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Common plants used in the treatment of typhoid fever, their active components and toxicity related issues : A review

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ABSTRACT: Plants and their extracts are a primary source of health care in most communities. The usage of plants in treating diseases has been observed in ancient times and is still applicable today. Plant extracts are used due to their easy availability and affordability. Some of these extracts are sold locally in markets, while others are manufactured and used in household settings. Most often, the producers of these extracts do not show proof of safety and efficacy before marketing these products. Consequently, the adverse effects and the downside following the consumption of these products remain unknown. Moreover, plant extracts are not regulated for purity and potency. Impurities present and the potency of the plant products might also contribute significantly to adverse effects following consumption. Typhoid fever has been one of the diseases in which most developing countries, especially in Africa, resort to using traditional methods involving plant extracts in its treatment. Various research has documented the anti-typhoid activity of these extracts based on the zone of inhibition against the pathogen. There is, however, a scarcity of information on the bioactive components possessed by these plants. This paper reviews the common plants used to treat typhoid fever, their active components and health risk following their indiscriminate usage. The review is composed of a literature search on herbal plants for typhoid fever obtained from PubMed and Google Scholar databases. Knowledge of the active components in these plants will help to standardize the safe dose needed to treat this disease effectively.

1. INTRODUCTION

Typhoid fever is a communicable disease and is still a major health concern worldwide, especially in Africa, Latin America, and South or Southeast Asia, where the disease is endemic. The faecal-oral route spreads the disease through contaminated food and water sources ((Akwa & Nguimbous, 2021). Clinical manifestations usually develop gradually, often appearing one to three weeks after exposure to the microorganism. Common signs and symptoms include fever, dizziness, nausea, vomiting, decreased appetite, abdominal pain, constipation or sometimes diarrhoea (Akwa & Nguimbous, 2021). Therapeutic agents commonly used in the treatment of typhoid include ciprofloxacin, ceftriaxone, cefixime chloramphenicol, trimethoprim, sulfamethoxazole or ampicillin (Butt et al., 2003). Unfortunately, recent findings show that *Salmonella typhi* has rapidly gained resistance to these agents (Crump et al., 2015). Thus,Typhoid fever is becoming an increasingly lethal disease on a daily basis. because of the emergence of multidrug-resistant *Salmonella typhi*, a situation that urges the need to develop a more effective therapeutic agent.

Over decades, a vast number of plants have been widely used traditionally to treat typhoid fever. Clinically, the extracts from the plant parts have been proven to contain antimicrobial properties and thus used locally and in some healthcare settings to treat diseases. The usage of traditional medicine as the preferred primary health care system in many communities to treat this disease may be due to factors such as affordability and accessibility. Much research has already been done in various parts of Africa to investigate various plants used in different communities against typhoid fever.

Plant's products assumed to be non-toxic have been used worldwide by herbalists and the local population to treat many diseases. However, it should be noted that although plants extracts are of natural origin, their usage is not entirely safe. Like synthetic drugs, these plant extracts possess active ingredients that are chemicals and thus highly effective under specific concentrations. However, prolonged usage of these plants extracts or in high concentrations may also be fatal to health (Hasan et al., 2017). Occasionally, some of these plants are taken in direct combination with prescribed drugs. There is a scarcity of information on the interaction of active

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components found in the plants and the prescribed drug. A direct combination of plants and drugs can bring about an unexpected concentration of their common active components, leading to adverse effects. Furthermore, traditional medicine made directly from plant products is not regulated for purity and potency.

While numerous studies have established that medicinal plants have against typhoid based on their MIC against the pathogenic organism, there is a scarcity of information on the bioactive components possessed by these plants. This document reviews the common plants used to treat typhoid fever, their bioactive components, and their health risks following their indiscriminate usage. Awareness of these components and their toxicity effects at specific dosage will lead to consumers' proper implementation of its usage.

The plants reviewed are typically used in regions where typhoid fever is endemic, typically in Africa.

