Original Research Article

Herbal medicines used in the treatment of typhoid in the Ga East Municipality of Ghana

Abstract

In Ghana, majority of the people patronize herbal medicines for the treatment of both chronic and acute ailments as well as infectious and noninfectious diseases. As such, herbal medicinal use in the treatment of enteric (typhoid) fever is very widespread. This study therefore investigates anti-typhoidal herbal medicinal formulations for sale on the Ghanaian market in regards to the contents on the product labels and assesses the various active plant components in the light of documented evidence of their use in the treatment of typhoid. Herbal products for the treatment of typhoid were sampled and assessed for the type of formulation, plant and non-plant constituents, dosage, indications, treatment duration and contraindications. Majority of the products (87 %, n=16) had FDA-Ghana Registration numbers whilst 13 % had none. These anti-typhoid formulations were simultaneously recommended for the treatment of malaria (56 %) (9 out of 16 products), jaundice (31 %), various types of pains (body pains, headache, menstrual pains) (8 %), stress (8 %) and fatigue (8 %). All the preparations had more than one plant as its active constituent. Forty four percent (44%) contained 2 plants species as the active ingredients, 37 % contained between 3 to 5 plant species, 13 % contained 6 to 10 plant species and 6 % contained more than 10 plant species. The most frequently occurring active plant constituents of these products were *Carica papaya* L. (Caricaceae), *Morinda lucida*. (Rubiaceae), *Citrus aurantifolia* (Rutaceae), *Vernonia amygdalina* (Compositae) and *Azadirachta indica* (Meliaceae). Thirty five different plant species belonging to 25 families were found to be present in these products. A literature search on these plants species showed that their use in the treatment of typhoid is well documented.

Keywords: typhoid fever, anti-typhoid herbal medicinal formulations, active plant constituents

List of abbreviations: FDA (Food and Drugs Authority of Ghana), nontyphoidal Salmonella (NTS)

1. Introduction

Typhoid fever, a common and sometimes fatal infection of both adults and children that causes bacteremia and inflammatory destruction of the intestine and other organs, is endemic countries, especially throughout Asia and Africa [1]. Chloramphenicol has been the treatment of choice for typhoid fever for 40 years, but the widespread emergence of multi-drug resistant *Salmonella typhi* (resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole) has necessitated the search for other therapeutic options [2]. Currently ciprofloxacin is the Drug of Choice in the treatment of enteric fever in Ghana. Alternatives such as azithromycin and ceftriazone are also recommended [3].

Typhoid fever, caused by the bacterium *Salmonella enterica* serovar typhi (*S. typhi*), has become rare in industrialized countries, yet it remains a major cause of enteric disease in children in developing countries [1], resulting in an estimated incidence of 50 cases per 100,000 persons per year, predominantly in young school-age children [4]. Globally, it is estimated that typhoid accounts for 16 million cases each year, resulting in over 600,000 deaths [5]. Typhoid fever therefore continues to be a public health problem in sub-Saharan Africa. The disease is common in developing countries and concomitant with poor public health and low socio economic indices [6]. Residents of poor communities lacking good water and sanitation system are those mostly affected. It is estimated that a total of 400,000 cases occur annually in Africa, an incidence of 50 per 100,000 persons per year [7, 8]. In Sub-Saharan Africa invasive nontyphoidal salmonella (NTS) is also a major cause of bacteremia in adults and children with an estimated occurrence of 175-388 cases per 100,000 children and 200-7500 cases per 100,000 HIV infected adults annually. In Ghana, typhoid fever ranks among the leading 20 causes of outpatient illness, accounting for 0.92 % of hospital admissions [9].

It is estimated that over 80 % of people in developing countries use herbal medicines for their primary healthcare [10]. As many as 70 % Ghana's population is estimated to rely on traditional medicine for their primary healthcare [11]. Correspondingly, majority of patients in Ghana patronize herbal medicines for the treatment of typhoid fever, hence the availability of a wide range of herbal medicines used in the treatment of typhoid fever. Concomitantly,

these same medicines are very often used to treat other common ailments such as malaria, jaundice etc. The widespread patronage of these herbal medicines explains the high rate of advertisements of these products on radio, television and other social media. This study therefore sought to determine the various types of herbal medicinal formulations used in the treatment of typhoid fever on the Ghanaian market and appraises these products via their product labels.

