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Herbal Formulation Approaches in the Management of Typhoid Fever: A Comprehensive Review

Mauli Gawade[1], Sakshi Girme[2], Amol Ghane[3], Pratap Hirwe[4], Kashish Ghosalkar[5], Reshma Dhakate[6]
[1, 2, 3, 4, 5]*Students,* [6]*Assistant Professor, Pharmaceutical chemistry, Sinhgad Institute of Pharmaceutical Sciences, Lonavala*

Abstract: ***Typhoid fever, caused by Salmonella typhi and Salmonella paratyphi, remains a significant infectious disease in developing regions where poor sanitation persists.[1] The rapid emergence of multidrug-resistant (MDR) strains has reduced the efficacy of conventional antibiotics, prompting interest in herbal alternatives.[4] Medicinal plants such as Azadirachta indica (Neem), Ocimum sanctum (Tulsi), Tinospora cordifolia (Giloy), Andrographis paniculata (Kalmegh), Curcuma longa (Turmeric), and Zingiber officinale (Ginger) exhibit antimicrobial, antioxidant, and immunomodulatory activities effective against Salmonella species.[5] These phytochemicals act by inhibiting bacterial growth, modulating host immunity, and reducing oxidative stress.[3] To enhance patient compliance and bioavailability, effervescent granule formulations of herbal extracts offer a novel delivery platform characterized by rapid solubility, pleasant taste, and improved stability.[6] Evaluation parameters include effervescence time, pH, dissolution rate, and stability. However, standardization, variability of phytochemical content, and microbial contamination remain challenges.[2] Future studies should focus on clinical validation, optimization of effervescent formulation techniques, and regulatory standardization to ensure the safety, efficacy, and affordability of herbal effervescent products for typhoid fever management.***

Index Words: ***Typhoid Fever, Salmonella Typhi, Herbal Formulation, Effervescent Technology, Antibiotic Resistance***

I. INTRODUCTION

Typhoid fever is a serious systemic and life-threatening infection caused primarily by *Salmonella enterica* serovar *Typhi* and *Salmonella paratyphi*, transmitted through contaminated food and water.[1] It remains a significant public health problem in developing nations, especially where sanitation and hygiene are poor. The global incidence of typhoid fever is estimated at over 21 million cases annually, with nearly 200 000 deaths, emphasizing the persistent burden of this disease.[10] Conventional management of typhoid fever relies mainly on antibiotics such as chloramphenicol, ampicillin, ciprofloxacin, and ceftriaxone. However, the widespread emergence of multidrug-resistant *Salmonella* strains has severely limited the efficacy of these therapies, necessitating the search for safer and more sustainable alternatives.[11] Herbal medicine has historically served as the foundation of healthcare in many societies and continues to play a major role in managing infectious diseases.[4] Medicinal plants such as *Azadirachta indica* (Neem), *Ocimum sanctum* (Tulsi), *Curcuma longa* (Turmeric), *Zingiber officinale* (Ginger), *Allium sativum* (Garlic), and *Tinospora cordifolia* (Giloy) possess strong antibacterial, antipyretic, antioxidant, and immunomodulatory properties.[7] These herbs exhibit multiple mechanisms—such as inhibiting bacterial growth, reducing oxidative stress, enhancing immunity, and supporting hepatic function—making them promising candidates for combating typhoid infection.[5] The increasing interest in herbal therapy has also stimulated the development of novel dosage forms to enhance patient compliance and therapeutic efficacy. Among these, effervescent formulations have gained attention for their improved solubility, stability, rapid disintegration, and enhanced bioavailability.[6] Effervescent herbal granules provide an attractive alternative to traditional decoctions or syrups, offering better taste masking and convenience for patients with typhoid-associated nausea or poor appetite. However, challenges such as standardization of herbal extracts, quality control, and optimization of effervescent reaction parameters remain major hurdles.[2]
Therefore, developing effervescent formulations of herbal products could provide a scientifically validated, patient-friendly, and effective approach to managing typhoid fever while addressing antibiotic resistance and formulation challenges. This review focuses on the pathophysiology of typhoid fever, limitations of current therapies, herbal alternatives with defined mechanisms, and formulation strategies for effervescent herbal preparations aimed at improving therapeutic outcomes.

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Figure 1 : Salmonella Enterica Serovar Typhi [19]

II. PATHOPHYSIOLOGY OF TYPHOID FEVER

Typhoid fever is a systemic infection caused primarily by *Salmonella enterica* serovar Typhi, a Gram-negative bacillus transmitted through contaminated food and water. Following ingestion, the bacteria resist gastric acid and reach the small intestine, where they penetrate the intestinal mucosa via M cells overlying Peyer's patches.[5] Once inside, *S. Typhi* invades macrophages and dendritic cells, allowing dissemination through the lymphatic system and bloodstream, leading to bacteremia.[11] The incubation period is typically 7–14 days.