2. AZADIRACHTA INDICA L

Azadirachta indica L., known commonly as Neem, is a Meliaceae member of the family (Gul et al., 2015). This plant is mostly seen growing in the tropics and semi tropics. The Neem plant has also been seen growing in islands found in the southern region of Iran. The fruit it produces is smooth and has an oval to roundish shape ranging from 14 to 28 mm (Rajakani et al., 2014). The fruit is the primary source of Neem oil used for many therapeutic purposes. Apart from *Salmonella infections*, the plant has also frequently been used in Pakistan to treat other infections caused by Gram-negative organisms such as Klebsiella and *Escherichia coli* infections (Gul et al., 2015).

2.1. Active component

The therapeutic role of *A. indica* L is a result of its rich source of different ingredients. Studies carried out by Brindha et al. (2012) demonstrates that the seeds produced by the Azadirachta indica L plant contain compounds such as azadirachtin, alkaloids, flavonoids, triterpenoids, phenols, carotenoids, steroids and ketones. The most important of its active component being used for various medical purposes is azadirachtin (Kokate et al., 2010). The leaves of the *A. indica* plant have also been shown to contain other components such as Nimbin, quercetin, ß-sitosterol and polyphenolic flavonoids, which when purified, possess both antibacterial and antifungal properties (Hossain et al., 2014). Extracts of *A. indica reported to share* similarities in antimicrobial effects to synthetic drugs. Studies carried out by Brindha et al. (2012) showed similar neem seed extract and ampicillin activity in inhibiting *Salmonella typhi* and *Pseudomonas aeroginosa*.

2.2. Toxicity

Many studies performed on animal models and clinical trials have proven the safety and toxicity of *A. indica* extract to depend on the dosage administered. Acute toxicity evaluation of neem oil extracts administered to rats showed that LD50 (median lethal dose) of neem oil was found to be 31.95 g/kg (Deng et al., 2013). Other findings on rat models have documented that *A. indica* leaf sap when administered at a low dose, resulted in an antianxiety effect but was not the case at a higher dose (Jaiswal et al., 1994). However, care should be taken when producing and administering these extracts, as contamination can also lead to poisoning. Acute neem oil intoxication causes nausea, vomiting, liver damage, and encephalopathy Lai et al. (1990).

3. HARUNGANA MADAGASCARIENSIS L

Harungana madagascariensis is a member of the family 'Hypericaceae, earlier called 'Guttiferae'. It is commonly found in Madagascar, Mauritius and tropical Africa, growing on the margins of wet forests (Orwa et al., 2009). The leaves are broad and egg-shaped, ranging from 10 to 20cm and 6 to 10 cm. The flowers produced are small and whitish; the fruits produced are also small with about 2 to 3 cm containing 2-4 seeds (Moronkola et al., 2015). In Cameroon, this plant is used not only to treat typhoid but also to treat malaria and skin diseases (More et al., 2018).

3.1. Active components

Reports by Oboh et al. (2010) documented that screening of phytochemicals in methanol and ethanol extracts obtained from stem barks of *Harungana madagascariensis* plant identified phenols, tannin, alkaloids, anthraquinone and saponin. Screening of methanol extracts from its seeds identified anthraquinones, flavonoids and aglycones, triterpenoids and terpenoids. These are bioactive compounds often used in the process of drug development.

3.2. Toxicity

Although research has shown *H. madagascariensis* to be of high medicinal value, its prolonged usage in treating diseases has to be done with great caution, taking into account its potential toxic effect. Studies on the toxicity of an ethanol extract from the fruit of *H. madagascariensis* on Wistar rats revealed inflammatory cells in the rats' portal tracts after they were treated with ethanol. Inflammation was shown to be proportional to dosage concentration and duration. At a dosage concentration of 1000 mg/kg, the greatest amount of periportal inflammation occurred (Shorinwa & Monsi, 2020).