2. Methods

2.1. Drug collection

Between the periods of January – March of 2016, fifteen Pharmacies and six Herbal Medicines Retail Shops within the Ga East Municipality, Accra-Ghana, were visited and all herbal medicines indicated for the treatment of typhoid fever were purchased. Only herbal medicines that had FDA (Food and Drugs Authority of Ghana) registration numbers were bought. Those without FDA registration numbers were however noted. Sampling was stopped when no new anti-typhoid formulations were being discovered.

2.2. Sampling Site

All the herbal products were collected within Haatso, Dome and Ashongman communities located within the Ga East Municipality of Accra Ghana (5° 44′ 17″ N, 0° 11′ 42″ W5.738056, -0.195). According to the Ghana Statistical Service, 2010 Population and Housing Census on the Ga East Municipality, it is located at the northern part of the Greater Accra Region and covers a land area of about 85.7 square kilometers. The population is almost 148,000. Males constitute 49 % and females represent 51 %. It has 40.3% of the population below 20 years. The population density of the Ga Municipal area stands at 1,725 persons per square kilometer. Households in the Municipal Area are more of extended family (56.2%) than nuclear family (43.8%). Almost 97.5 % of the population in the Municipal Area is Ghanaians. Nearly 60 % are literate. Of the employed population, 35.1 % are engaged as service and sales workers while 22.6 % are craft workers and traders [12].

2.3. Appraisal of product labels

The products were given unique codes for identification and were appraised in regards to contents on their labels. Information used to assess the product labels included the presence or absence of FDA registration numbers, place of manufacture, type of formulation (solid or liquid), the plant and non-plant constituents present, the adult dosage per day, the various indications and duration of treatment and the contraindications. The acceptable scientific names of the active plants constituents as stated on the product labels were determined by searching in online taxonomic sources such as The Plant List (TPL) (http://www.theplantlist.org/) and International Plant Name Index (www.ipni.org).

3.0. Results

Of all the anti-typhoidal finished formulations sampled on the market, most had been registered by the Food and Drugs Authority of Ghana, and this was indicated by the presence of FDA registered numbers on the products. Figure 1 below, displays the percentage of products that had FDA registered numbers and those that did not have.

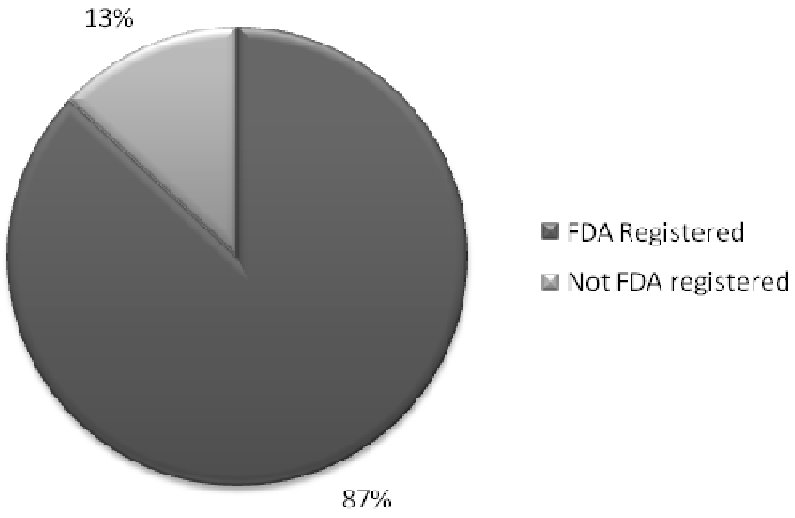

Figure 1: Proportion of Anti-typhoidal herbal medicinal products sold within the Ga East Municipality having FDA (Food and Drugs Authority of Ghana) registered numbers and those that did not have, as percentage of the number of product (n = 16).

