Heavy metal content and health risk assessment of commonly patronized herbal medicinal preparations from the Kumasi metropolis of Ghana

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Running title: Heavy metal content of herbal medicinal products

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Abstract

Purpose

To address the question of whether users of herbal products (HPs) are exposed to harmful contaminants, we evaluated six HPs mostly patronized in Kumasi for heavy metal contamination and assessed the health risk associated with their use. This study is one of the first safety evaluation studies on finished multiherbal products in the region.

Method

Three antimalarial, two antidiabetic and one antihypertensive HPs were selected after a mini-survey and coded randomly as HP A-F. The HPs were acid digested for quantitative analysis of heavy metals using Inductively Coupled Plasma Mass Spectrometer. Hg quantification was carried out using cold vapour atomic absorption spectroscopy.

Results

The cancer risk estimation values for the carcinogenic metals ranged between $1.54x10^{-9}$ to $3.73x10^{-4}$ and were all within acceptable limits. The non-cancer health risk evaluation revealed that, some of the products pose health risk to consumers. The estimated daily intake (EDI) for As in HPF was $2.48x10^{-4}$ mg/kg/day compared to the reference limit of $1.67x10^{-4}$ mg/kg/day. HPF also had high hazard index (HI) of 5.70 (HI >1) in children as compared to 1.68 (HI >1) in adults showing a 3.4 folds increase in the health risk among the former.

Conclusion

The six polyherbal products exhibited carcinogenic risk within acceptable limits. Although, the non-carcinogenic risk assessment of products HPA to HPE suggests safety, this can only be ascertained

after further characterization of their health risks in detailed chronic toxicity studies. The high HI for product HPF suggests health risk for consumers of this product.

Keywords: Cancer risk, estimated daily intake, exposure, hazard index, hazard quotient, heavy metals, herbal medicinal products, risk assessment.

1.0 Introduction

The use of Herbal Medicines (HM) for healthcare delivery dates back in centuries, and it is likely one of the oldest methods of healthcare delivery in many parts of the world, [1]. HMs are used for preventive, curative and chronic disease management. HM forms the fabric of the healthcare systems in many low income and middle-income countries and has had an enormous contribution to the health care system in Ghana. In recent years, the production and patronage of herbal medicinal products (HMPs) in Ghana for therapeutic purposes have increased substantially, [2]. The WHO estimated that close to 80% of the developing world's population rely on herbal medicine for their basic healthcare needs, [3]. In the light of modern tools and technologies, HMs in Ghana have seen substantial improvement in dosage form formulations, packaging and reported efficacies, [4]. Medicinal value of these herbal preparations is usually due to the presence of essential phytochemicals such as tannins, alkaloids, flavonoids and phenolic compounds that serve as active compounds in these medicinal products, [5]. The phytochemicals are secondary plant metabolites produced and or stored for a variety of reasons including defence and protection against pest and diseases. In addition to the presence of active principle or compound(s), the herbal mixture may contain foreign toxic substances including pesticides and heavy metal residues which may cause a health risk to human systems and animals, [6].

Elevated heavy metal levels in medicinal plants have been associated with plants exposed to heavy metal polluted waters, the use of pesticides and other agrochemicals, plants growing along heavy traffic ways, previous dump-sites and near mining arrears, [7, 8]. When the herbal medicinal plants are processed into herbal preparations and consumed by humans, the heavy metal contaminants enter into the human system and cause health problems, [5]. It is believed that herbal medicine is one of the commonest modes of human exposure to heavy metals. Heavy metal intake through herbal products should, therefore, be regulated to avoid excessive build-ups in humans, [5, 6]. Though Ghana's Food and Drugs Authority (FDA) has been charged with controlling commodities for human use including herbal products and the organization is doing its best. Many HPs still enters the market without FDA registration and or without pre-market and post-market safety data. The FDA is also unable to carry out regular post-market surveillance of HPs on the market probably due to resource strength compared to the huge HPs on the market resulting in data gap. There is, therefore, a call for regular monitoring and surveillance studies to protect the health of the general public.