Also, similar studies carried out by Biapa et al. (2012) on the effects of ethanol extracts of the stem barks from *H. madagascariensis* on the liver histology of rats demonstrated nephrotoxic and hepatotoxic effects occurring at specific doses. He reported that kidney inflammation, hepatocytes degeneration, and other congestive changes of kidney tissues occurred at 1.25 and 2.5 g/kg) This shows that prolonged usage of this extract should be carried out with caution.

4. GLYCYRRHIZA GLABRA

Glycyrrhiza glabra, commonly known as Licorice, is a member of the Papilionaceae family (Gul et al., 2015). Liquorice is a herbaceous plant and usually grows to a height of about one metre. The plant contains pinnate leaves of length

ranging 7 to 15 cm, having 9–17 leaflets (Bensky, 2004). Purple blooms are produced in a loose inflorescence. The fruit is oval, 2–3 cm long, and contains multiple seeds (Bensky, 2004). Like *A. indica*, the usage of Glycyrrhiza glabra is also employed to treat some Gram-negative infections caused by Klebsiella and *Escherichia coli* (Gul et al., 2015).

4.1. Active components

Glycyrrhizin, also referred to as saponin glycoside, is the major active component of the Glycyrrhiza glabra plant. This component is commonly extracted from the roots of the plant. Apart from its antibacterial activity, which makes it an effective treatment for bacterial infections, glycyrrhizin is also utilised as a preventative and therapeutic agent for a variety of significant body disorders in all age groups (Roshan, 2012). In 2013, Glycyrrhiza root extract was found to have antioxidant and hydroxyl radical scavenging properties (Yu et al., 2017). *G. glabra* has also been shown to contain other active components such as flavonoids, which enhance antimicrobial activity (Gul et al., 2015).

4.2. Toxicity

Those foods that include glycyrrhizin, a liquorice derivative, are safe at low to moderate levels, according to the FDA (Olukoga & Donaldson, 2000). Further implementations suggest that a maximum level of daily glycyrrhizin intake should range between 100 mg to 200 mg (Omar et al., 2012). The major dose-limiting toxicities of Glycyrrhiza glabra plant extracts are corticosteroids in nature. This is because its principal active ingredient, glycyrrhizin, inhibits the breakdown of cortisol. The effect produced from this breakdown process includes edema, hypokalaemia, weight gain and high blood pressure (Armanini et al., 2002). The usage of *G. glabra* plant extract or its derivatives should also be avoided during pregnancies.

5. PAULLINIA PINNATA

Paullinia pinnata, commonly referred to as "bread" or "cheese" plant, is a wood or sub-woody climber and belongs to Sapindaceae. A native of tropical America, it can also be found in the savanna zones of Africa and Madagascar. In Cameroon's West Region, P. pinnata has been extensively used in the treatment of typhoid fever, particularly in the West Region (More et al., 2018). Other African research have demonstrated the effectiveness of this herb in treating infectious disorders (Burkill, 2000). The leaf of the plant has been described traditionally to be a general panacea (Akinyemi et al., 2005). In Ivory Coast, Tanzania, Gabon, Congo and Ghana, the leaf is used by gynaecologists to ease childbirth. Still, in the same line, the leaves are also used to treat other pregnancy-related issues such as sterility, menstrual discomfort, and prevention of miscarriages (Burkill, 2000).

5.1. Active components

Phytochemicals such as phenolic compounds and flavotannin have been isolated from the leaves of *P. pinnata*. Abourashed et al. (1999) identified the presence of two flavone glycosides, ndiosmatin-7-0 and tricetin-4'-0-methyl-7-0, from the leaves of the plants. Lunga et al. (2015) demonstrated that some pure compounds such as Methylinositol screened from Paullinia plant leaves had both anti-typhoid activity and anti-oxidant properties. Azaleic acid, which has also been screened from this plant's methanol root extract, has demonstrated antibacterial activity against organisms like *Pseudomonas aeruginosa*, *E. coli*, *S. aureus*, *B. subtilis*, *M. flavus*, *S. faecalis* and resistant *S. aureus* strains (Annan et al., 2009).