The cost of these herbal preparations ranged from 7 to 15 Ghana Cedis, with an average cost of 10 Ghana Cedis per product. All the herbal preparations were formulated as liquid decoctions, ranging from 180 mL to 1000 mL volumes. The adult daily doses on these products ranged from 45 mL to 300 mL with an average volume of 157 mL to be consumed daily. Measurements of the daily doses were stated as tablespoonfuls, millilitres or in most instances a combination of both tablespoonfuls and millilitres. Figure 2 below, summarizes the percentage of products labeled as such.

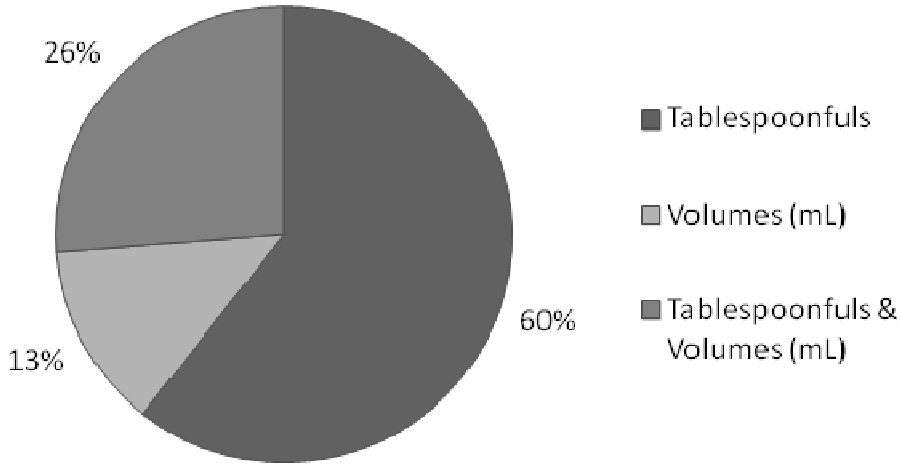

Figure 2: Measurement of doses of anti-typhoid herbal formulations; tablespoonfuls, volumes (mL) or stated as both tablespoonfuls and volumes (mL). Results presented as percentage of the total number of products (n = 16).

All the products encountered on the market were locally manufactured within the country (Ghana), with 71 % being manufactured in Accra and the other 19 % being manufactured within the Ashanti Region of Ghana. The duration of treatment as indicated on the product label ranged from one to three weeks. On 38 % of the products, the duration of treatment was not stated at all. The herbal preparations sold for the treatment of typhoid was in all cases simultaneously used to treat at least one other disease condition, namely malaria, jaundice,

pains (body pains, menstrual pains and headache), fatigue and stress. Figure 3 displays the percentage of these products that were indicated for the simultaneous treatment of particular conditions. On 56 % of the products, indications for the treatment of malaria were also made, while on 31 % of the products, treatment of jaundice was also recommended.