The increased use of agrochemical such as pesticides in Ghana to fight pest has increased the risk of heavy metal contamination these days and poses a health risk. The surge in the use of mercury and arsenic for small-scale illegal gold mining operations popularly known as ‘galamsey’ in the country in recent years is a major health concern both to policymakers and public health professionals. The heavy metals may finally end up in the tissues of these higher medicinal plants and into humans through the herbal preparations. Recently, waters near the Obuasi and Takwa gold mines in Ghana were found to be contaminated with heavy metals, [7, 9]. Some foodstuffs [10] and tea products [11] were also found to be contaminated with heavy metals and unsafe for consumption. Mutations in the genetic material, cancer, central nervous system disorders, liver and kidney toxicities are among the reported health problems associated with heavy metals [5]. **As, Cd, Pb and Hg** are among the most toxic metal contaminants based on previous reports, [12, 13]. Lead poisoning causes abdominal pain,

severe anaemia and haemoglobulinuria [5] and arsenic poisoning may cause skin lesions, cancer [12], diabetes and lung disease [14, 15]. Mercury poisoning has been associated with cardiovascular problems, neuropathy, tremors, nephrotoxicity, immunotoxicity, carcinogenicity and death, [13, 16]. Cadmium, on the other hand, has been associated with increased risk of hormone-dependent cancers including endometrial cancer [17], nephrotoxicity, skeletal damage and cardiovascular health problems, [18].

Due to methodological challenges and the complex nature of multi-herbal mixtures, researchers shy away from it until recently resulting in a paucity of data concerning multi-herbal preparations on the market. There is also the lack of pre-market and post-market safety and quality control data on most certified and uncertified herbal medicinal products on the Ghanaian market, [19]. The present study, therefore, determined the presence of heavy metal contaminants in six commonly used herbal medicinal products in Kumasi metropolis of Ghana and evaluated the health and cancer risks associated with their consumption.

2.0 Method

2.1 Sample selection

A mini survey was carried out among some randomly selected herbal medicine users and pharmacy shops that also sell herbal medicine on wholesale or in retail. The mini survey was carried out in Kejatia, Bantama and Ash-town districts in the Kumasi Metropolis. Herbal medicine users were asked about the anti-malarial, anti-hypertensive and anti-diabetic herbal medicinal products they go for when unwell. Also, the wholesale and retail pharmacy shops involved in the study were asked about the most patronized antimalarial, anti-diabetic and anti-hypertensive HMPs in their collections. Participation in the interview was entirely voluntarily, interviewees were free to opt out of the study

at any time, no minors were involved in this study and the minimum age of the participants was over 20 years. To partake in this mini-interview, the herbal medicine user needed to be at least 18 years and over and gave their consent and wiliness to part take in the study. Participants were asked not to give any identification numbers or their family names during the short interview. The list was compiled and tallied. The top 3 antimalarial (fig. 4A), top 2 anti-diabetics (fig. 4B) and the top 1 anti-hypertensive (fig. 4C) were selected for the heavy metal study. The six HMPs were randomly coded for ethical reasons and henceforth shall be represented by their random codes; HPA, HPB…HPF.

2.2 Wet di-acid digestion of the herbal products (HPs)

For the herbal preparations wet di-acid digestion comprising of nitric acid (HNO_3) and perchloric acid ($HClO_4$) digestion method was employed, [20 - 22]. Measurements were made in triplicate and the averages were reported.

2.3 Agilent ICP-MS 7700 series heavy metal and elemental analysis

Heavy metals and trace elements present in the digested herbal samples were analyzed using Inductively Coupled Plasma-Mass Spectrometer (ICP-MS); Agilent ICP-MS 7700x (Agilent Technologies, Inc. Hachioji-shi, Tokyo, Japan). Analytical grade calibration standards solution and blank were run prior to sample injection. All solutions used were of analytical grade. The ICP-MS 7700x has high detection power, [23-24] and the obtained results were in parts per billion (ppb) and the final results were obtained by calculating back into the undiluted solution. The Pb, As, Cd, Cr, Cu, Ni, and Mn content in the HMPs were determined using this ICP-MS instrument and standard method for metal analysis with this instrument was followed.