5.2. Toxicity

Studies performed on animal models have proven the safety and toxicity of *P. pinnata* extracts to be dose-dependent. Reports by Salami and Makinde (2013) on the effect of methanol extracts using male Wistar rats documented the safe dose to be 200 mg/kg. Similar findings by Nnah and Uche (2014) on Wister rats showed the LD50 of ethanol leaf extract of leaves of *P. pinnata* to be 1190 mg/kg. Result of biochemical analysis following administration of methanol extracts of *P. pinnata* on male and female rats for the treatment of *Salmonella typhimurium* induced typhoid showed that the male rats were adversely affected than the female at higher dosage (446 mg/kg) with a relative alteration in organ weight (Lunga et al., 2015).

6. ALOE BARBADENSIS MILLER

Aloe barbadensis miller, commonly referred to as Aloe vera, is a perennial, succulent, cactus-like green colour plant. It is a member of the family Asphodelaceae (Liliaceae) and the genus Aloe. In areas of low rainfall and other places with limited water supply, this succulence is probably what enables the species to survive. In Greece, this plant is considered a panacea (Amar et al., 2008a). It is cultivated worldwide but mainly grows in the dry regions of Africa, Asia, Europe and America. Aloe produces two substances; a gel and a latex, which are mainly used for medicinal purposes. A study conducted by Roger et al. (2013) in Western Cameroon demonstrated its effective use as a medicinal plant in treating typhoid fever. Another study of medicinal plants conducted in Indonesia by Lelimiska et al. (2020) also highlighted Aloe vera as an alternative therapy for typhoid fever. Although many research studies have documented this plant extract's broad use as a herbal remedy, controlled trials are essential to determine its effectiveness, dosage, and toxicity-related issues.

6.1. Active components

Polymannans, acetylated mannans, anthraquinone C-glycosides, anthrones, and anthraquinone derivatives such as emodin and lectins are found in the Aloe vera leaves (Eshun & He, 2004). There are 75 possible active metabolites in this plant: vitamins and enzymes as well as minerals and

carbohydrates as well as lignin, saponins, salicylic acids, and amino acids (Atherton, 1998).

6.2. Toxicity

Even though Aloe vera has a wide range of characteristics and uses, it has some harmful consequences when used orally. An Aloe vera leaf extract that does not have its colour altered is included in the list of substances known to cause cancer or reproductive toxicity when taken orally by the OEHHA and goldenseal (OEHHA, 2015). Using Aloe vera for an extended period of time has been linked to an increased risk of colorectal cancer and electrolyte imbalances (Amar et al., 2008b). This electrolyte imbalance may be associated with its laxative effect. Adverse interactions have been observed when aloe products are used in combination with prescribed pharmaceutical drugs. Furosemide and aloe vera may raise the risk of potassium depletion and lower blood sugar levels when used together (Amar et al., 2008b). Overdose of Aloe vera may lead to intestinal cramps, ulcers or irritated bowels. Aloe vera overdose can cause colicky stomach spasms, discomfort, and the development of thin, watery faeces. According to WHO guidelines, *Aloe vera* should not be used by pregnant women except under medical supervision.

7. CASSIA SIAMEA

The Fabaceae family includes Cassia siamea, an angiosperm. However, it has spread to the continents of Africa, Latin America and Oceania. Leaf lengths range from 15 to 10 cm, with 6–14 leaflets, and the plant can reach a height of 10–12 cm (Kamagaté et al., 2014). Large, vivid yellow blooms are produced. C. siamea's leaves, stems, and roots have been used in Africa to treat malaria and other infectious disorders (Otimenyin et al., 2010). In the Northern Region of Nigeria, the plant is trendy for its local usage in treating typhoid fever (Doughari et al., 2007). The antibacterial activity of methanol extracts of *C. siamea* showed an intense growth inhibitory activity in the growth of *B. cereus*, *L. monocytogenes*, *E. coli*, *K. pneumoniae*, *P. fluorescens*, *S. typhimurium*, *S. aureus* and *Y. enterocolitica*.