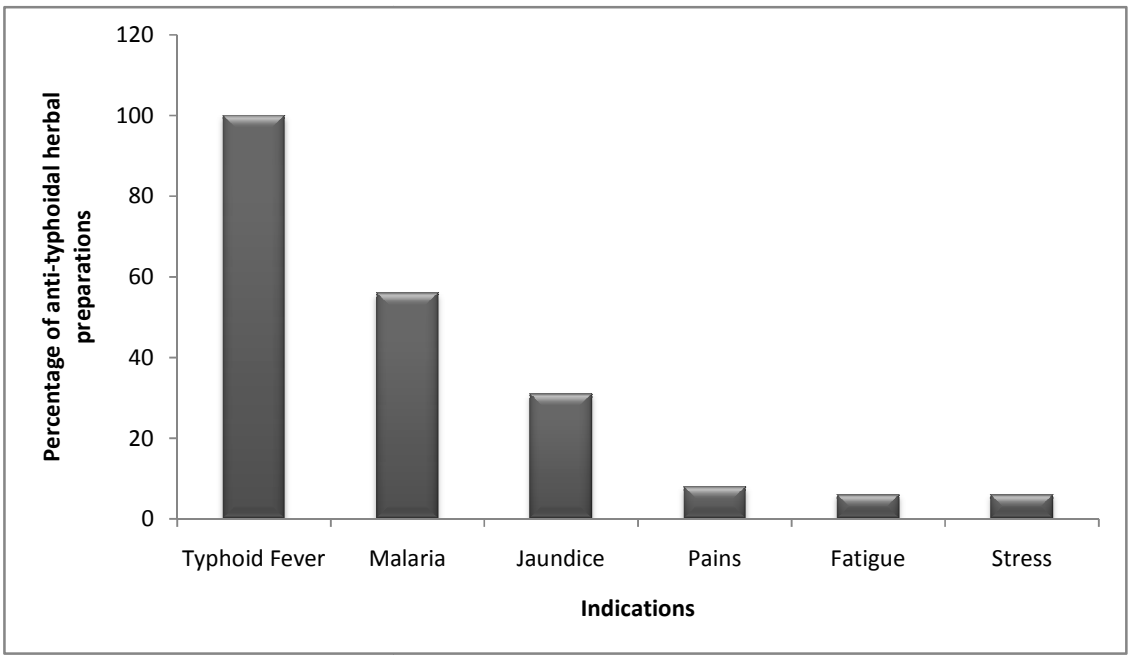

Figure 3: Indications for which anti-typhoidal herbal medicinal preparations

An assessment of the contraindications for these products showed that all the products were contraindicated in pregnancy, lactating mothers and children below either 6 yrs or 12 yrs of age. No other groups of people were indicated as being contraindicated.

Of all the products (100 %) that were appraised, the active components were stated to be plant extracts. No artificial constituents or excipients in the form of preservatives, flavours or sweeteners were indicated to be present. The number of different plant species used to formulate these products ranged from two to twelve different plants. The products contained an average of four different plants species per formulation. Figure 4 displays a breakdown of the percentage of products containing the different number of plant species. Some particular plant species were identified to be present in a number of these formulated products while others were unique to only one product. Table 1 below contains the various plant species

identified in the herbal preparations. A total of 39 plant species belonging to 25 families were identified to be used for the formulation of herbal medicines used for treatment of typhoid fever in Ghana.

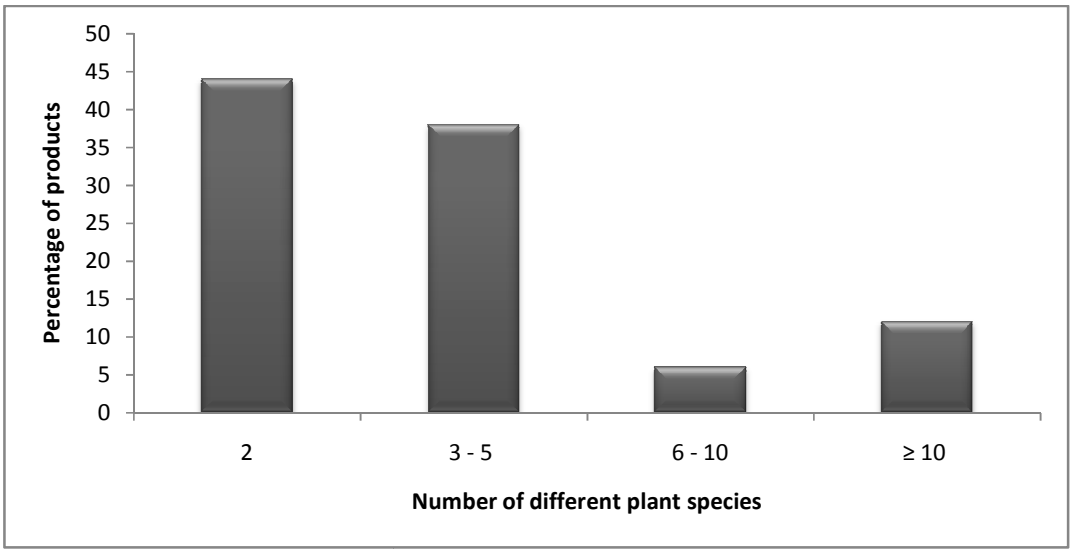

Figure 4: The percentage of products containing 2, 3 - 5, 6 - 10 and more than 10 different plant species as the active ingredients.

