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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 caused by *Salmonella typhi* and *S. paratyphi* 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 a deadly disease day by day 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 such as leaves, stems, barks and roots 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.

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There is a scarcity of information on the interaction of active 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.

Although various research has documented the anti-typhoid activity of medicinal plants based on the zone of inhibition against the causative 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 from this plant have been shown 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. Neem oil poisoning results in vomiting, hepatic toxicity, metabolic acidosis 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 carried out by Shorinwa and Monsi (2020) on the toxicity of ethanol extract from the fruit of *H. madagascariensis* on Wistar rats showed inflammatory cells in the portal tract of the ethanol-treated rats. The level of inflammation was proportional to the dosage concentration and duration. Maximum periportal inflammation occurred at a dosage concentration of 1000 mg/kg.

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 histology of the liver 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 higher doses of (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). The flowers produced in a loose inflorescence are purple. The fruit that emerges is oblong with a length ranging from 2 to 3 cm and contains several 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 the anti-bacterial activity of glycyrrhizin, which makes it helpful in treating bacterial infections, it is also used as a prophylactic and therapeutic agent for major body ailments within any age group (Roshan, 2012). In 2013, the phytochemical analysis and antioxidant activity of Glycyrrhiza root extract identified scavenging hydroxyl radical activities (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

The United States Food and Drug Administration (FAD) highlights that foods that contain liquorice and its derivatives (such as glycyrrhizin) are safe at low to moderate doses (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 due to the inhibitory effect that its main active component, glycyrrhizin, have on cortisol breakdown. 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. It is a native of tropical America and has also been seen growing in the savanna zones of tropical Africa and Madagascar. The local usage of *P. pinnata* in treating diseases has extensively been observed in the West Region of Cameroon, especially in the treatment of typhoid fever (More et al., 2018). Other studies carried out in some parts of Africa have shown this plant's usage in the treatment of infectious diseases (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*, *Escherichia col*i, *Staphylococcus aureus*, *Bacillus subtilis*, *Micrococcus flavus*, *Streptococcus faecalis* and resistant *Staphylococcus 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

The Aloe vera leaves contain phytochemicals such as acetylated mannans, polymannans, anthraquinone C-glycosides, anthrones, and anthraquinone derivatives, such as emodin and lectins (Eshun & He, 2004). This plant contains 75 potentially active constituents: vitamins, enzymes, minerals, sugars, lignin, saponins, salicylic acids and amino acids (Atherton, 1998).

6.2. Toxicity

Despite its broad spectrum of properties and applications, Aloe vera has some toxic effects associated with its oral consumption. The Office of Environmental Health Hazard Assessment (OEHHA) and goldenseal classified non-decolourized Aloe vera leaf extract among chemicals known to cause cancer or reproductive toxicity when used orally (OEHHA, 2015). Prolonged use of Aloe vera has been shown to cause electrolyte imbalances (low potassium levels) and increase the risk of colorectal cancer (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. Aloe vera in combination with furosemide may increase the risk of potassium depletion and decrease blood sugar levels (Amar et al., 2008b). Overdose of Aloe vera may lead to intestinal cramps, ulcers or irritated bowels. Additionally, colicky abdominal spasms, pain, and the formation of thin, watery stools can occur following *Aloe vera* overdose. According to WHO guidelines, *Aloe vera* should not be used by pregnant women except under medical supervision.

7. CASSIA SIAMEA

Cassia siamea is an angiosperm and a member of the family Fabaceae. It is a native of Southeast Asia though it has been widely distributed in Africa, Latin America, and Oceania. The plant often grows to a height of 10 to 12 cm, with leaves of length ranging from 15 to 10 cm, with 6–14 leaflets (Kamagaté et al., 2014). The flowers produced are bright yellow and large. Medicinally, the leaves, stems, and roots of *C. siamea* have been used to treat malaria and infectious diseases in some tropical regions of Africa (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). Studies on the antibacterial activity of methanol extracts of *C. siamea* showed an intense growth inhibitory activity in the growth of *Bacillus cereus*, *Listeria monocytogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas fluorescens*, *Salmonella typhimurium*, *Staphylococcus aureus* and *Yersinia 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. Findings based on clinical trials indicate that the crude extracts of the leaves of *C. siamea* 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, commonly known as 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 also referred to as horseradish tree (due to the taste of the roots, which resembles horseradish), drumstick tree (because of its long, slender, triangular seed-pods) or benzolive tree (because ben oil is extracted from the tree), is a small, fast-growing and drought-resistant deciduous tree belonging to the family Moringaceae. It is native to the Indian subcontinent but presently is found in the Caribbean islands, Central America and most African countries. It is an essential crop in India, Ethiopia, the Philippines and Sudan (Fao, 2014).

Moringa is a widely cultivated plant, and its leaves, young seed pods, bark, sap, roots, and flowers are extensively used for traditional herbal medicine.

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. At this high level, Moringa can interfere with prescribed drugs affecting cytochrome P450 (including CYP3A4) and is likely to inhibit the anti-hyperglycemic effect of sitagliptin. It is strongly advised that the usage of Moringa should be avoided during pregnancy.

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

Garlic has a wide range of bioactive compounds, some of which include: organosulfur compounds such as diallyl thiosulfonate (allicin), diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), E/Z-ajoene, S-allyl-cysteine (SAC), and S-allyl-cysteine sulfoxide (alliin) [57,58 and 59]. 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 focus of this review was to document common plants used in the treatment of typhoid fever and their toxicities. Numerous *in-vitro* studies performed have shown the inhibitory effect of extracts from these plants against *Salmonella typhi*. It is thus clear that these plants possess pharmacological properties which make them suitable for the treatment and management of typhoid fever. However, from the review based on *in-vivo* therapeutic plant extract activity using experimental animals, it is clear that the bioactive components of these plants at high concentrations, prolonged usage and concurrent intake with drugs, toxic effects may arise.

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 declare no conflict of interest in the submission and publication of this research.

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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.. All authors have read and agreed to the published version of the manuscript.

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