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A REVIEW OF COMMON PLANTS USED IN THE TREATMENT OF TYPHOID FEVER: ACTIVE COMPONENTS AND TOXICITY RELATED ISSUES

Simone Pierrette Nguimbous, Teh Exodus Akwa*
Kenyatta University, Department of Biochemistry, Microbiology and Biotechnology, Nairobi, Kenya

**Corresponding Author: Teh Exodus Akwa*
E-mail: exodusakwateh@gmail.com

Abstract
Majority of plants and their extracts are a primary source of health care in most communities. The usage of plants in the treatment of diseases has been observed in ancient times and still applicable in the present. Plants extracts are used due to their easy availability and affordability. Some of these extracts are being sold locally in markets while others 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 negative effects and the downside following the consumption of these products remain unknown. Moreover, the 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. In most developing countries especially Africa, traditional methods involving plant extracts have mostly been employed in the treatment of typhoid fever. Even though the extracts from these plants have proven to be efficient in the treatment of typhoid, there's currently not enough evidence to make precise dosage recommendations for each of the common plant products. This document reviews the common plants used in the treatment of typhoid fever, their active components and the toxicity related issue following their indiscriminate consumption. Knowledge of the risk and toxicity effects will lead to the control of the usage of the product by consumers. There is however a need to subject the extracts from these plants to further studies so as to effectively standardize the safe dose needed in the treatment of this disease.
Keywords: Plant extracts; Active components; Toxicity; Typhoid fever

INTRODUCTION

Typhoid fever caused by *Salmonella typhi* and *S. paratyphi* i 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 [1]. Therapeutic agents commonly used in the treatment of typhoid includes; ciprofloxacin, ceftriaxone, cefixime chloramphenicol, trimethoprim, sulfamethoxazole or ampicillin [2]. Unfortunately, recent findings show that *Salmonella typhi* has rapidly gained resistance to these agents [3]. Thus, typhoid fever is becoming a deadly disease day by day because of the emergence of multidrug resistant *Salmonella typhi*, a situation which urges the need for the development of a more effective therapeutic agent.

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

Plants products assumed to be non-toxic have been used worldwide by herbalist and local population in the treatment of many diseases. It should be however be noted that although plants extracts are of natural origin, its usage is not completely safe. Just like synthetic drugs, theses plant extracts used possess active ingredients which are chemicals and thus highly effective under certain concentrations. However, prolonged usage of these plants extracts or in high concentrations may also be fatal to health [4]. Occasionally, some of these plants are taken in direct combination with prescribed drugs. As a result of this, no consideration is taken on the interaction between the active components found in the plants and that of the prescribed drug. Direct combination of plants and drugs can bring about an unexpected concentration of their common active components which can lead to adverse effects. Furthermore, traditional medicine made directly from plant products are not regulated for purity and potency.

There is therefore a scarcity in studies carried out on the quality control of these plants in disease therapy. Even though these plant extracts have proven to be efficient in the treatment of typhoid, there's currently not enough evidence to make precise dosage recommendations for each of the common plant products. Thus more research has to be done on the dosage required for each treatment

regimen. This paper highlights the common plants used in the treatment of typhoid fever, their active components and some of the risk following their indiscriminate usage. The awareness of the risk and toxicity effects will lead to the proper usage of the product by consumers.

Outlined below are the common plants used in the treatment of typhoid fever, their bioactive components and adverse effects resulting from indiscriminate usage

1. AZADIRACHTA INDICA L.

Azadirachta indica L. (Fig 1) which is known commonly as Neem, is a member of the family Meliaceae [5]. This plant is mostly seen growing in the tropics and semi tropics. The Neem plant have 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 with size ranging from 14 to 28 mm [6]. The fruit is the major source of the Neem oil used for many therapeutic purposes. Apart from *Salmonella* infections, the plant has also frequently been used in Pakistan for the treatment of other infections caused by Gram negative organisms such as, *Klebsiella* and *Escherichia coli* infections [5].

Fig. 1. Azadirachta indica plant (Neem)

Active components

The therapeutic role of *Azadirachta indica* L is as a result of its rich source of different ingredients. Studies carried out by Brindha et al. [7] demonstrates that the seeds produced by the *Azadirachta indica* L plant contains compounds such as azadirachtin, alkaloids, flavonoids, triperpenoids, phenols, carotenoids, steroids and ketones. The most important of its active component being used for various medical purposes is azadirachtin [8]. The leaves of *Azadirachta 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 [9]. Extracts from this plant have been shown to share similarities in antimicrobial effect to that of synthetic drugs. Studies carried out by Brindha et. al. [7] showed similar activity of neem seed extract and ampicillin in the inhibition of *Salmonella typhi* and *Pseudomonas aeroginosa*.