Table 1: Active plant constituents in anti-typhoid herbal medicinal formulations. Group I (very frequently occurring plant species, recorded more than 3 - 6 times on the products) and Group II (less frequently occurring plant species, recorded 1-2 times on the products).

Group I	
Carica papaya L. (family Caricaceae)	*Morinda lucida* Benth. (family Rubiaceae)
Citrus aurantifolia (family Rutaceae)	*Vernonia amygdalina* Delile. (family Compositae)
Azadirachta indica A. Juss (family Meliaceae)	*Cassia alata L.*(family Caesalpiniaceae)
Khaya senegalensis (Desv.) A. Juss (family Meliaceae)	*Momordica charantia L.* (family Curcubitaceae)
Group II	
Persea americana Mill. (family Lauraceae)	*Cocos nucifera* L. (family Araceae)
Phylanthus fratenus G.L. Webster (family Phyllantiaceae)	*Khaya ivorensis* A. Cheo (family Meliaceae)
Trema orientalis L. Blume (family Cannabeceae)	*Cryptolepis sanguinolenta (*Lindl.) Schltr (family Apocynaceae)
Psidium guajava L. (family Myrtaceae)	*Cymbopogon citrates* DC. (family Apocynaceae)

Pycnanthus angolensis (Welw.) Warb, (family Myristicaceae)	*Lantana camara* L. (family Verbanaceae)
Rauwolfia vomitoria Afzel (family Anarcadiaceae)	*Mangifera indica L.* (family Anarcadiaceae)
Spondiasis mombin L.(family Anacardiaceae)	*Cassia sieberiana* DC. (family Leguminosae)
Carapa procera DC. (family Meliaceae)	*Nauclea latifolia* Sm. (family Rubiaceae)
Bidens pilosa L. (family Asteraceae)	*Ocimum viridi Willd.*(family Lamiaceae)
Alstonia boonei De Wild (family Apocynaceae)	*Paullina pinata* (family Sapindaceae)
Aloe schweinfurthii Baker (family Aloaceae)	*Zingiber officinale* Roscoe (family Zingiberaceae)
Ocimum gratissimum (family Lamiaceae)	*Cnestis ferruginea* Vahl ex DC.(family Connarceae)
Cassia siamea Lam.(family Caesalpiniaceae)	*Vitex grandifolia* Gürke (family Lamiaceae)
Anthocleista nobilis G. Don (family Gentianaceae)	

Several errors in the names of the active plant constituents were discovered. A number of plant names on the product labels could not be readily identified or were wrongly spelt. Some labels mentioned only the plant genus but failed to state the particular species. After online verification of the plant names, literature search showed that out of the 39 plants identified, anti-typhoid activity has been documented for at least 89% (32), (Table 2).

Table 2. Literature review on plants

Species	Cross-reference
Aloe schweinfurthii	No reference found.
Alstonia boonei	The ethanol extract of this plant showed better antibacterial activity than the water, methanol and hexane extracts against *S. typhi* [13].
Anthocleista nobilis G. Don	*A. nobilis is* commonly used for treating typhoid fever, amongst several other diseases in North-Central Nigeria [14].
Anthocleista vogelii	Both the ethanol and aqueous extracts of the leaves had good antibacterial effect against *S. typhi* when compared to Chloramphenicol [15].
Azadirachta indica	When the antibacterial activity of *A. indica* (Neem) was evaluated, the methanolic leaf extracts showed the highest zone of inhibition against salmonella as compared to other extracts [16].
Bidens pilosa	*B. pilosa* is part of a number of plant species traditionally used in the management of typhoid fever in the Bamboutos Division of the West Region of Cameroon [17].
Carapa procera	*C. procera* is part of the Cameroonian pharmacopeia which when evaluated against gastroenteritis-causing bacteria including *S. typhi*, the crude extracts and methanolic fractions of the leaves and barks were active against four (4) bacterial species including *S. typhi* and *S. paratyphi*. Active extracts and fractions gave MICs ranging from 2.5