During this time, the bacteria multiply within the reticuloendothelial system, particularly in the liver, spleen, and bone marrow. The systemic spread triggers an inflammatory immune response characterized by fever, malaise, and abdominal discomfort.[7] *S. Typhi*'s ability to survive intracellularly within macrophages contributes to chronic infection and relapse. The Vi capsular antigen, flagellar (H) antigen, and somatic (O) antigen play critical roles in immune evasion by inhibiting complement activation and phagocytosis.[9] Pathological changes are most pronounced in the ileum, where hyperplasia and necrosis of Peyer's patches can cause intestinal ulceration, bleeding, or perforation in severe cases.[4]

The endotoxin release leads to endothelial dysfunction and cytokine surge (TNF-α, IL-6), which manifest as high-grade fever, hypotension, and sometimes septic shock. The liver often exhibits typhoid nodules and hepatomegaly due to bacterial colonization and macrophage activation.[1]If untreated, the infection progresses through four clinical stages—rising fever and bacteraemia, abdominal distension, ulceration with complications, and finally convalescence. Chronic carriers, such as those with gallbladder colonization, continue to shed bacteria even after recovery, facilitating transmission.[3] Overall, the pathophysiology of typhoid fever involves a complex interaction between *Salmonella Typhi* virulence factors, host immune evasion, and systemic inflammatory responses, leading to multi-organ involvement and significant morbidity.