Instrument conditions and quality control

The instrument was rinsed with water and recalibrated after every ten runs. Linear analytical range (LAR) standards of known concentrations (cal zero, 25 ppb, 50 ppb and 100 ppb) of each metal were used as external standards. The analysis was first carried out in no gas mode (without the introduction of He gas). It was repeated in a gas mode (He gas was introduced) due to the polyvalent metals like Cr. The detector was set at analogue mode during the no gas mode analysis, but the detector was set at pulse during the gas mode analysis. The recovery for the standards of Cr, Pb, As, Cd, Mn, Cu and Ni were between 91% and 108%. The relative standard deviations between replicate analyses were all less than 6%. Continue calibration verification standard (CCV) of 25 ppb was run after every 10 samples and at the end of every sequence. The measured CCV values ranged from 23.0 ppb to 27.31 ppb (within ± 10%). The quality control parameters of all steps of validation proved the accuracy of the results, [23-25]. The limit of detection (LOD) for Cr, As, Cd, Mn, Pb, Cu and Ni was 0.004 ppm.

2.4 Mercury analysis with cold vapour atomic adsorption spectrometer (CV-AAS)

Mercury analysis and quantification was carried out on cold vapour atomic adsorption spectrometer Varian SpectrAA.240FS (Varian Inc, California, USA) equipped with cold vapour generation accessory (VGA-77) using the cold vapour technique. Mercury in the digested sample was reduced to elemental mercury using $SnCl_2$ solution as reductant and deionized water as an acid to cold vapour VGA system. Freshly prepared Hg standard solution (1 mL/L) was made by appropriate dilution and used for prepared working standard solution, [26-27]. Standard samples and blanks were analysed following the same procedure. The system plots calibration curve for the standards which it uses to determine the Hg content in the diluted sample. The final concentrations were obtained by calculating back the Hg concentrations in the original samples.

Instrument conditions and quality control for Hg

169 The Varian SpectrAA.240FS cold vapour atomic absorption spectrometer equipped with autosampler
170 was set at automix sampling mode for mercury analysis. Measurements were done as described before
171 [26-28]. The peak height measurement mode was used for the analysis. Measurements were carried
172 out in triplicate. Smoothing was set at 10 points and reading was done at 253.7 nm with a slit width
173 of 0.5R nm and a lamp current of 4.0 mA. Gain for the analysis was at 83%. Standards of 10 µg/L,
174 20 µg/L and 50 µg/L were used. Re-slope rate was 500 with 2 re-slope standards. Re-slope lower
175 limit was 85% and the upper limit was 115%. Calibration algorithm was set to linear with a lower
176 calibration limit of 75% and an upper calibration limit of 150%. Measurement time was 5.0 seconds
177 with a pre-read delay of 45 seconds. The relative standard deviation between replicate analyses ranged
178 from 2.3% to 4.4 %. The 'r' value was 0.9998. The linear absorption equation for the estimation of
179 analyte concentration (C) was

180 $$Abs = 0.01731*C + 0.01271 \quad \ldots\ldots (1)$$

181 Where Abs is the sample absorption at 253.7 nm wavelength.

182

183 **2.5 Health risk assessments**

184 **2.5.1 Estimated Daily Intake of the heavy metals**

185 The estimated daily intake (EDI) of each heavy metal (Cr, Mn, Ni, Cu, As, Cd, Pb and Hg) present
186 in the mixture was determined by the following equation [29, 30];

187 $$EDI = \frac{E_D \times C}{W_{AB}} \quad \ldots\ldots (2)$$

188 Where; EDI is the estimated daily intake of the heavy metal, C is the determined heavy metal
189 content in the HP, E_D is the daily dosage of the HP and W_{AB} is the Ghanaian average body weight;
190 (65 kg adults, 24 kg children), [30-31]. International oral reference dose values for the heavy metals
191 RfDo (mg kg^{-1} day^{-1}) used in this study were; 0.02 for Cr (VI); 0.14 for Mn; 0.02 for Ni; 0.001 for
192 Cu; 0.003 for As; 0.001 for Cd; 0.004 for Pb and 0.0001for Hg. The reference values as stated by