	to 10 mg/mL [18].
Carica papaya	The seeds of *C. papaya* are effective against *E. coli, Salmonella* and *Staphylococcus* infections. While the leaf and stem extracts have demonstrated high activities against Gram negative bacteria and Gram positive bacteria, with the highest activity demonstrated against *S. typhi*. This study therefore recommended that *C. papaya* may be used for the treatment of gastroenteritis, urethritis, otitis media, typhoid fever and wound infections [19].
Cassia alata(Senna alata)	The Bamboutos division in Cameroon uses this plant in the treatment of typhoid. This plant showed the highest zones of inhibition with diameter of 24, 22.5 and 20.5 mm against *S. paratyphi A, S. paratyphi B and S. typhi* respectively at 160 mg/mL concentration [20].
Cassia siamea (Senna siamea)	The ethanol and ethyl acetate extracts showed inhibition against *S. typhi* [21].
Cassia sieberiana	Ethanol and chloroform extracts of the leaves of *C. siberiana* showed activity against *S. typhi* at 100 mg/mL.
Citrus aurantifolia	This plant is widely used in West Africa for its antimicrobial activity against gastrointestinal pathogens including *Salmonella* [22, 23].
Cnestis ferruginea	The ethanol extracts of the stem of *C. ferruginea* demonstrated activity against various bacteria including Salmonella. MIC and MBC against the bacterial isolates were in the range of 3.2 – 6.3 mg/mL [24].
Cocos nucifera	*C. nucifera* mesocarp powder showed very high activity against *Salmonella typhi* [25].
Cryptolepis sanguinolenta	A 2 mg/mL each of 70% ethanol, hot and cold aqueous extract of *C. sanguinolenta* exhibited activity against *S. typhimurium,* three strains each of *Salmonella typhi* and several other microorganisms [26].
Cymbopogon citratus	*C. citrates* was documented in an ethnomedicinal survey of plants used for the treatment of typhoid fever in Ijebu Ode Local Government Area of Ogun State Nigeria [27]. It was also observed in another study to possess high antimicrobial activity against *S. typhi* [28].
Khaya senegalensis	The ethanol and aqueous extracts of the stem bark extracts of *K. senegalensis* showed activity against *S. typhi* at a concentration of 50 mg/mL with an inhibition zone of 15 mm respectively [29].
Khaya ivorensis	Reference not found.
Lantana camara	*L. camara* has activity against *S. gallinarum* with MIC starting at 5 mg/mL [30].
Mangifera indica	Aqueous extract of *M. indica* showed good antisalmonella activity against clinical isolates of *S. typhi,* with 98.8% inhibition at 200 µg/mL concentration. IC50 required for killing Salmonella ranged from 101.3 to 800 µg/mL [31], other studies have also supported the anti-typhoid activity of this plant [32].
Momordica charantia	Marked reduction in infection level was observed in rats treated with extracts from *M. charantia* when compared to standard drugs [33].
Morinda lucida	The water and chloroform extracts of leaves of *M. lucida* has produced antibacterial effects comparable to those of standard