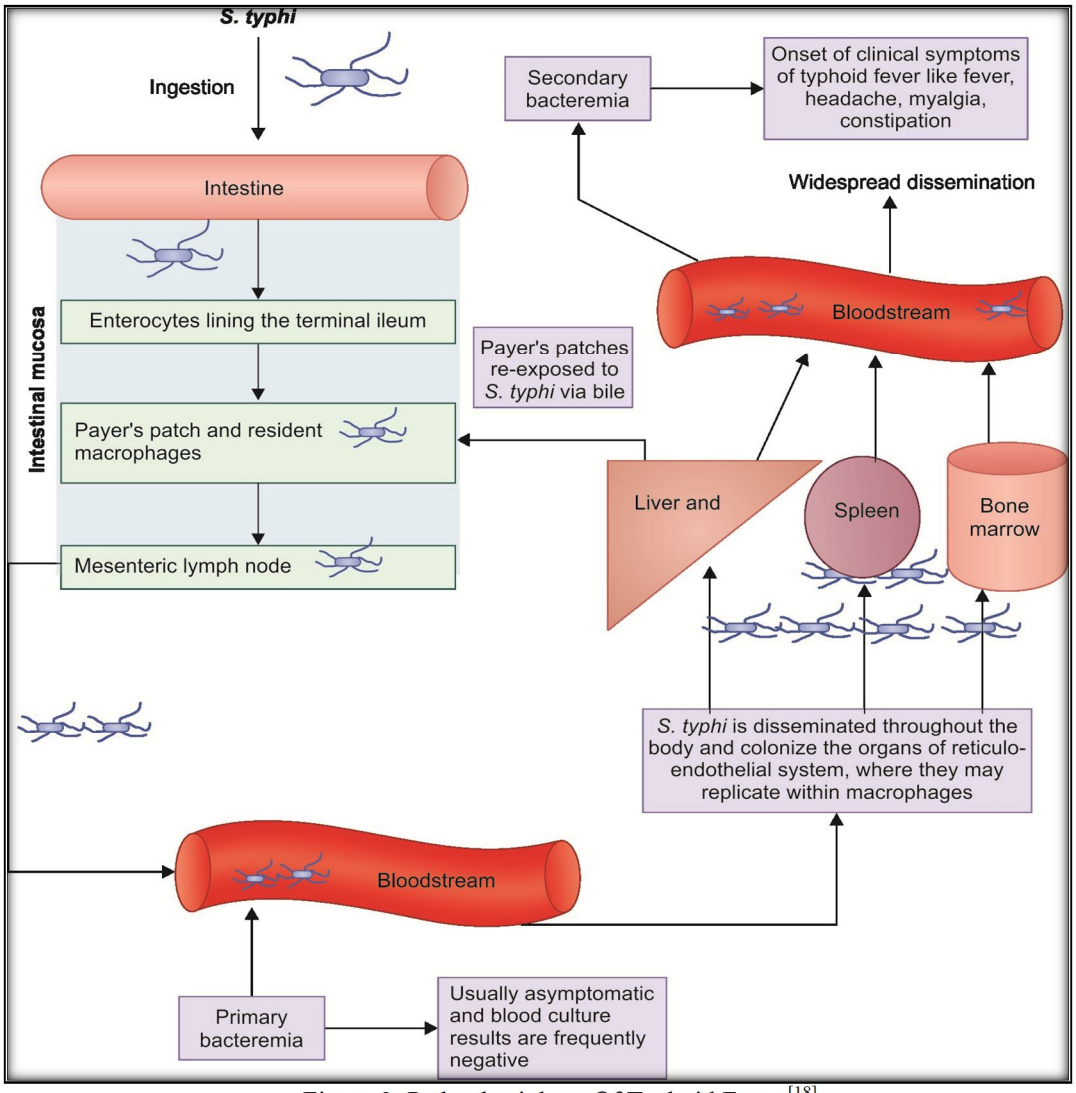

Figure 2: Pathophysiology Of Typhoid Fever [18]

III. ANTIBIOTIC THERAPY FOR TYPHOID FEVER

Typhoid fever, caused by *Salmonella enterica* serovar *Typhi*, requires prompt antibiotic therapy to prevent complications and reduce transmission. Historically, first-line treatments included chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole. However, widespread resistance has rendered these drugs less effective in many endemic regions.[16]

Currently, fluoroquinolones such as ciprofloxacin and ofloxacin are preferred agents due to their excellent intracellular penetration and bactericidal activity against *S. Typhi*. Nevertheless, the emergence of nalidixic acid-resistant strains has reduced their efficacy, leading to clinical failures and prolonged fever clearance times.[13] In such cases, third-generation cephalosporins—notably ceftriaxone and cefotaxime—are widely used as empirical therapy, particularly in severe or complicated cases. Cefixime, an oral option, is useful for outpatient management. These β-lactams act by inhibiting bacterial cell wall synthesis and are effective against multidrug-resistant (MDR) *S. Typhi* strains.[17] Azithromycin, a macrolide antibiotic, has emerged as an effective oral therapy for uncomplicated typhoid fever, especially in regions with high fluoroquinolone resistance. Its long half-life, intracellular activity, and favourable safety profile make it particularly suitable for paediatric and outpatient use.[14] In the case of extensively drug-resistant (XDR) typhoid, such as those reported from Pakistan, carbapenems (e.g., meropenem) and tigecycline may be required.[15] Supportive care with fluid and electrolyte management remains essential alongside antibiotic therapy. Rational antibiotic selection based on local resistance patterns and susceptibility testing is vital to curb resistance development and ensure optimal clinical outcomes.

A. Limitations Of Current Therapy

The treatment of typhoid fever primarily relies on antibiotics such as chloramphenicol, ampicillin, ciprofloxacin, ceftriaxone, and azithromycin. However, the emergence of multidrug-resistant (MDR) strains of *Salmonella typhi* has significantly reduced the effectiveness of conventional antibiotic therapy. Continuous and unregulated antibiotic use has led to resistance against first-line and even newer antibiotics, complicating disease management.[1] Additionally, the toxicity, cost, and availability of certain antibiotics pose challenges in low-resource settings.[7] Recurrent infections due to incomplete treatment and carrier states further undermine the success of current therapies.[3] The lack of new antimicrobial agents targeting resistant *S. typhi* strains exacerbates the issue. Moreover, antibiotic use disrupts gut microbiota, delays immune recovery, and may lead to relapse. Thus, despite the historical efficacy of antibiotics, their diminishing potency and adverse effects necessitate exploration of alternative therapies, including herbal formulations with proven antimicrobial and immunomodulatory properties.[4]