193 FAO/WHO (Codex Alimentarious Commission) [32], US EPA 2015 [33] and other published
194 materials [27- 30, 34].
195
196 **2.5.2 Target hazard quotient for non-carcinogenic risk**
197 The equation below was used to estimate the targeted hazard quotient (THQ) of the non-
198 carcinogenic effects of the heavy metals present in the herbal products.
199 $$THQ = \frac{EFr \times EDtot \times IFR \times C}{RfDo \times BWa \times ATn} \quad \ldots\ldots (3)$$
200 Where;
201 EFr (exposure frequency): Malaria incidence density of approximately 5 infections per person per
202 year was considered for sub-Saharan African and for this study [35]. Anti-malarials: 5 malaria
203 incidences a year and dosages as written on the product label were used. Anti-diabetic or hypertensive
204 drugs are used as stated on the product label or throughout the year due to the chronic nature of the
205 disease; 365 days a year and dosages as stated on the product label.
206
207 ED_{tot} (Length of exposure) was set to 65 years as the average for Ghanaian males and females based
208 on the average life expectancy in Ghana, adult dose as stated on the product labels starts from age 12
209 years (i.e. ED is 65-12 = 53 years) for HPA - HPE and from age 6 years (i.e. ED is 65-6 = 59 years)
210 for HPF. IFR: Dosages as indicated on the product bottles (kg/person/day). C is the concentration of
211 the contaminant metal/pesticide in the HMP (mg/kg). RfDo is the oral reference dose (mg /kg/day);
212 BWa is the adult body weight (65 kg); ATn is the average exposure time for non-carcinogens can
213 also be estimated as:
214 $$ATn = EFr \times ED_{tot} \quad \ldots\ldots (4)$$
215

If the value of THQ is less than 1, then the exposed local population (consumers) is said to be safe. But if THQ is equal to or higher than 1, is considered as not safe for human health, therefore poses potential health risk, and related interventions and protective measurements should be taken.

2.5.3 Hazard Index (HI)

To estimate the risk to human health through more than one contaminant in a given product, the HI has been developed by US EPA, 1989, [36-37]. The chronic hazard index (HI) is the sum of more than one hazard quotient for multiple toxicants in the HP. It is believed that, exposure to two or more pollutants may result in additive and/or interactive effects, [38]. Assuming the additive effects, THQs can be summed across constituents to generate a hazard index (HI) for an oral dosage pathway combination, [38].

$$\text{HI} = \sum_{n=1}^{i} \text{THQn} \quad (5)$$

Where; THQn is the targeted hazard quotient for the nth term of contaminant, HI is the hazard index

2.5.4 Cancer risk estimation

$$\text{CR} = \text{CSF} * \text{EDI} \quad (6)$$

Where, CSF is the oral carcinogenic slope factor of 0.0085 (mg/kg/day) −1 for Pb set by CalEPA (OEHHA) [39] and 1.5 (mg/kg/day)−1 for arsenic (As) set by US EPA [40]. EDI is the estimated daily intake of heavy metals. Acceptable risk levels for carcinogens range from 10^{-4} (risk of developing cancer over a human lifetime is 1 in 10,000) to 10^{-6} (risk of developing cancer over a human lifetime is 1 in 1,000,000), [22, 25].

Ethical clearance

Study participants provided a written informed consent to participate in the study. Ethical clearance for the study was issued by the University of Cape Coast Institutional Review Board (UCCIRB) (ethical approval number: UCCIRB/EXT/2017/07).

3.0 Results and discussion

The internationally established legally permitted maximum residual limits (MRLs) were obtained from the literature, [22, 32, 41-42]. The toxicant level above the established MRLs poses a health risk to consumers and vice versa. It must be stated that chromium IV and VI have different toxicities and MRL for chromium (VI) was used for this study due to its higher toxicity compared to chromium (IV). In this study, all the measured chromium was assumed to be chromium VI with a similar reason as above. In this study, the maximum residual content of Cr, Mn, Ni, Cu and As were above the MRL in all the six herbal preparations (Table 1). This indicates that these metal contents are above the legal limits to be on the market. Pb contents for HPC, HPE and HPF were also below the MRL. It must be stated, however, that the MRLs are state or country dependent and vary from one state to the other. MRLs are essential for legal purposes but not conclusive for health risk estimation due to differing consumption frequencies, dosage variations and body weight differences.