	antibiotics against *S. typhi* and other microorganism [34]. The stem bark, roots and leaves infusions are also documented to be used as an anti-dysentery [35].
Nauclea latifolia	The aqueous and alcoholic extracts of the leaves and roots of *N. latifolia* showed no appreciable inhibitory effect against *S. typhi* [36].
Ocimum gratissimum	The steam distillation extract of *O. gratissimum* has shown activity at 0.01% against *S. typhimurium* and 0.001% against *S. typhi* [37].
Ocimum viride	Reference not found.
Paullina piñata	Reference not found.
Persea americana	The ethyl acetate, chloroform and methanol extracts did not demonstrated pronounced activity against *S. typhi* [38].
Phylanthus fratenus	The methanol extract of the root of *P. fraternus* showed maximum antibacterial activity against *S. typhi* B with a zone of inhibition of 11 mm and minimum activity against *S. typhi* A, with zone of inhibition of 10 mm [39].
Psidium guajava	The administration of 10-30 mg/100g of the aqueous extract of *P. guajava* to *S. typhi* infected rats over 12 h through the oral route produced a recovery within seven days [40].
Pycnanthus angolensis	Methanol leaf extract caused inhibition against *Salmonella* [41].
Rauwolfia vomitoria	*R. vomitoria* has a lot of medical potential in curing and preventing ailments including typhoid [42].
Spondiasis mombin	The aqueous and organic solvents extract of fresh leaves of *S. mombin* exhibited anti-microbial activity against *S. typhi* [43].
Trema orientalis	Reference not found.
Vernonia amygdalina	Aqueous, ethanol and acetone extracts of *V. amygdalina* leaf, stem and roots were tested at a concentration of 100 mg/mL against antibiotic-resistant *Salmonella* species. Aqueous extracts of the leaf, stem and roots showed no activity against antibiotic resistant *Salmonella* isolate, while the ethanol and acetone extracts showed activity rates of 20% and 17% for roots, 14.3% and 12.9% for stem, and, 15.7% and 11.4% for leaf [44]. The anti-Salmonella activity has been further confirmed by the ethanolic extract [45].
Vitex grandifolia	Ethanol extracts demonstrated broad spectrum antibacterial activity against Salmonella [46].
Zingiber officinale	Soybean oil extract of ginger showed high zone of inhibition (11.67±1.53 mm) against *Salmonella* spp [47].

4. Discussion

The wide spread use of herbal medicines in the treatment of typhoid in Ghana is a small indication of how widespread herbal medicines are used in Ghana. An estimated 80 % of rural villagers in southern Ghana rely on plants as their main medicinal source [48]. The widespread use of herbal medicines in the Coastal areas of Ghana, which includes Accra is

168 attributed to rapid urbanization in an area with a high level of endemic plant taxa and a
169 population heavily dependent on herbal medicines for their primary health care [49]. The fact
170 that all these products were manufactured locally could be indications of how traditional
171 herbal medicines are widely used within this area and the widespread belief in the efficacy of
172 these herbs. This may also indicate the high level of patronage of these products and the
173 availability of the various plant species used in the production of these products. All the
174 products were formulated as liquid decoctions. This could be indicative of probably the
175 preference for liquid formulation by the consumers or as a result of the manufacturers lacking
176 sophisticated techniques to produce the other dosage forms. Most manufacturers of herbal
177 medicines in Ghana are believed to be small to medium scale businesses. The daily dosage of
178 these products ranged from 45 to 300 mL. These daily volumes are quite high, and may be an
179 indication that the products can be better formulated so that the daily doses are smaller in
180 volumes. This may require standardization of the preparation to increase the concentration of
181 the active ingredients in the final products and improve the quality [50]. This will result in a
182 decrease in the final product volumes which currently ranges from 180 – 1000 mL. Only two
183 out of the 16 products provided measuring cups, this will promote inaccurate measurement of
184 the medicines. Measuring spoons and cups can probably be included in all the products and
185 the dosage stated in millilitres to enhance accurate measurement of doses [51].

