, passing on the bacterium through the contamination of food and water sources. One prominent example is the case of "Typhoid Mary" or Mary Mallon, who caused at least seven typhoid outbreaks during her job as a cook in the 19th century.

3. Pathophysiology of Typhoid

Typhoid fever pathogenesis involves factors like infectious species, virulence, host immunity, and infectious dose. The larger the bacterial dose the shorter the incubation period and higher attack rates. While *S. typhi* is usually destroyed by stomach acid, it can colonize in individuals with low stomach acidity, immunocompromised individuals are more susceptible (Lianou, Nychas, and Koutsoumanis 2017). Virulence factors include typhoid toxin, Vi antigen, liposaccharide O antigen, and flagellar H antigen. Vi antigen shields the bacterium from macrophages, enhancing serum resistance. The flagellar H antigen aids mobility and adherence to the gut wall. Invasion occurs through flagella and the type III secretion system, transferring proteins into enterocytes, M cells, or direct mucosal penetration. Bacteria, attached to M cells, are absorbed, damaging them and exposing the basal lamina, facilitating invasion(Kohbata, Yokoyama, and Yabuuchi 1986). The cystic fibrosis transmembrane conductance regulator (CFTR) plays a role. Interestingly, an abnormal CFTR protein can confer resistance to typhoid(van de Vosse et al. 2005). The pathogen induces Peyer's patch proliferation, leading to necrosis and ulceration. They reach the reticuloendothelial system, including the gallbladder, through the lymphatic system and bloodstream. The asymptomatic early bacteremic phase transitions to symptomatic secondary bacteremia. Endotoxin, released by *S. typhi*'s lipopolysaccharide, contributes to shock-like reactions, vascular hyperactivity, and tissue damage(DeVos 2023).

Symptoms and signs of typhoid include fever, headache, weight loss, lethargy, stupor, malaise, leukopenia, thrombocytopenia, gastrointestinal bleeding, and in some instances, neurological complications(Yang, Chong, and Song 2018).

4. Conventional Typhoid Treatment Plan

Treatment duration for typhoid fever typically lasts between 5 to 21 days. Traditional first-line antibiotics used for typhoid treatment include chloramphenicol, ampicillin, and cotrimoxazole. Later fluoroquinolones became the preferred treatment medication, due to advantages, including faster symptomatic relief compared to the first-line antibiotics and lower rates of post-treatment carriage. The third line of treatment