7.1. Active components

Screening of the leaves, barks and stems of C. siamea has identified various phytochemicals and bioactive compounds. Typical of these compounds include chromones and polyphenols such as anthraquinones, anthrones, flavonoids, isoflavonoids, phenolics and tannins (Mohammed et al., 2013). Similar research carried out by Doughari and Okafor (Doughari et al., 2007) also identified saponins, tannins, barakol and glycosides in leaf extracts of C. siamea.

7.2. Toxicity

Based on its wide usage in herbal remedies, *C. siamea* seems less toxic. However, the toxicity of the extract is dependent on the dosage administered and the organ involved. Research on Wistar rats administered with root's aqueous extract of *C. siamea* showed that concentrations of 400 mg/kg and 1500 mg/kg were less toxic to the blood and hepatic cells, respectively. However, at concentrations higher than this, acute toxicity was observed (Mohammed et al., 2013). Other studies have depicted a relationship between the toxicity of *C. siamea* extract and the duration of administration. The clinical trials indicate that the *C. siamea* leave extracts when used continuously over six months reduced the number of humans' hematocrit and neutrophils. Findings by Lawanprasert et al. (2001) on in vitro hepatotoxicity assessment of barakol using human hepatoma cell line HepG2 shows cytotoxic effects following prolonged usage.

8. CARICA PAPAYA L

*Carica papaya (*pawpaw), is a widely used plant for medicinal purposes (Ong et al., 2011). It is a member of the family Caricaceae. The plant is believed to have originated from tropical and central America. It is a herbaceous perennial plant containing a single and unbranched stem which often grows to a height ranging 3 to 9 m (Krishna et al., 2008). The leaves are spirally arranged at the top of the trunk and measures 50 to 70 cm in diameter. The fruit is cylindrical to spherical, originally green and hard but becomes yellow and soft when ripe (Heywood et al., 2007)

8.1. Active components

Recent research has documented the presence of phytochemical compounds in different parts of the *C. papaya* plant. The occurrence and proportion of these compounds differ concerning the plant parts. Phytochemical analysis has revealed that the leaves of the *C. papaya* plant contain active components such as saponins, benzyl glucosinates, glycosides, alkaloids and phenolic compounds. The fruits contain flavonoids, minerals, and vitamins, typical of vitamins A and C (Ayoola & Adeyeye, 2010). The vast phytochemical and bioactive compounds present in the *C. papaya* plant makes it suitable for therapeutic purposes. Test performed on its root extract for antimicrobial properties shows a significant inhibitory effect against gram-positive and gram-negative bacteria growth. The highest growth inhibitory effect was observed in *Salmonella typh*i (Doughari & Okafor, 2008). A similar study has also proved aqueous and methanolic extract of *C. papaya* seeds to be effective in inhibiting the growth of Salmonella pathogen (Peter et al., 2014). Apart from *S. typhi*, *C. papaya* has also been frequently associated traditionally in the treatment of malaria. Studies carried out by Titanji et al. (2008) have reported the frequent use of *C.papaya* leaves in Cameroon's traditional treatment of malaria.

8.2. Toxicity

Though various studies have demonstrated *C. papaya* to be non-toxic, it should be noted that unripe *C. papaya* releases a latex fluid that can cause severe irritation and ulcers in the esophagus when consumed as extracts in large doses.

9. MORINGA OLEIFERA

Moringa oleifera, commonly known as horseradish tree, drumstick tree, or benzolive tree, is a tiny, fast-growing and drought-resistant deciduous tree belonging to the Moringaceae family. The roots of Moringa oleifera have a horseradish-like flavour. As a result, it can be found in the Caribbean, the Central American countries as well as most African countries. India, Ethiopia, the Philippines, and Sudan all depend on it as a food source (Fao, 2014).

To use Moringa leaves, young seed pod adn other parts of this plant for traditional herbal treatment is a common practise around the world.