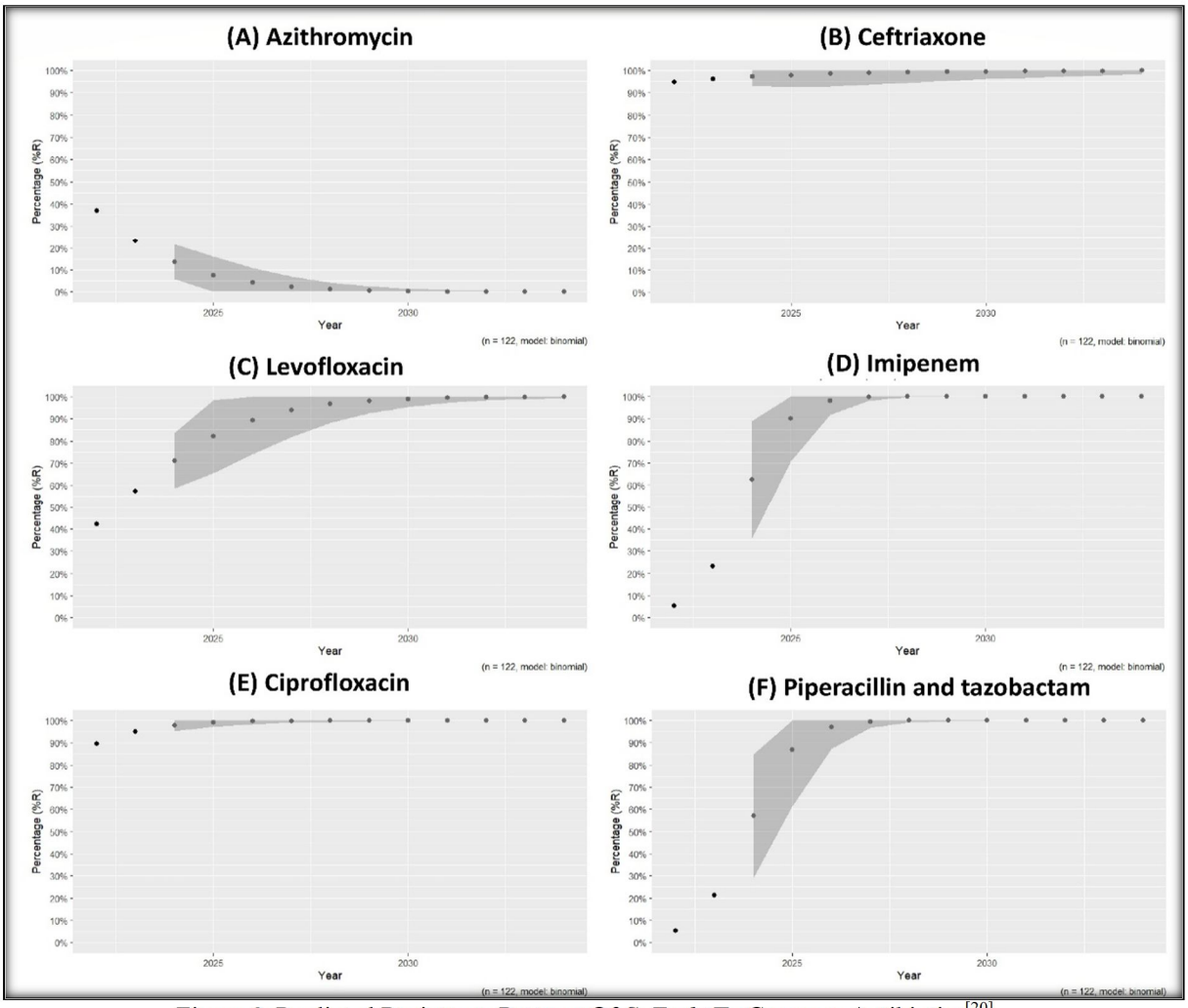

Figure 3: Predicted Resistance Patterns Of *S. Typhi* To Common Antibiotics[20]

IV. HERBAL ALTERNATIVES

Herbal medicine presents a promising complementary or alternative approach for the treatment of typhoid fever, especially in regions where antibiotic resistance to *Salmonella typhi* and *S. paratyphi* has become a major challenge. Various medicinal plants exhibit potent antibacterial, antioxidant, and immunomodulatory properties that contribute to the inhibition of bacterial growth, reduction of inflammation, and enhancement of host defence mechanisms. Among the most widely studied herbs, *Azadirachta indica* (Neem) demonstrates significant antibacterial and anti-inflammatory activity due to its bioactive compounds such as azadirachtin and nimbidin, which disrupt bacterial cell walls and inhibit the synthesis of essential enzymes necessary for bacterial survival (Kumbhar et al., 2015; Shaheen et al., 2023).