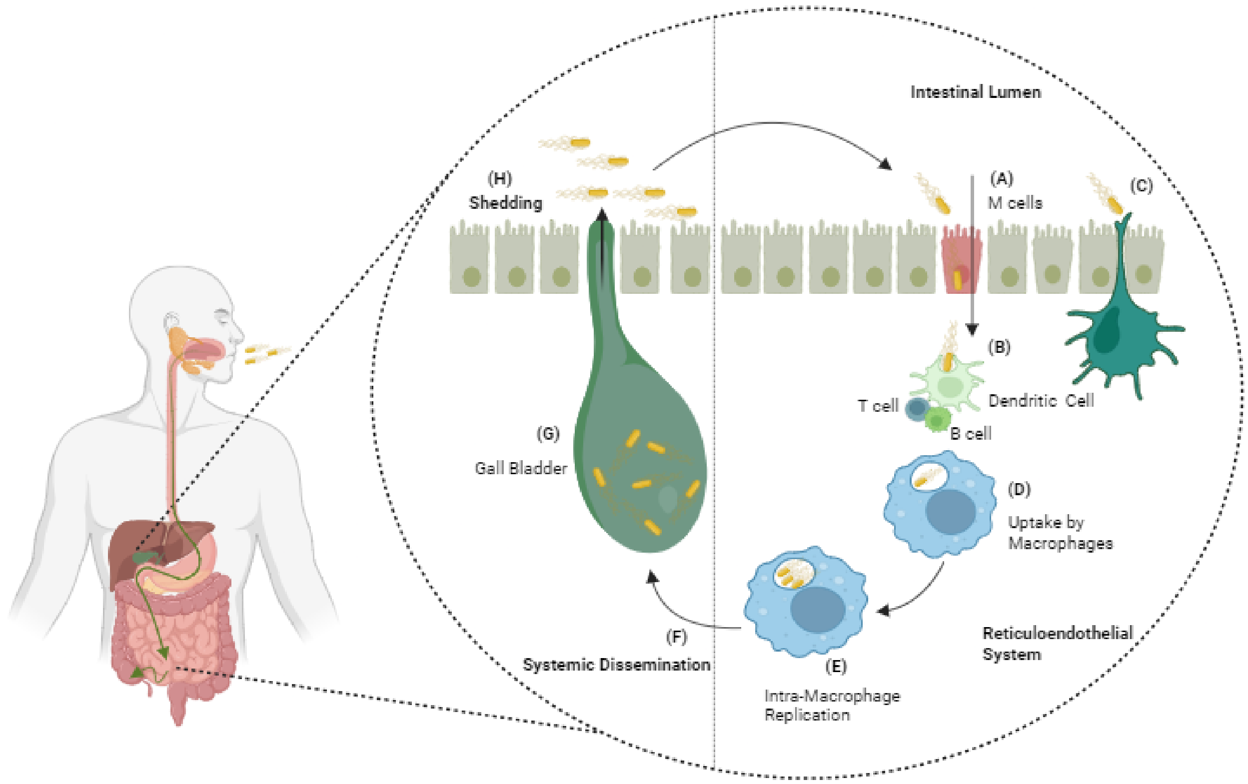

Figure 1: **The course of *S. typhi* infection and long-term carriage. Following the ingestion, (A) *S. typhi* preferentially enters M cells, (B) which transport them to the lymphoid cells (T and B) in the underlying Peyer's patches. (C) It can also be taken up by dendritic cells, elongated dendrites through the intestinal epithelial barrier. (D) Once across the epithelium, *Salmonella* serotypes associated with systemic illness enter intestinal macrophages, and (E) they undergo intra-macrophage replication (F) The pathogen disseminates throughout the reticuloendothelial system, leading to systemic infections. (G) Further colonization of the gallbladder leads to (H) chronic carriage and the bacterium's shedding through this mechanism.**

includes the use of novel, costly, and less readily available antibiotics, like third-generation cephalosporins, and azithromycin. Moreover, Expanding coverage of typhoid conjugate vaccines (TCVs) through routine immunization can reduce the need for antibiotics may thwart further emergence of drug-resistant typhoid strains, and save lives(consortium).

5. Challenges Associated with the Typhoid Treatment

In endemic countries, excessive and irrational antibiotic use has led to AMR, including MDR and extensively drug-resistant (XDR) strains. The emergence of resistance to reserved antibiotics in low- and middle-income countries is of serious concern(Saeed, Usman, and Khan 2019). This phenomenon has remained unchecked, first-line antibiotic-resistant strain, commonly referred to as MDR, emerged in the 1970s. Subsequently, typhoid evolved to resist even the 2nd and 3rd line antibiotics, giving rise to XDR strains(consortium). A study conducted in Nepal evaluated the typhoid treatment outcomes in 2092 patients and called for a revision of the treatment guidelines since the minimum inhibitory concentrations (MICs) against fluoroquinolones, including gatifloxacin, had increased significantly since 2005. They observed that patients infected with ciprofloxacin-resistant *S. typhi* strains (with a MIC of ≥0.12µg/mL) were more likely to experience treatment failure when treated with ofloxacin or

Table 1. Phytoextracts effective against *S. typhi*.