Toxicity

Many studies performed on animal models and clinical trials have proven the safety and toxicity of *Azadirachta indica* extracts to be dependent on the dosage administered. Acute toxicity evaluation of neem oil extracts administered to rats showed that LD50 (median lethal dose) of neem oil were found to be 31.95 g/kg [10]. Other findings on rat models have documented that *Azadirachta indica* leaf sap when administered at a low dose resulted in an antianxiety effect but was not the case at higher dose [11]. Care should however be taken when producing and administering these extracts as contamination of the extracts can also lead to poisoning. Neem oil poisoning results in vomiting, hepatic toxicity, metabolic acidosis and encephalopathy [12].

2. HARUNGANA MADAGASCARIENSIS L

Harungana madagascariensis (Fig 2) is a member of the family 'Hypericaceae, earlier called 'Guttiferae'. It is commonly found in Madagascar, Mauritius and tropical Africa growing on margins of wet forests [13]. The leaves are broad and egg shaped with length ranging 10 to 20cm and width 6 to 10 cm. The flowers produced are small and whitish; fruits produced are also small with size of about 2 to 3 cm containing 2- 4 seeds [14]. In Cameroon, this plant is used not only in the treatment of typhoid but also in the treatment of malaria and skin diseases [15].

Fig. 2. Harungana madagascariensis plant

Active components

Reports by Oboh et al. [16] 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.

Toxicity

Although research has shown *Harungana madagascariensis* to be of high medicinal value, its prolong usage in the treatment of diseases has to be done with great caution taking into accounts its potential toxic effect. Studies carried out by Shorinwa and Monsi [17] on the toxicity of ethanol extract from fruit of *Harungana madagascariensis* on wistar rats showed the presence of 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. [18] on the effects of ethanol extracts of the stem barks from Harungana madagascariensis on the histology of the liver of rats demonstrated nephrotoxic and hepatotoxic effects occurring at certain 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.

3. GLYCYRRHIZA GLABRA

Glycyrrhiza glabra (Fig 3) commonly known as Licorice is a member of the Papilionaceae family [5]. 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 [19]. The flowers produced in a loose inflorescence are purple. The fruit that emerges is oblong with length ranging from 2 to 3 cm and contains several seeds [19]. Just like *Azadirachta indica*, the usage of *Glycyrrhiza glabra* is also employed in the treatment of some Gram negative infections caused by *Klebsiella* and *Escherichia coli* [5].

Fig. 3. Glycyrrhiza glabra plant (licorice)

Active components

Glycyrrhizin also referred to as saponin glycoside is the major active component of *Glycyrrhiza glabra* plant. This component is commonly extracted from the roots of the plant. Apart from the anti-bacterial activity of glycyrrhizin making it useful in the treatment of bacteria infections, it is also used as a prophylactic and a therapeutic agent for major body ailments within any age group [20]. Studies carried out in 2013 on the phytochemical analysis and anti-oxidant activity of Glycyrrhiza root extract identified scavenging hydroxyl radical activities [21]. *Glycyrrhiza glabra* have also been shown to contain other active components such as flavonoid which possess enhance antimicrobial activity [5].

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 dose [22]. Further implementations suggest maximum level of daily glycyrrhizin intake should range between 100 mg to 200 mg [23]. The major dose-limiting toxicities of *Glycyrrhiza glabra* plant extracts are corticosteroid in nature. This is due to the inhibitory effect that its main active component, glycyrrhizin have on cortisol breakdown. The effect produced as a result of this breakdown process includes edema, hypokalaemia, weight gain and high blood pressure [24]. The usage of *Glycyrrhiza glabra* plant extract or it derivatives should also be avoided during pregnancies.

4. PAULLINIA PINNATA

Paullinia pinnata (fig 4) commonly referred to as "bread" or "cheese" plant is a wood or sub-woody climber and belong to the family 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 *Paullinia pinnata* in the treatment of diseases has greatly been observed in the West Region of Cameroon especially in the treatment of typhoid fever [15]. Other studies carried out in some parts of Africa has shown the usage of this plant in the treatment of infectious diseases [25]. The leaf of the plant has been described traditionally to be a general panacea [26]. In Ivory Coast, Tanzania, Gabon, Congo and Ghana the leaf is used by gynaecologist to ease the process of child birth. Still in the same line, the leaves are also used for treating other pregnancy related issues such as sterility, menstrual discomfort and prevention of miscarriages [25].