Ocimum sanctum (Tulsi) and *Andrographis paniculata* (Kalmegh) possess antimicrobial and hepatoprotective effects that help alleviate fever and enhance liver detoxification. These herbs stimulate macrophage activity and cytokine release, thus improving immune response during infection.[7] *Curcuma longa* (Turmeric) contains curcumin, a polyphenolic compound with powerful anti-inflammatory and antioxidant properties. Curcumin suppresses the production of pro-inflammatory mediators like TNF-α and IL-6, thereby reducing systemic inflammation associated with typhoid fever.[5] Similarly, *Zingiber officinale* (Ginger) exerts antibacterial activity through inhibition of bacterial quorum sensing and suppression of prostaglandin synthesis, while also relieving gastrointestinal symptoms such as nausea and abdominal pain.[7] *Allium sativum* (Garlic) contains allicin, a sulfur compound that directly inhibits *Salmonella* growth by interfering with thiol-containing enzymes and disrupting bacterial metabolism.[7] *Tinospora cordifolia* (Giloy) exhibits immunostimulant and antipyretic activity, enhancing leukocyte function and neutralizing oxidative stress, which are crucial during infection recovery. Other significant herbs include *Carica papaya*, *Moringa oleifera*, *Cassia alata*, *Vernonia amygdalina*, and *Nauclea latifolia*, which have all shown inhibitory effects against *S. typhi* in vitro.[4] These plants contain flavonoids, alkaloids, tannins, and saponins—secondary metabolites that interfere with bacterial cell wall synthesis and nucleic acid replication. Synergistic herbal formulations combining multiple plants, such as those containing *Cymbopogon citratus* and *Carica papaya*, have demonstrated enhanced antibacterial effects through multi-target mechanisms.[6] Overall, herbal alternatives act by three primary mechanisms: (1) direct antibacterial inhibition, (2) modulation of immune responses, and (3) reduction of oxidative and inflammatory damage. While these herbs demonstrate considerable promise, challenges remain in standardizing doses and validating clinical efficacy through controlled trials.

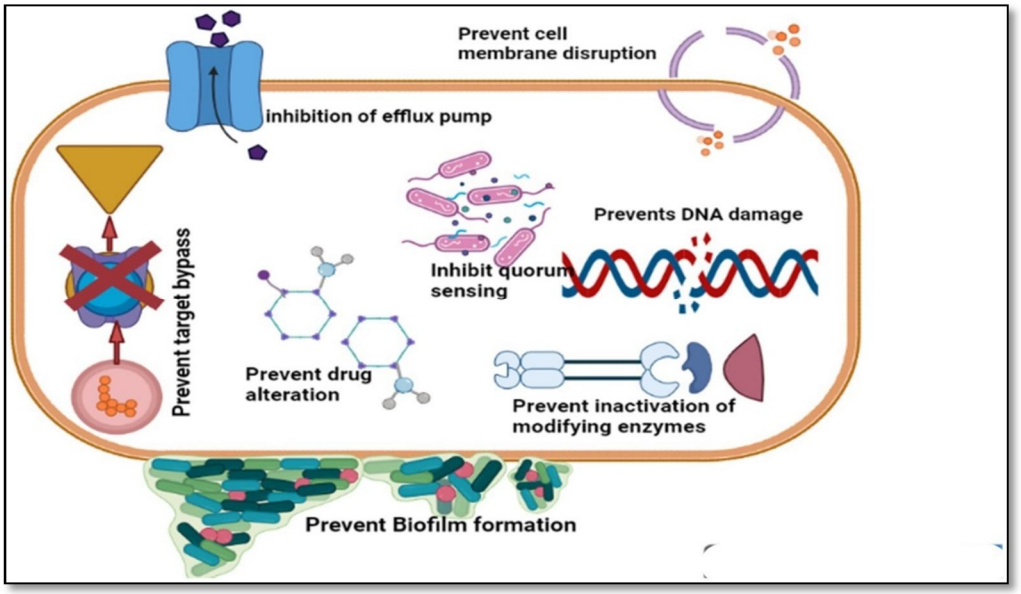

Figure 4: Overview Of Mechanisms By Which Herbal Medicines Act Against Salmonella Typhi Infection.[21]

A. Recent Advances In Herbal Effervescent Technology

Herbal effervescent technology represents a modern innovation in the delivery of phytopharmaceuticals, enhancing bioavailability, patient compliance, and stability of herbal actives. Recent research focuses on formulating effervescent granules and tablets using medicinal plant extracts with antibacterial and immunostimulant properties for managing diseases such as typhoid fever. The effervescent system—based on acid–base reactions between citric acid and sodium bicarbonate—facilitates rapid disintegration and improved solubility of poorly water-soluble phytoconstituents.[1] Studies like demonstrated optimized effervescent granule formulations containing standardized herbal extracts for antityphoid efficacy, improving taste and onset of action compared to conventional decoctions. This technology also supports controlled dosage, reduced microbial contamination, and enhanced shelf life. Current advances integrate nanotechnology and polymer coating techniques for sustained release and improved stability of herbal actives. Furthermore, regulatory interest and consumer preference for natural, fast-acting supplements have accelerated development of effervescent herbal nutraceuticals for immune support, gastrointestinal health, and infection prevention. Despite these advancements, challenges remain in standardization, scalability, and ensuring consistent therapeutic efficacy of effervescent herbal formulations.[3]

V. EFFERVESCENT FORMULATION STRATEGIES FOR TYPHOID TREATMENT

Effervescent formulations have gained attention in herbal drug delivery due to their improved patient compliance, enhanced solubility, and rapid onset of action. In the management of typhoid fever, the development of effervescent granules containing herbal extracts has been proposed as a means to improve bioavailability and stability of phytoconstituents while ensuring convenience and palatability, especially for paediatric and geriatric patients.[1] The formulation approach involves combining selected herbal extracts with a suitable acid–base effervescent system, typically citric acid and sodium bicarbonate, which react in aqueous solution to release carbon dioxide. This reaction not only improves dissolution rate but also enhances the taste and masking of bitter herbal constituents.[1] optimized the ratio of these effervescent agents to ensure rapid effervescence without compromising granule integrity.