Plant	Family	Part used	Extract type	Reference
Azadirachta Indica	Meliaceae	Leaves	Methanol extract	(Ali et al. 2020)
Carica papaya	Caricaceae	Leaves	Methanol extract	(Ngwanguong et al. 2023)
Saraca asoca	Leguminosae	Leaves, dried callus	Methanol extract	(Vignesh, Selvakumar, and Vasanth 2022)
Simarouba glauca DC	Simaroubaceae DC.	Leaves, stem bark	Aqueous extract	(Nagaraj et al. 2021)
Psidium guajava	Myrtaceae	Leaves	n-hexane, methanol, ethylacetate extracts	(Olubunmi et al. 2021)
Flacourtia indica, Swartzia madagascariensis and Ximenia caffra	Flacourtiaceae, Fabaceae, and Olacaceae	Bark, leaves	Aqueous and ethanolic extract	(Chingwaru, Bagar, and Chingwaru 2020)
Amaranthus hybridus	Amaranthaceae	Seed, and Leaves	n-Hexane extract	(Naz, Alam, et al. 2022)
Hylocereus polyrhizus and Hylocereus undatus	Cactaceae	Fruit	Aqueous, ethanol, ethyl acetate extract	(Nur et al. 2023)
Citrus limon	Rutaceae	Fruit	Ethanol fraction	(Rahman, Alimsardjono, and Zakaria 2020)
Punic granatum	Punicaceae	Seed	Aqueous extract	(Majeed, AbdAlkadhim, and Jawad 2020)
Piper nigrum and Syzygium aromaticum	Piperaceae and Myrtaceae	Fruits	Aqueous extract	(Ismail et al. 2017)
Thymus vulgaris and Cinnamomum verum	Lamiaceae and Lauraceae	Leaves, bark	Ethanol, ethylactete extracts	(Ahmed et al. 2023)

gatifloxacin compared to patients infected with ciprofloxacin-susceptible *S. typhi* (MIC < 0.12µg/mL). This shows that ciprofloxacin resistance is associated with a higher risk of treatment failure in patients receiving ofloxacin or gatifloxacin(Thompson et al. 2017).

While typhoid vaccines have been available since 1896 and are cost-effective as well, many countries with a high disease burden have been unable to reap its benefits. The challenges in implementing typhoid vaccination programs include:

a) Low Immunogenicity: The licensed injectable Vi polysaccharide and the oral live-attenuated Ty21a vaccines have lower immunogenicity in infants and young children, making them less effective in these age groups.
b) Short Duration of Protection: These vaccines also offer a relatively short duration of protection, which may require booster doses, making the development of TCVs crucial.
c) Accessibility and availability of TCVs remain a challenge for the economically disadvantaged area(Khanam et al. 2022)

In addition to resistance development, the standard treatment drugs have been found to cause damage to growing cartilage, tendonitis (tendon rupture in extreme cases), and renal insufficiency(Ekenjoku, Ekenjoku, and Ekenjoku 2023). Also, the use of chloramphenicol can cause effects such as bone marrow suppression, leading to the dreaded side effect: aplastic anemia(Rahman, Alimsardjono, and Zakaria 2020).

6. Remedies from Medicinal Plants

Medicinal plants have been used as remedies for many ailments (Hussain et al. 2010, Imran et al. 2012, Ahmed et al. 2014). Medicinal plants have the potential to transform the current typhoid remedial practices. They can not only treat the disease but also act as synergists, additives, and scaffolds to the conventional *S. typhi* antibiotics. This review article presents various anti-typhoid phytocompounds that have been studied in in-vivo and in-vitro settings. Many of the following phytochemicals can target resistance mechanisms and structures that make *S. typhi* immune to various antimicrobial agents.

