

-:Abstract:-

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Thesis Title: **Validation of antimicrobial activity of selected herbs against multidrug-resistant *Salmonella* Typhi isolates: development of antityphoid herbal formulation**

Salmonella enterica subsp. *enterica* serotype Typhi, or *Salmonella* Typhi, is a common food-contaminating bacterium that causes human-restricted typhoid. In 2021, over 9 million cases of typhoid and 100,000 deaths were reported. Over time, typhoid has disappeared from many developed countries, but the emergence of drug-resistant strains has become a growing concern in low- to middle-income countries. The rise of resistant strains of *S. Typhi* demands the development of new antibacterial agents against this pathogen. Plants can serve as a valuable natural source of antibacterial agents due to their cost-effectiveness and sustainability. The methanolic leaf extract of *Senna occidentalis* and the methanolic root extract of *Scoparia dulcis* were tested against clinical isolates of *S. Typhi*. Both extracts demonstrated antibacterial activity against *S. Typhi*; however, the root extract of *Scoparia dulcis* exhibited greater efficacy, with MIC and MBC values of ≤ 7.5 (> 3.75) mg/ml and ≥ 15 (> 7.5) mg/ml, respectively, compared to the leaf extract of *Senna occidentalis*. Both crude extracts were fractionated by column chromatography, and each collected fraction was tested against *S. Typhi* to identify the most active fractions. A total of forty-three phytochemicals were identified through LC-MS from five selected fractions. All identified phytochemicals were virtually screened to assess their physicochemical properties and predict their druglikeness and toxicity class. Furthermore, five phytochemicals were selected for further evaluation: three flavonoids- acacetin, apigenin, and luteolin and two benzoxazinoids- 6-methoxybenzoxazolinone and benzoxazolinone, to delve deeper into their effectiveness against *S. Typhi*. Luteolin showed comparatively greater effectiveness than the other four, with the lowest MIC of ≤ 0.03 (> 0.01) mg/ml. The effect of flavonoids was bacteriostatic, while it was bactericidal for benzoxazinoids. All phytochemicals inhibited biofilm formation, inhibition of invasion of *S. Typhi* into macrophage cells and inhibition of the activity of *S. Typhi* DHFR protein. In *S. Typhimurium* challenged mice, phytochemical treatment resulted in 100% survivability with significantly less bacterial colonization in the intestine and liver of infected models. This study suggests that the root of *S. Dulcis* can serve as a herbal remedy for *S. Typhi* infection and as a source for new antibacterial agents. Additionally, the five studied phytochemicals- acacetin, apigenin, luteolin, 6-methoxybenzoxazolinone, and benzoxazolinone- show great potential to become anti-typhoid drugs and may inform future studies.

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