The selection of herbal ingredients was guided by their known antibacterial and immunostimulatory properties. For instance, plants such as *Azadirachta indica*, *Zingiber officinale*, and *Carica papaya* exhibit strong antimicrobial activity against *Salmonella typhi* and are commonly incorporated into antityphoid herbal formulations.[5] Such extracts contribute to the therapeutic efficacy of the effervescent formulation by synergistically targeting bacterial infection and supporting immune function. Formulation success depends on process parameters including moisture control, granulation technique, and excipient choice. Since effervescent mixtures are highly sensitive to humidity, non-aqueous granulation methods are preferred.[1] used ethanol as a granulating agent to prevent premature effervescence during processing. Moreover, anhydrous citric acid and airtight packaging were employed to maintain product stability.[2] highlighted that microbial contamination remains a major challenge in herbal formulations due to inadequate hygiene and poor storage. Therefore, the effervescent formulation strategy also serves a hygienic advantage—by ensuring low water activity and minimal microbial growth through dry processing and sealed packaging. Evaluation parameters for the developed granules included effervescence time, moisture content, flow properties, dissolution rate, and antimicrobial potency. The optimal formulation achieved complete effervescence within 2 minutes and demonstrated significant antibacterial activity against *Salmonella typhi*.[1] In comparison with conventional decoctions or suspensions, effervescent granules provide enhanced chemical stability and dosage accuracy, reducing variability seen in unstandardized herbal mixtures sold in markets.[12] Additionally, the rapid dispersion and pleasant taste improve patient compliance, which is crucial in prolonged typhoid management.

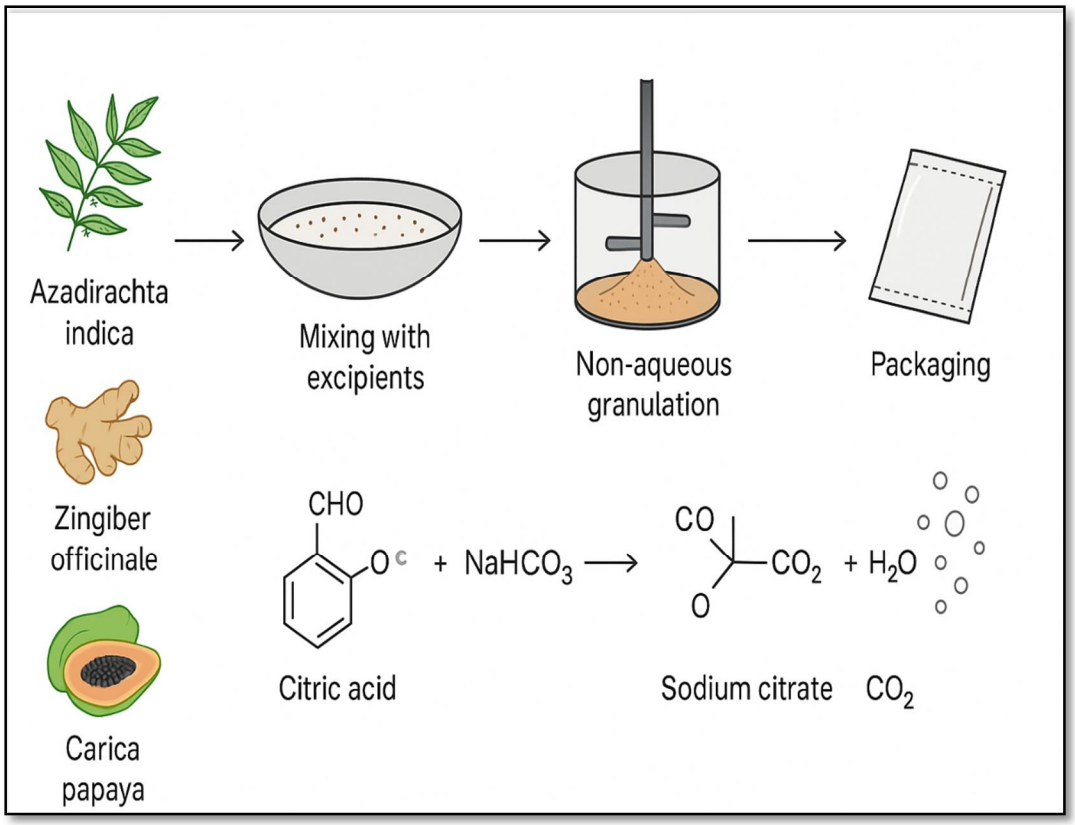

Figure 5: Systemic Representation Formulation Of Herbal Effervescent Tablet[1]