Fig 4. Paullinia pinnata plant

Active components

Phytochemicals such as phenolic compounds and flavotannin has been isolated from the leaves of *Paullinia pinnata*. Abourashed et al. [27] 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 [28] demonstrated that some pure compounds such Methylinositol screened from *Paullinia* plant leaves had both anti-typhoid activity and anti-oxidant property. Azaleic acid which also been screened from methanol root extract of this plant has demonstrated antibacterial activity against organisms such as *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *Micrococeusflavus*, *Streptococcus faecalis* and *resistant Staphylococcus aureus strains* [29].

Toxicity

Studies performed on animal models have proven the safety and toxicity of *Paullinia pinnata* extracts to be

dose dependent. Reports by Salami and Makinde [30]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 [31] on Wister rats showed the LD50 of ethanol leaf extract of leaves of *Paullinia pinnata* to be 1190 mg/kg. Result of biochemical analysis following administration of methanol extracts of *Paullinia 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 [28].

5. ALOE BARBADENSIS MILLER

Aloe barbadensis miller (Fig 5) 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 of 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 universal panacea [32]. 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 mostly used for medicinal purposes. A study conducted by Roger et al. [33], in Western Cameroon demonstrated its effective use as a medicinal plant in the treatment of typhoid fever. Another study of medicinal plants conducted in Indonesia by Lelimiska et al. [34] also highlighted the use of Aloe vera as an alternative therapy for typhoid fever. Although many research have documented the broad use of this plant extract as a herbal remedy, controlled trials are essential to determine its effectiveness, dosage and toxicity-related issues.

Fig 5. Aloe vera plant

Active components

The leaves of Aloe vera contain phytochemicals such as acetylated mannans, polymannans, anthraquinone C-glycosides, anthrones, and anthraquinone derivatives, such as emodin and lectins [35]. This plant contains 75 potentially active constituents: vitamins, enzymes, minerals, sugars, lignin, saponins, salicylic acids and amino acids [36].

Toxicity

Despite its wide spectrum of properties and applications, Aloe vera has some toxic effects associated with its oral consumption. The Office of Environmental Health Hazard Assessment (OEHHA) together with goldenseal, classified non-decolorized Aloe vera leaf extract among chemicals known to cause cancer or reproductive toxicity when used orally [37]. Prolonged use of Aloe vera has been shown to cause electrolyte imbalances (low potassium levels) and increase the risk of colorectal cancer [38]. 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. The use of Aloe vera in combination with furosemide may increase the risk of potassium depletion and also decrease the blood sugar level [38]. Over dose of Aloe vera may lead to intestinal cramps, ulcers or irritated bowels. Additionally, colicky abdominal spasms, pain, as well as the formation of thin, watery stools can occur following Aloe vera over dose. According to WHO guidelines, Aloe vera shoud not be used by pregnant women except under medical supervision.

6. CASSIA SIAMEA

Cassia siamea (Fig 6) is an angiosperme and a member of the family Fabaceae. It is a native of Southeast Asia though has been found to be widely distributed in Africa, Latin America and in Oceania. The plant often grows to a height of 10 to 12 cm containing leaves of length ranging 15 to 10 cm, having 6–14 leaflets [39]. The flowers produced are bright yellow and large. Medicinally, the leaves, stems and roots of *Cassia siamea* has been used in the treatment of malaria and infectious diseases in some tropical regions of Africa [40]. In the Northern Region of Nigeria, the plant is very popular for its local usage in the treatment of typhoid fever [41]. Studies performed on the antibacterial activity of methanol extracts of *C. siamea* showed a strong growth inhibitory activity in the growth of *Bacillus cereus*, *Listeria monocytogenes,Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas fluorescens*, *Salmonella typhimurium*, *Staphilococcus aureus* and *Yersinia enterocolitica*.