Health risk estimation based on the estimated daily intake (EDI) of the heavy metal contaminant is one of the vital health risk assessment tools. It takes into account the frequency and duration of exposure and the body weight of the exposed persons. The EDI for Cr, Mn, Ni, Cu, As, Cd, Pb, and Hg were all within the upper tolerable daily intake reference limits for HPA-HPE (Table 2). This indicates that the daily intake of these herbal products poses no short to mid-term heavy metal health risk to the public. The EDI for As was determined to be higher ($2.48*10^{-04}$ mg/kg/day) than the upper tolerable daily intake reference limit ($1.67*10^{-04}$ mg/kg/day) for HPF. This indicates that consumers of HPF are exposed to short-term to long-term arsenic health risk. Based on previous knowledge,

overexposure to arsenic is associated with risk of skin lesions, high blood pressure and diabetes mellitus [43]. There is also an increased risk of cancer [44].

The herbal products do not pose long-term health risk per the metal considered if the Hazard risk index (HRI) value is less than 1; and poses a health risk if the HRI is equal to or greater than 1. HRI for non-carcinogenic effects measures the long-term exposure of the heavy metal contaminants present in the herbal preparations. The HRI for Cr, Mn, Ni, As, Cd, Pb, and Hg, were all less than 1 (Table 3). This means that the consumption of these (HPA - HPF) poses no health risk due to these metals. However, the HRI of Cu for HPF (1.68) is greater than 1. This indicates that long-term exposure to HPF poses a health risk due to overexposure to copper. Copper is a microelement, but overexposure to this essential mineral has been reported to predispose the consumer to gastrointestinal mucosal ulcerations and bleeding, hepatic necrosis, coma, cardiotoxicity, hypotension [45], leukaemia and cancer [46]. Cd and Hg contents, on the other hand, were well below the MRL limits for all the 6 HPs.

It is known that an HI value less than 1 implies that the exposed population is unlikely to experience any adverse health effect in their lifetime. However, if the THQ (Tables 4 and 5) is equal to or higher than 1, [25, 47-48], there is a potential health risk to the exposed population and related interventions and protective measures needed to be taken to protect the population. The HI values for HPA – HPE were less than 1. This indicates the combined effects of the heavy metal contaminants present in a particular herbal preparation poses no health risk in the long term for both adults (Fig. 2) and children (Fig. 3). The HI for HPF was higher than 1 probably due to a high daily intake of Cu in this HP. This poses the consumer Cu adverse health effects especially among children due to the very high HI value (>4.5) (Fig. 3).

The total cancer risk was within the acceptable limits for all the studied herbal products (fig. 3). Acceptable risk levels for carcinogens range from 10^{-4} (risk of developing cancer over a human lifetime is 1 in 10000) to 10^{-6} (risk of developing cancer over a human lifetime is 1 in 1000000), [35]. Values of CR lower than 10^{-6} are considered as negligible, above 10^{-4} are considered to be unacceptable and lying in between 10^{-6} and 10^{-4} are considered an acceptable range, [35]. The cancer risk estimation for As and Pb present in the six herbal products ranged between the values of $1.54*10^{-09}$ (least) to $3.73*10^{-04}$ (highest) and were all within the acceptable limits. The total cancer risk due to the sum total of risk presented by the individual carcinogenic metals presents per herbal preparation was also all within the acceptable limit. This observation indicates that the consumption of these herbal products does not pose any long-term cancer risk to the public.

4.0 Conclusion

The polyherbal products (HPA – HPF) evaluated in this study exhibited carcinogenic risk within acceptable limits. The non-carcinogenic health risk assessment suggests that five of the products (HPA to HPE) may be safe. However, this safety can be ascertained only when the health risks of these products are further characterized in detailed chronic toxicity studies. The high HI recorded for HPF, on the other hand, suggests increased health risks for consumers of this product. We advise, therefore, that the use of these polyherbal products, especially HPF, should be done with much caution. We also recommend that all relevant national and international agencies should be alive to the responsibility of promoting public safety and global health by periodically reviewing and enforcing existing policies regulating the herbal medicine industry.

Note (N.B).:

The manufacturers of the herbal products including HPF have been briefed with the findings from this study. Recommendations were also made to the manufacturers to take steps in preventing metal contamination and ensure good manufacturing practices.