VI. CHALLENGES AND PROSPECTS

The use of herbal formulations for the management of typhoid fever presents promising therapeutic potential but faces numerous challenges that limit their global acceptance and standardization. One of the major challenges is the lack of standardization in herbal product formulation. Variations in plant parts, age, environmental conditions, and extraction methods significantly influence phytochemical composition and therapeutic efficacy.[3] Moreover, dosage inconsistency and labelling errors in locally prepared herbal medicines often lead to sub-therapeutic dosing or toxicity.[6] The absence of Good Manufacturing Practice (GMP) compliance and weak regulatory monitoring further exacerbate this issue, particularly in developing countries where herbal preparations dominate primary healthcare.[12] Another critical challenge is microbial contamination during collection, preparation, and storage. Studies have reported high microbial loads in herbal typhoid formulations, with frequent detection of *Staphylococcus aureus* and *Escherichia coli*, indicating poor hygiene and contamination risks.[12] This compromises patient safety and undermines the perceived "natural safety" of herbal products. Additionally, the absence of clinical validation and toxicity profiling limits their integration into evidence-based medicine.[7] Herbal medicines often contain multiple bioactive compounds that may interact synergistically or antagonistically with conventional antibiotics, leading to unpredictable outcomes.[4] Lack of awareness among practitioners and patients regarding potential herb–drug interactions further complicate their safe therapeutic use. On the other hand, the prospects for herbal and effervescent formulations in typhoid management remain highly promising. The increasing antibiotic resistance of *Salmonella typhi* has created an urgent need for alternative therapies.[1] Many plant-based compounds such as azadirachtin from *Azadirachta indica* (Neem) and curcumin from *Curcuma longa* (Turmeric) have demonstrated strong anti-*Salmonella* activity comparable to standard antibiotics.[5] Furthermore, effervescent herbal formulations offer enhanced solubility, stability, and patient compliance, enabling faster onset of action and improved bioavailability of herbal actives. Such formulations also mask the unpleasant taste of herbal extracts, increasing patient acceptability.[1] The integration of modern pharmaceutical technology with traditional herbal medicine thus presents a novel approach to developing standardized, safe, and efficacious herbal effervescent products for typhoid fever. Future directions should focus on clinical trials, pharmacovigilance systems, and bioactive compound isolation to ensure therapeutic consistency and international regulatory recognition.

VII. FUTURE SCOPE

The future of herbal antityphoid therapy lies in systematic standardization, mechanistic elucidation, and clinical validation of promising plants such as *Azadirachta indica*, *Curcuma longa*, *Vernonia amygdalina*, and *Khaya senegalensis*. Modern analytical tools—HPLC, LC-MS, and metabolomics—should be used to characterize bioactive constituents responsible for antibacterial and immunomodulatory actions.[5] Bioassay-guided fractionation and molecular docking can identify target interactions with *Salmonella typhi* enzymes. Nanocarrier-based delivery systems and effervescent formulations may improve bioavailability and patient compliance.[1] Integration of herbal extracts with low-dose antibiotics could overcome multidrug resistance and minimize side effects.[4] Future studies should include multicenter clinical trials, toxicity profiling, and pharmacovigilance to establish safety and efficacy.[7] Furthermore, microbial quality assessment of commercial herbal preparations is essential to ensure safety and regulatory compliance.[12] Collaboration among pharmacognosists, microbiologists, and formulation scientists will advance evidence-based phytomedicine development and promote WHO-endorsed traditional medicine integration. Thus, herbal therapeutics represent a sustainable, accessible, and eco-friendly alternative for managing typhoid fever globally.