7. Phytoextracts against *S. typhi*

a. *Azadirachta indica*

Azadirachta indica, commonly referred to as "neem tree", belongs to the family Meliaceae. A study was conducted to test the anti-typhoid activity of its leaf extract. For this purpose, *A. indica* leaves were subjected to methanol extraction, and its minimum inhibitory concentration (MIC) was observed through nutrient broth and *S. typhi* strain-containing test tube. The zone of inhibition(ZOI) produced by the leaf extract was 21.70 mm at 200 mg/mL compared to that of ciprofloxacin i.e. 25.30 mm at 100 mg/ml. whereas, the MIC was 6.25 – 25 mg/ml, minimum bactericidal concentration (MBC) ranged from 12.5 – 50 mg/ml. The antibacterial activity of *A. indica* was attributed to its phytochemical constituents, like alkaloids, tannins, anthraquinone, flavonoids, phenols, and steroids(Ali et al. 2020).

b. *Carica papaya*

Carica papaya has a significant place as a remedy for typhoid in Cameroonian ethnopharmacology. To validate these practices, a study was conducted using *C. papaya* methanolic leaf extract. Following the extraction, the bioactive compound assessment indicated that it is rich in alkaloids, phenols, flavonoids, steroids, triterpenoids, tannins, saponins, and anthraquinones. In-vivo analysis revealed that the methanol extract exhibited an impressive MIC of 64µg/ml; additionally, the leaf extract also demonstrated bactericidal tendencies. This study not only validated the traditional practice of this plant as an anti-typhoid medicine but also suggested using it to develop phytomedicines against *S.typhi* infections that are readily available to all citizens, cheap, non-toxic with minimal side effects (Ngwanguong et al. 2023).

c. *Saraca asoca*

Saraca asoca, belonging to the Detarioideae subfamily of the Legume family, is an ancient and significant tree species of Peninsular India and Sri Lanka. An investigation into *S. acosa* usage in Ayurveda, and its anti-*S. typhi* potential was carried out. For this purpose, the phytochemical and pharmacological activities were compared with different solvents of in-vivo leaf and in-vitro callus extracts of *S. asoca.* Chromatographic analysis revealed that flavonoids, such as quercetin, naringenin, and epiafzelechin, were the predominant bioactive compounds. It also indicated the presence of alkaloids and fatty acids. In the present study in vitro callus ethanol and methanol extracts showed a maximum ZOI (19.1 mm) against *S. typhi* strain at 75µg/ml. The study also Proposed a mechanism of action based on flavonoids' ability to form an irreversible complex with proline-rich protein resulting in the inhibition of protein cell synthesis(Chandekar 2016). Other studies also suggest that flavonoids can inhibit RNA and DNA synthesis in bacteria by intercalation or formation of hydrogen bonds, stacking of nucleic acid bases, and influencing the DNA gyrase activity(Mori et al. 1987, Wu et al. 2013). Hence, the study empirically backed the traditional usage of this plant as a medicinal remedy(Vignesh, Selvakumar, and Vasanth 2022).

d. *Simarouba glauca DC*

Simarouba glauca DC (family: Simaroubaceae DC) is a rich source of pharmaceuticals. It is used not only in infectious but also in non-infectious diseases as well. A study aimed at phytochemical analysis and anti-typhoid properties of the plant was carried out. Initial screening of the leaves and stem bark aqueous extracts indicated the presence of alkaloids, flavonoids, tannins, terpenoids, carbohydrates, and essential metals, such as Cu^{2+}, Fe^{2+}, Mg^{2+}, and Zn^{2+}. The MIC and MBC values of 5 to 10mg/ml against *S. typhi* exhibited its potential to be used for further development of plant-based anti-typhoid regimens or nutraceuticals(Nagaraj et al. 2021).

e. Psidium guajava

Psidium guajava (Myrtaceae), commonly known as guava is an important part of tropical enthotherapeutic practices. It is also reported to be used in traditional typhoid treatment. To investigate its use as an antibacterial in typhoid management, a study was conducted. In that study, n-hexane extract (hPg), methanol extract (mPg), and ethyl acetate extract (ePg) from the fresh leaves of *P. guajava* were prepared. Subsequently, the extracts were subjected to in-vivo sensitivity assessment against *S. typhi*. The results demonstrated strong bactericidal activity as hPg extract inhibited biofilm up to 62.45% at a dose of 25mg/ml, whereas, mPg produced a significant ZOI, spanning 15.07mm. The minimum biofilm inhibition concentration ranged from 0.39-12.5mg/ml. In-vivo analysis, conducted on *S. typhi*-infected rats, indicated that ePg and hPg reduced bacterial load ($p<0.05$), and improved overall hematological profile. The results of this study supported the traditional use of *P. guajava* as a potent anti-typhoid remedy(Olubunmi et al. 2021).