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Conflict of interest

The authors declare that they have no conflict of interest in carrying out any part of this work

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FIGURES AND TABLES

Table 1: Maximum heavy metal content (mg/kg) of the herbal medicinal products

Sample	Cr	Mn	Ni	Cu	As	Cd	Pb	Hg
HPA	1.34427	3.34838	0.89544	8.32478	1.28474	0.0083	0.11961	ND
HPB	1.35674	3.33046	0.94961	8.13625	1.02657	0.00832	0.13969	0.00005
HPC	1.23508	3.92038	1.21877	8.78602	1.14446	0.00866	0.08068	ND
HPD	1.24268	2.28998	0.93383	8.57095	1.01004	0.00834	0.11712	0.002739
HPE	0.29191	0.84375	0.17287	1.75486	0.25989	0.00181	0.02338	ND
HPF	1.67602	2.82811	1.20886	9.171	1.35453	0.0083	0.0733	ND
MRLs	**0.05**	**0.26**	**0.6**	**0.1**	**0.02**	**0.06**	**0.1**	**0.01**

HPA-F: herbal product A-F; MRL: maximum residual limits; ND means not detected

474

475 **Table 2**: **Estimated daily intakes (EDI) of the heavy metals**

Sample	Cr	Mn	Ni	Cu	As	Cd	Pb	Hg
HPA	$4.77*10^{-05}$	$1.19*10^{-04}$	$3.18*10^{-05}$	$2.96*10^{-04}$	$4.56*10^{-05}$	$2.95*10^{-07}$	$4.25*10^{-06}$	0
HPB	$8.35*10^{-06}$	$2.05*10^{-05}$	$5.84*10^{-06}$	$5.01*10^{-05}$	$6.32*10^{-06}$	$5.12*10^{-08}$	$8.60*10^{-07}$	$3.08*10^{-10}$
HPC	$1.47*10^{-05}$	$4.67*10^{-05}$	$1.45*10^{-05}$	$1.05*10^{-04}$	$1.36*10^{-05}$	$1.03*10^{-07}$	$9.61*10^{-07}$	0
HPD	$8.99*10^{-06}$	$1.66*10^{-05}$	$6.75*10^{-06}$	$6.20*10^{-05}$	$7.30*10^{-06}$	$6.03*10^{-08}$	$8.47*10^{-07}$	$1.98*10^{-08}$
HPE	$2.26*10^{-06}$	$6.54*10^{-06}$	$1.34*10^{-06}$	$1.36*10^{-05}$	$2.02*10^{-06}$	$1.40*10^{-08}$	$1.81*10^{-07}$	0
HPF	$3.07*10^{-04}$	$5.19*10^{-04}$	$2.22*10^{-04}$	$1.68*10^{-03}$	$2.48*10^{-04}$	$1.52*10^{-06}$	$1.34*10^{-05}$	0
					Upper tolerable daily intake Reference limits			
CA HP (mg/kg/day)	$3.33*10^{-04}$	NA	NA	NA	$1.67*10^{-04}$	$1.00*10^{-04}$	$3.33*10^{-04}$	$3.33*10^{-04}$
WA (mg/kg/day)	$8.33*10^{-04}$	$4.33*10^{-03}$	$2.33*10^{-02}$	$5.00*10^{-02}$	$3.33*10^{-04}$	$1.00*10^{-03}$	$1.67*10^{-03}$	$1.67*10^{-04}$

476 CA is for Canadian upper tolerable daily intake reference limits for finish herbal products (HP) in mg/kg
477 (bw/day),[1] and 'WA' is for WHO/FAO (mg/kg bw/day)[42].
478 HPA-F: herbal product A-F. NA means the upper tolerable daily intake reference limit for that particular
479 metal is not available from that authority/ body.
480

Table 3: Hazard risk index (HRI) for HRI for non-carcinogenic effects

Sample	Cr	Mn	Ni	Cu	As	Cd	Pb	Hg
HPA	$2.39*10^{-03}$	$8.49*10^{-04}$	$1.59*10^{-03}$	$2.96*1^{0-01}$	$1.52*1^{0-02}$	$2.95*10^{-04}$	$1.06*10^{-03}$	0
HPB	$4.17*10^{-04}$	$1.46*10^{-04}$	$2.92*10^{-04}$	$5.01*10^{-02}$	$2.11*10^{-03}$	$5.12*10^{-05}$	$2.15*10^{-04}$	$3.08*10^{-06}$
HPC	$7.35*10-^{04}$	$3.33*10-^{04}$	$7.26*10^{-04}$	$1.05*1^{0-01}$	$4.54*10^{-03}$	$1.03*10^{-04}$	$2.40*10^{-04}$	0
HPD	$4.49*10^{-04}$	$1.18*10^{-04}$	$3.38*10^{-04}$	$6.20*10^{-02}$	$2.43*10^{-03}$	$6.03*10^{-05}$	$2.12*10^{-04}$	$1.98*10^{-04}$
HPE	$1.130*10^{-04}$	$4.670*10^{-05}$	$6.70*10^{-05}$	$1.36*10^{-02}$	$6.72*10^{-04}$	$1.40*10^{-05}$	$4.53*10^{-05}$	0
HPF	$1.54*10^{-02}$	$3.71*10^{-03}$	$1.11*10^{-02}$	**1.682**	8.28^{*10-02}	$1.52*10^{-03}$	$3.36*10^{-03}$	0