VIII. CONCLUSION

Typhoid fever continues to pose a significant threat in developing countries due to poor sanitation and the emergence of multidrug-resistant *Salmonella typhi* strains. While antibiotics remain the mainstay of therapy, the escalating resistance crisis necessitates exploration of safer, sustainable alternatives. Herbal medicine provides a promising adjunct or substitutes due to its broad pharmacological properties, including antibacterial, antioxidant, immunostimulant, and hepatoprotective actions. Plants such as *Azadirachta indica*, *Curcuma longa*, *Zingiber officinale*, *Tinospora cordifolia*, and *Ocimum sanctum* exhibit potent antimicrobial activity against *Salmonella* species and aid in immune modulation and recovery. Recent formulations, including effervescent herbal granules, enhance patient compliance, bioavailability, and acceptability while maintaining stability and rapid dissolution. However, limitations such as lack of standardization, microbial contamination, dosage inconsistency, and limited clinical validation hinder widespread acceptance. To advance herbal therapy in typhoid management, integration of modern formulation strategies, such as effervescent technology and quality-controlled extraction, is crucial. Future research should emphasize bioactive compound isolation, pharmacokinetic profiling, toxicological evaluation, and multicentric clinical trials.

With adequate scientific validation and regulatory oversight, herbal effervescent formulations may become viable, safe, and cost-effective therapeutic alternatives to synthetic antibiotics for typhoid fever.

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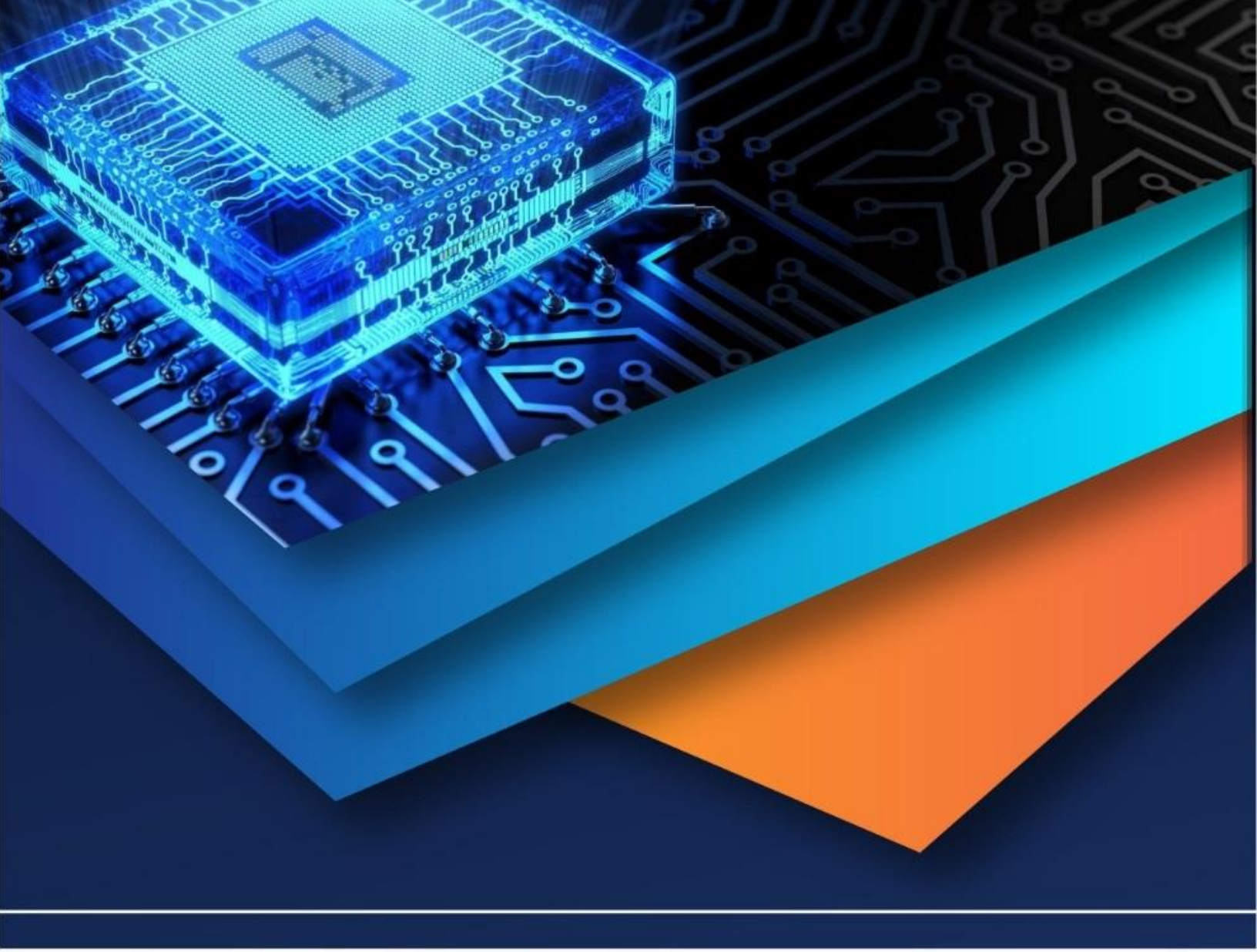

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