f. Flacourtia indica, Swartzia madagascariensis,* and *Ximenia caffra:

A study was conducted to evaluate the anti-typhoidal effects of *Flacourtia indica* (Flacourtiaceae), *Swartzia madagascariensis* (Fabaceae), and *Ximenia caffra* (Olacaceae). In this, hot water (THWE), cold water (CWEC), and ethanolic extract (EEC) were made from the bark of *F. indica* and leaves of *S. madagascariensis*, and *X. caffra*. In-vitro studies of these extracts indicated that THWE showed more inhibition at 3.1 mg/ml to 30 mg/ml. The results of an analysis of variance, conducted on the ZOI for different plant extracts at a concentration of 100 mg/ml, demonstrated that THWE of *F. indica* and *S. madagascariensis* were the most effective against *S. typhi* as compared to their EEC($F = 25$, $p = 0.008$) and ($F = 32$, $p = 0.005$), respectively. While, EEC of *F. indica* yielded significantly greater antimicrobial activities against *S. typhi* compared to CWEC ($F = 132$, $p = 0.003$). Moreover, *X. caffra* EEC and CWEC exhibited greater antimicrobial activities compared to THWE, ($F = 1.5$, $p = 0.290$) and ($F = 32$, $p = 0.02$), respectively. Furthermore, ZOI measurement at a concentration of 100 mg/ml for the extracts and 300μg/ml for streptomycin showed that THWE of *F. indica* bark and all three extracts of *X. caffra* leaves had stronger inhibitory effects against *S. typhi* compared to streptomycin. In conclusion, the study recommended the use of the THWE method for the preparation of medicinal products from all 3 plants for *S. typhi*-induced diarrhea management(Chingwaru, Bagar, and Chingwaru 2020).

g. Amaranthus hybridus

To evaluate the efficacy of *Amaranthus hybridus* (Amaranthaceae) against MDR *S. typhi*, an analytical study was performed by (Naz, Alam, et al. 2022). Hexane extracts were prepared from the seeds and leaves of *A. hybridus* and subjected to in-vitro evaluation against the resistant strain of *S. typhi*. Ertapenem was used as a control drug as the bacterial strain was sensitive to this drug only. The MIC results indicated that the seed extract inhibited bacterial growth by 93.70% at a 1.25mg/ml dose, whereas the leaf extract managed to inhibit microbial growth by 87.80% at the same dose. Furthermore, spectroscopic and chromatographic screening confirmed the presence of alkaloids, tannins, and flavonoids, phenolic, antioxidants which can degrade the

Table 2: Phytocompounds effective against *S. typhi.*

Plant	Family	Part used	Crude extract	Antibacterial compound	Reference
Curcuma longa	Zingiberaceae	rhizome	Commercially bought curcumin	Curcumin, berberine	(Febriza et al. 2019) (Naz, Kumar, et al. 2022)
Quercus infectoria and Phyllanthus emblica	Fagaceae and Phyllanthaceae	Galls and fruit	Methanolic extract	1, 2, 3 Benzenetriol	(Nair et al. 2020)
Canarium schweinfurthii	Burseraceae	stem bark	chloroform and ethyl acetate fractions	Scopoletin (Coumarin)	(Sokoudjou et al. 2020)

oxygen-reactive species through damage to their DNA, RNA, and proteins(Naz, Alam, et al. 2022).