9.1. Active components

Just as other plants used for medicinal purposes, studies performed on the extracts of Moringa has demonstrated the presence of a wide range of bioactive components, which makes it suitable to be used for therapeutic purposes. Extracts from leaves, flowers, and roots contain significant bioactive compounds such as polyphenols, vitamins, phenolic acids, flavonoids, isothiocyanates, tannins and saponins (Sreelatha & Padma, 2009; Vergara-Jimenez et al., 2017).

9.2. Toxicity

Although *M. oleifera* contains bioactive components that make it suitable as a therapeutic agent, care must be taken upon dosage level for consumption. At lower levels (less than or equal to1000 mg/kg), intake of M.oleifera has proven to be safe (George et al., 2012). However, *M. oleifera* has potential genotoxic properties at supra-supplementation levels of 3000 mg/kg. If Moringa is taken in excessive doses, it may interfere with prescribed medicines that alter cytochrome P450 (CYP3A4), including sitagliptin. Pregnant women are strongly recommended not to use Moringa products.

10. ALLIUM SATIVUM

Allium sativum, commonly known as Garlic, is a perennial, herbaceous flowering plant growing from a bulb formed in the base of the leaves. It belongs to Amaryllidaceae and is related to onion, leeks, and chives (Harper, 2018). The garlic plant is native to Central Asia and northeastern Iran, and it is used worldwide as a food flavouring and common dish seasoning. The bulb of garlic is also extensively used in traditional medicine, mainly in the dehydrated form, fresh or steam-distilled oil. Research conducted by Adebolu et al. (2011) demonstrated the antibacterial activity of garlic against Salmonella typhi. In Indonesia, Lelimiska et al. (2020) screened several potential plants believed to have antibacterial activity against Salmonella; *A.sativum* was shown to be one of them.

10.1. Active components

A large variety of metabolites, including organosulfur compounds such as diallyl thiosulfonate (allicin), DAS, DDS, DATS, E/Z-ajoene, S-allyl-cysteine, and S-allyl-cysteine sulfoxide (SAC), are found in garlic, which has been shown to have a wide range of bioactive properties (alliin). Other studies on active compounds from garlic have identified saponins, phenols and polysaccharides (Hang, 2005; Nagella et al., 2014).

10.2. Toxicity

Despite its general use in food seasoning and medicinal purposes, garlic and other species of Allium have been seen to cause allergic reactions to some people. Additionally, a high dose of garlic consumption produces gastrointestinal discomfort, sweating, dizziness, allergic reactions, bleeding, and menstrual irregularities (Nccih, 2012). In rare cases, anaphylaxis may occur during garlic consumption. Furthermore, interactions may occur when anticoagulant medications are taken with higher doses of garlic, leading to a higher risk of bleeding (Brown et al., 2015).

11. CONCLUSION AND RECOMMENDATION

The primary goal of this review was to assemble information on the toxicity of common typhoid fever-treating herbs. Extracts from these plants have been demonstrated to have an inhibiting impact on Salmonella typhi. Typhoid fever can be effectively treated and managed with the help of these plants, as evidenced by their pharmacological qualities. Toxic effects may develop when high quantities, prolonged use, and concurrent use with medications are combined with therapeutic plant extracts, according to the review based on in-vivo therapeutic plant extract activity.

It is recommended that these plants be used with great care and under the close supervision of ethnobotanists and herbal specialists. Finally, there is a need to subject the extracts from these plants to further studies to effectively standardise the safe dose needed in the treatment of this disease hence limiting eventual side effects most commonly related to over-dosage.

CONFLICTS OF INTEREST

The authors of this study declare that they have no competing interests in its submission and publication.

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AUTHOR CONTRIBUTIONS

Conceptualization, T.E.A, and S.P.N; Writing— original draft preparation, T.E.A, and S.P.N, Selected bibliographic sources, T.E.A, and S.P.N; T.E.A, and S.P.N was coordinated the working group; Writing-review & editing, T.E.A, and S.P.N. The manuscript has been read and approved by all of the authors.

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