Fig 6. Cassia siamea plant

Active components

Screening of the leaves, barks and stems of *C. siamea* has identified various phytochemicals and bioactive compounds. Typical of these compounds includes; chromones and polyphenols such as anthraquinones, anthrones, flavonoids, isoflavonoids, phenolics and tannins) [42]. Similar research carried out by Doughari and Okafor, [41] also identified saponins, tanins, barakol and glycosides in leaf extracts of *C. siamea.*

Toxicity

Based on its wide usage in herbal remedy, *Cassia siamea* seems less toxic. However, the toxicity of the extract has shown to be dependent on the dosage administered and the organ involved. Research carried out on wistar rats administered with root's aqueous extract of Cassia 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 [42]. Other studies have depicted a relationship between the toxicity of C. siamea extract and duration of administration. Findings based on clinical trials indicates that the crude extracts of the leaves of *Cassia siamea* when used continuously over a period of six months reduced the number of humans' hematocrit and neutrophils. Findings by Lawanprasert et al. [43] on in vitro hepatotoxicity assessment of barakol using human hepatoma cell line HepG2 shows cytotoxic effects following prolonged usage.

7. CARICA PAPAYA L

Carica papaya (Fig 7) commonly known as pawpaw is one of the widely used plant for medicinal purposes [44]. 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 9m [45]. 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 in shape, originally green and hard but becomes yellow and soft when ripe [46]

Fig 7. Carica papaya

Active components

Several research has documented the presence of phytochemical compounds in different parts of *Carica papaya* plant. The occurrence and proportion of these compounds differ with respect to the plant parts. Phytochemical analysis has revealed that the leaves of *Carica papaya* plant contains active components such as saponins, benzyl glucosinates, glycosides, alkaloids and phenolic compounds. The fruits contains flavonoids, minerals and vitamins, typical of which is vitamin A and C [47]. The vast phytochemical and bioactive compounds present in the *Carica papaya* plant makes it suitable for therapeutic purposes. Test performed on its root extract for antimicrobial properties shows a significant inhibitory effect against growth of gram positive and gram negative bacteria. Highest growth inhibitory effect was observed on *Salmonella typhi* [48]. Similar study has also proved aqueous and methanolic extract of Carica papaya seeds to be effective in inhibiting the growth of *Salmonella* pathogen [49]. Apart from *Salmonela typhi*, *Carica papaya* has also been frequently associated traditionally in the treatment of malaria. Studies carried out by Titanji et al. [50] has reported the frequent usage of *Carica papaya* leaves in the traditional treatment of malaria in Cameroon.

Toxicity

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

8. MORINGA OLEIFERA

Moringa oleifera (fig 8) also referred to as horse radish tree (due to the taste of the roots, which resembles horseradish), drumstick tree (because of its long, slender, triangular seed-pods) or benzolive tree (due to the fact that 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 important crop in India, Ethiopia, the Philippines and Sudan [51].

Fig 8. Moringa oleifera

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

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 bioactive compounds in significant amounts such as such polyphenols, vitamins, phenolic acids, flavonoids, isothiocyanates, tannins and saponins [52,53].

Toxicity

Although *Moringa oleifera* contains bioactive components which makes it suitable as a therapeutic agent, care have to be taken upon dosage level for consumption. At lower levels (less than or equal to1000 mg/kg), intake of Moringa oleifera has proven to be safe [54]. However, *Moringa oleifera* has potential genotoxic properties at supra-supplementation levels of 3000 mg/kg. At this high level, Moringa has the ability to 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.

9. 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 the family Amaryllidaceae and is related to onion, leeks, and chives [55]. Garlic plant is native to Central Asia and north eastern Iran and it's used worldwide as a food flavouring and common dish seasoning. The bulb of garlic is also extensively used in traditional medicine, mostly in the dehydrated form, fresh or as a steam-distilled oil. A research conducted by Adebolu et al. [56], demonstrated the antibacterial activity of garlic against *Salmonella typhi*. In Indonesia, Lelimiska et al. [34] screened several potential plants believed to have antibacterial activity against *Salmonella*, *Allium sativum* was shown to be one of them.

Fig 9. Allium sativum

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 has identified saponins, phenols and polysaccharides [60,61].

Toxicity

Despite its broad use in food seasoning and medicinal purposes, garlic and other species of Allium have been seen to cause allergic reactions to some people. Additionally, high dose of garlic consumption produces effects such as gastrointestinal discomfort, sweating, dizziness, allergic reactions, bleeding, and menstrual irregularities [62]. 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 [63].

Conclusion and Recommendation

The focus on 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, the review demonstrates that though this plants are of medicinal value, at high dosage, prolonged usage and concurrent intake with drugs, toxic effects may arise.

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

CONFLICT OF INTEREST

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

CONSENT FOR PUBLICATION

On behalf of the other authors, I (Corresponding Author) confirm that the manuscript has been read and is approved for submission

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