h. Hylocereus polyrhizus and *Hylocereus undatus*

To evaluate the medicinal value of natural colorants derived from *Hylocereus polyrhizus* and *Hylocereus undatus,* also known as dragon fruit, research to measure the antibacterial activity of extracted colorants from two species (*H. polyrhizus and H. undatus*) was done. Through the cold extraction method, aqueous, ethanol, and ethyl acetate extract were prepared from the fruits. The in-vivo analysis revealed that at the concentration of 200 mg, the aqueous colorant extract exhibited a significant anti- *S. typhi* activity. The MIC for *S. typhi* was 5mg/ml, whereas the ZOI was 8.54 mm. In comparison, the reference antibiotics (Ampicillin and Erythromycin) ZOI ranged from 13.60 mm to 22.50 mm. Further exploration of *H. polyrhizus* and *H. undatus* as an ingredient in pharmaceutical medications is recommended(Nur et al. 2023).

i. Citrus limon

A laboratory experimental study found that *Citrus limon*, of the family Rutaceae, showed promising antimicrobial potential. For evaluation, freshly squeezed lemon juice was soaked with 96% ethanol for 24 hours, followed by filtration. Various concentrations of the preparation were tested against *S. typhi*. The study determined the MIC to be 3.125 ppm, and MBC was 6.250 ppm. In-depth research is needed to further expand on these findings to harness the full potential of these plant-sourced antimicrobial components(Rahman, Alimsardjono, and Zakaria 2020).

j. Punic granatum

An increase in the trend of using natural products as adjunct therapy is being observed. To test the adjunct potential of *Punic granatum* (Punicaceae) with standard anti-typhoid antibiotic, co-trimoxazole, and the efficacy of this combination in S. typhi resistance prevention, a study was carried out. For this objective, an aqueous extract from the seeds of *P. granatum* was subjected to MIC assays, individually and in combination with co-trimoxazole. The results indicated a noticeable increase in potency compared to individual agents. The MIC was 125µg/ml and 250µg/ml, for co-trimoxazole and *P. granatum* aqueous extract. The combination showed a significant drop in MIC to 62.5µg/ml (P-value<0.05). The study confirmed a strong synergy between cotrimoxazole and *P. granatum* aqueous extract against *S. typhi* (Majeed, AbdAlkadhim, and Jawad 2020).

k. Piper nigrum and Syzygium aromaticum

A study aimed at exploring the anti-typhoid qualities of *Piper nigrum* (Piperaceae) and *Syzygium armoaticum* (Myrtaceae), in combination with other conventional typhoid antibiotics, was performed. The essential oils, hypothesized to be anti-*S. typhi*, were extracted from the crushed fruits of *P. nigrum* and *S. aromaticum* by hydro distillation method. The inoculated *S. typhi* strains were then exposed to the extracted oils and antibiotics for MIC and MBC determination. The results revealed MIC of *S. aromaticum* essential oil was 625 ppm, while the MIC of *P. nigrum* was between 5000 and 10,000 ppm. The researchers also performed a phytochemical analysis of these plants to map out their antibacterial mechanism of action. The bactericidal effect of *S. aromaticum* was attributed to eugenol, which interacts with bacterial cell walls and membrane, and tampers with various virulence factors, leading to the destabilization and eventually bacterial death(Marchese et al. 2017). Additionally, terpenes in *P. nigrum* are considered to be responsible for producing an antibacterial effect against gram-negative bacteria(Dorman and Deans 2000). Furthermore, synergistic and additive effects of these oils with antibiotics were also observed. *P. nigrum* essential oil exhibited a synergistic association with amoxicillin/clavulanic acid, ampicillin, ciprofloxacin, and gentamicin against *S. typhi*. Moreover, *S. aromaticum*-derived essential oil had synergistic associations with antibiotics in *S. typhi*. Furthermore, an additive effect was observed when combined with gentamicin. Generally, more positive results were observed with *S. aromaticum* in combination with antibiotics compared to *P. nigrum*. The study concluded that combining essential oils with antibiotics can enhance antibiotic activity and potentially reduce antibiotic concentrations and associated adverse effects. The inhibition of bacterial efflux pumps by essential oils was suggested as a possible mechanism underlying synergistic and additive effects with antibiotics(Ismail et al. 2017).