186 The cost of these herbal preparations ranged from 7 to 15 Ghana Cedis, with an average cost
187 of 10 Ghana Cedis per product. It is generally believed that herbal medicines are inexpensive
188 [52], however, for most of these products more than one bottle of medication will need to be
189 taken before one can complete the recommended duration of treatment. Hence a critical cost
190 analysis will need to be made to really determine whether the costs of these herbal
191 preparations are lower or higher when compared to the available alternative orthodox drugs
192 such as ciprofloxacin which is the drug of choice for treating typhoid in Ghana [3]. The
193 duration of treatment as indicated on the product labels ranged from one to three weeks. On
194 38 % of the products, the duration of treatment was not stated at all. This puts the patient at a
195 high risk of either under dosage or over dosage of the medicine. Under dosage could lead to
196 treatment failure and over dosage may increase the chance of toxicity. An assessment of the
197 duration of treatment and the daily dosage showed that majority of these products will need
198 more than one product to be able to complete the recommended duration of treatment.

The anti-typhoid herbal formulations were simultaneously used for the treatment of malaria, jaundice, pains (body pains, menstrual pains and headache), fatigue and stress. A lot of Ghanaians accept that one herbal medicine could be the cure for many ailments and this notion may be the reason for which high numbers of plant species (up to 12) is found in each formulation. An average of 4 different plant species was used in formulating these products. The inclusion of several plants could mean that the products were probably formulated to multipurposely treat several ailments. Some plants on their own are also multi-purpose medicinal plants [53]. *Azadirachta indica* [54], *Vernonia amygdalina* [55], *Momordica charantia* [56], are all plants documented to have multipurpose medicinal actions and available in these preparations. The presence of a wide range of plant species (36) give a snapshot of the country's medicinal flora and, reflect the concerns about health and illness and the importance of traditional medicine among Ghanaians [49]. However, mistakes in the names of the plant species will need to be critically checked to aid in correct identification of the components. In Ghana, typhoid fever ranks among the leading 20 causes of outpatient illness, accounting for 0.92% of hospital admissions [9]. Malaria on the other hand remains hyper endemic in Ghana and is the single most important cause of mortality and morbidity especially among children under five years, pregnant women and the poor [57]. These are therefore two prevalent infections in Ghana. The rationale to combine several active plants extracts is in itself not a bad idea, but studies will have to be conducted on these herbal formulations to ascertain stability of the active components, physical and chemical interactions between the various components and safety in consuming such high numbers of different extracts (compounds). On the average, each plant extract may contain several of chemical compounds. From another reasoning, these plants extracts may be combined because the manufacturers may have very little or no clue as to the active components of the extracts. It may therefore be recommended that bioactivity guided isolation and characterization be performed on these formulations to identify the possible active plant fractions or compounds. This will result in the exclusion of unnecessary or harmful compounds or fractions from the formulation. This will make the resulting formulation safer for consumers to use and even more effective in the treatment of typhoid due to higher concentrations of the active ingredients. An assessment of the contraindications showed that all the products were contraindicated in pregnancy, lactating mothers and children below either 6 yrs or 12 yrs old. This is very useful in preventing possible toxicity in such vulnerable groups since very little or no toxicity studies may have been conducted in these

sensitive groups of patients to ascertain the product safety. However due to the wide patronage of these products, both acute and chronic toxicity studies may need to be conducted in other groups of patients. This will also ascertain the safety of these products when used in other co-morbid conditions and age groups.

No artificial constituents whether in the form of active constituents and inactive constituents such as preservatives, flavours or sweeteners were indicated to be present in the products. This may raise the question as to whether the components of these formulations are anti-microbially active enough to preserve the products for their respective shelf lives and during the usage period. All the products were aqueous based and hence the high concentration of water makes them very prone to microbiological contamination not to mention the high incidence of the presence of several microbial pathogens in herbal products and their toxins [58].

A literature search performed on the plants used in formulating these anti-typhoidal preparations (*Carica papaya* [59], *Vernonia amygdalina* [60-62], *Morinda lucida* [34, 35], *Azadirachter indica* [16] and *Citrus aurantifolia* [23] etc.) showed that their inclusion as active ingredients may be well justified.

5. Conclusions

The active plant components of the anti-typhoidal formulations seem to be well justified and probably indicate that the resulting products could be highly active. The labeling of these products can also be improved in respect of the names of the active components and directive for dosage. Improvement can also be made in terms of formulation of the products to reduce the daily dosage and product volumes.

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