l. ***Thymus vulgaris* and *Cinnamomum verum***

An investigation to examine the ability of medicinal plants *Thymus vulgaris* (Lamiaceae) and *Cinnamomum verum* (Lauraceae) to modulate the properties of *S. typhi* isolates, instead of killing them. For this purpose, the active compounds from these plants were extracted using ethanol and ethyl acetate. In addition to MIC calculation, the biofilm and expression of invasion (*invA*) and flagellar (*fliC*) genes of the bacterium were also studied when exposed to sub-inhibitory concentrations of the plant extracts. For *T. vulgaris,* MIC values ranged between 20-25 mg/ml and 10-15mg/ml for ethanol and ethyl acetate extracts, respectively. Whereas, the MIC of *C. verum* ethanol extract was 18-25, and 10-15 mg/ml for ethyl acetate extract. Moreover, the study's findings revealed a significant decrease in the composition of biofilms by isolates when treated with the plant extracts. The transcription expression profiles of *invA* and *fliC* genes were also down-regulated, following the phytoextract treatment. The results suggest that both of these plants' extracts may have promising activity against the biofilm and virulence of S. typhi (Ahmed et al. 2023).

8. Phytocompounds against *S. typhi*

a. Curcumin and Vitamin D

Curcumin, a bright yellow chemical produced by *Curcuma longa* (Zingiberaceae), is sold as an herbal supplement and cosmetic ingredient. It is known for its anticancer, anti-inflammatory, and antibacterial effects. An in-vivo study to investigate the effect of curcumin and vitamin D therapy for *S. typhi* inhibition was done. The rationale behind this investigation was the presumption curcumin elicits antimicrobial response by binding with vitamin D receptors (VDR), which enhances the expression of cathelicidin antimicrobial peptides. Due to VDR involvement, Vitamin D was added to the study to see if combining curcumin and vitamin D combination can produce a synergistic effect.

After 5 days of therapy, the group receiving curcumin therapy (200-400mg/kg) and the group on curcumin and vitamin D combination demonstrated a decrease in the number of bacterial colonies. However, in the long term, the combination had the persistent ability to inhibit *S. typhi* growth even up to 30 days after infection(Febriza et al. 2019).

b. Berberine Chloride

Berberine is an important phytocompound, usually found in the roots, leaves, stems, and bark of plants such as barberry, Oregon grape, and tree turmeric. In a study, researchers aimed at finding the natural inhibitors for the cell division protein FtsZ. It is crucial in the cell wall synthesis in bacteria as the polymerization of the FtsZ provides the essential mechanical constricting force and flexibility to modulate the cell wall synthesis. Any interference in the FtsZ polymerization could potentially produce bactericidal or bacteriostatic effects. Based on this principle, the researchers selected some plant-derived compounds, like berberine, to hit the target. As a result, berberine chloride not only performed well in the molecular docking evaluation (by inhibiting FtsZ from *S. typhi*) but also showed the best MIC of 500µg/ml against the gram-negative bacterial strains. The findings support that it can be used as a scaffold to develop a broad spectrum of antibacterial agents(Naz, Kumar, et al. 2022).

c. Quercus infectoria* and *Phyllanthus emblica

A study, aiming to assess the antibacterial potentials of *Quercus infectoria* (gall), and *Phyllanthus emblica* (fruit) individually and synergistically against AMR *S.typhi*, was carried out. Phytochemical screening revealed that *Q. infectoria* extract contained tannins, cardiac glycosides, phenols, steroids, flavonoids, terpenoids, and saponins, whereas *P. emblica* methanolic extract, except for cardiac glycosides, had a phytochemical profile similar to that of *Q. infectoria*. In-vitro evaluation of these extracts, made from gall and fruits of the previously-mentioned sources, showed that the bactericidal dose of *Q. infectoria* was 50mg/ml, and that of *P. emblica* was 25mg/ml. Notably, they produced a synergistic effect at the dose of 12.5 mg/ml, superior to individual responses ($p<0.001$). Overall, the findings support the use of *Q. infectoria* and *P. emblica* methanolic extracts as effective herbal remedies to combat AMR *S. typhi.* Particularly, the presence of 1, 2, 3 benzenetriol phytocompound in these extracts elicit a highly potent bactericidal effect at a higher dosage and a bacteriostatic effect at a lower dosage against AMR *S. typhi*. Notably, 1, 2, 3 benzenetriol is known to alter microbial cell permeability and produce reactive oxygen species. The combination of these extracts can play a promising role; however, the identified phytocompounds need to be further purified and studied to serve as a platform for formulating effective phytotherapeutics (Nair et al. 2020).

d. Canarium schweinfurthii

To assess the anti-*S. typhi* activity of *Canarium schweinfurthii* (Burseraceae), chloroform and ethyl acetate fractions were made from its stem bark, in addition to phytocompounds separation. The results indicated that the isolated compounds appeared more active than the crude extract and partitions. However, chloroform and ethyl acetate fractions showed the best antibacterial activity. Among the isolated compounds, scopoletin showed the highest MIC of 16-32µg/ml against *S.typhi*. Moreover, MIC values of other compounds and extracts ranged between 128 and 1024µg/ml, while other residual fractions were less active, with MICs of 512 or 1024µg/ml. This study adds credence to the use of *C. schweinfurthii* in folk medicine(Sokoudjou et al. 2020). In addition, another study examined the impact of scopoletin on *S. typhi's* survival in macrophages. No cytotoxicity was observed below 50µg/ml of scopoletin. After 10 hours, scopoletin-treated experiments showed a significant decrease in viable *S. typhi* cells compared to untreated ones ($p < 0.05$, t-Test), suggesting potential intracellular activity and bacterial replication reduction (Acharya, Bogati, and Risal 2013).

9. Conclusion and Future Directions

Antibiotic resistance is a public health disaster in waiting, and the seismic waves of this crisis are being felt in low and middle-income countries where antibiotic regulation is lacking(Al Meslamani 2023). There is a growing momentum toward the exploration of novel methods and techniques like phage therapy, postbiotics, and alternative antibiotic sources like plant-derived antimicrobials. Since they don't promote the spread of antibiotic resistance, this aspect increases the reliability and durability of these methods(Ozma et al. 2023). This review article presented many promising candidates that may become the future of anti-typhoid treatment. For instance, *A. hybridus*, *C. verum*, *S. aromaticum, P. granatum, X. caffra, P. gujava*, *Q. infectoria*, *P. emblica,* and scopoletin phytocompound from *C. schweinfurthii* are among the most promising candidates. In addition to becoming a future source of antibiotics, these compounds could also be integrated into the diet or used as adjunct therapy for those suffering from typhoid. Examples include curcumin and vitamin D, *H. polyrhizus*, and *H. undatus* (dragon fruit)

Furthermore, it is essential to conduct extensive replications of these studies, ensuring a comprehensive understanding of the toxicological profiles of the promising agents. This is crucial for transforming them into robust antimicrobial assets. Moreover, despite the availability of various methods for the extraction and purification of plant-based substances, isolating pure compounds remains a laborious process. Additionally, Sustainability issues also need to be redressed when developing extraction methods. Also, the extraction process generates a huge volume of plant waste, necessitating proper utilization to ensure economic viability(Li et al. 2024). Moreover, climate change is leading to the extinction of many plant species like *S. asoca,* which is classified as 'vulnerable' under the International Union for Conservation of Nature red list. This is why the researchers need to devise ways to extract bioactive compounds without destroying the whole plant(Vignesh, Selvakumar, and Vasanth 2022).

Conflict of Interest

The authors declare that they have no competing interests.

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NS carried out all the data collection, bench work, and manuscript writing. TS helped in data collection and analysis. NS conceptualized and supervised the study.

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Data is available upon reasonable request from the corresponding author.

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