HPA-F: herbal product A-F. The bolded value represents HRI value above the reference limit.

Table 4: THQ for adults using a body mass of 65 kg

Sample	Cr	Mn	Ni	Cu	As	Cd	Pb	Hg
HPA	$2.39*10^{-03}$	$8.49*10^{-04}$	$1.59*10^{-03}$	$2.96*10^{-01}$	$1.52*10^{-02}$	$2.95*10^{-04}$	$1.06*10^{-03}$	0
HPB	$4.00*10^{-05}$	$1.40*10^{-05}$	$2.80*10^{-05}$	$4.80*10^{-03}$	$2.02*10^{-04}$	$4.91*10^{-06}$	$2.06*10^{-05}$	$2.95*10^{-07}$
HPC	$2.12*10^{-04}$	$9.61*10^{-05}$	$2.09*10^{-04}$	$3.02*10^{-02}$	$1.31*10^{-03}$	$2.97*10^{-05}$	$6.92*10^{-05}$	0
HPD	$2.46*10^{-04}$	$6.48*10^{-05}$	$1.85*10^{-04}$	$3.41*10^{-02}$	$1.33*10^{-03}$	$3.30*10^{-05}$	$1.16*10^{-04}$	$1.09*10^{-04}$
HPE	$1.13*10^{-04}$	$4.67*10^{-05}$	$6.70*10^{-05}$	$1.36*10^{-02}$	$6.72*10^{-04}$	$1.40*10^{-05}$	$4.53*10^{-05}$	0
HPF	$1.54*10^{-02}$	$3.71*10^{-03}$	$1.11*10^{-02}$	**1.68**	$8.28*10^{-02}$	$1.52*10^{-03}$	$3.36*10^{-03}$	0

HPA-F: herbal product A-F; THQ: targeted hazard quotient. The bolded value represents THQ value above the reference limit.

493

494 **Table 5: THQ for kids using a body mass of 24 kg**

Sample	Cr	Mn	Ni	Cu	As	Cd	Pb	Hg
HPA	$6.46*10^{-03}$	$2.30*10^{-03}$	$4.306*10^{-03}$	$8.01*10^{-01}$	$4.12*10^{-02}$	$7.98*10^{-04}$	$2.88*10^{-03}$	0
HPB	$5.42*10^{-05}$	$1.90*10^{-05}$	$3.79*10^{-05}$	$6.50*10^{-03}$	$2.73*10^{-04}$	$6.65*10^{-06}$	$2.79*10^{-05}$	$4.00*10^{-07}$
HPC	$5.73*10^{-04}$	$2.60*10^{-04}$	$5.65*10^{-04}$	$8.15*10^{-02}$	$3.54*10^{-03}$	$8.03*10^{-05}$	$1.87*10^{-04}$	0
HPD	$3.33*10^{-04}$	$8.78*10^{-05}$	$2.51*10^{-04}$	$4.60*10^{-02}$	$1.81*10^{-03}$	$4.47*10^{-05}$	$1.57*10^{-04}$	$1.47*10^{-04}$
HPE	NA	NA	NA	NA	NA	NA	NA	NA
HPF	$4.16*10^{-02}$	$1.00*10^{-02}$	$3.00*10^{-02}$	4.56	$2.24*10^{-01}$	$4.12*10^{-03}$	$9.10*10^{-03}$	0

495 HPA-F: herbal product A-F; THQ: targeted hazard quotient; NA: not applicable, for the product
496 'HPE' is not administered to patients below 12 years.
497

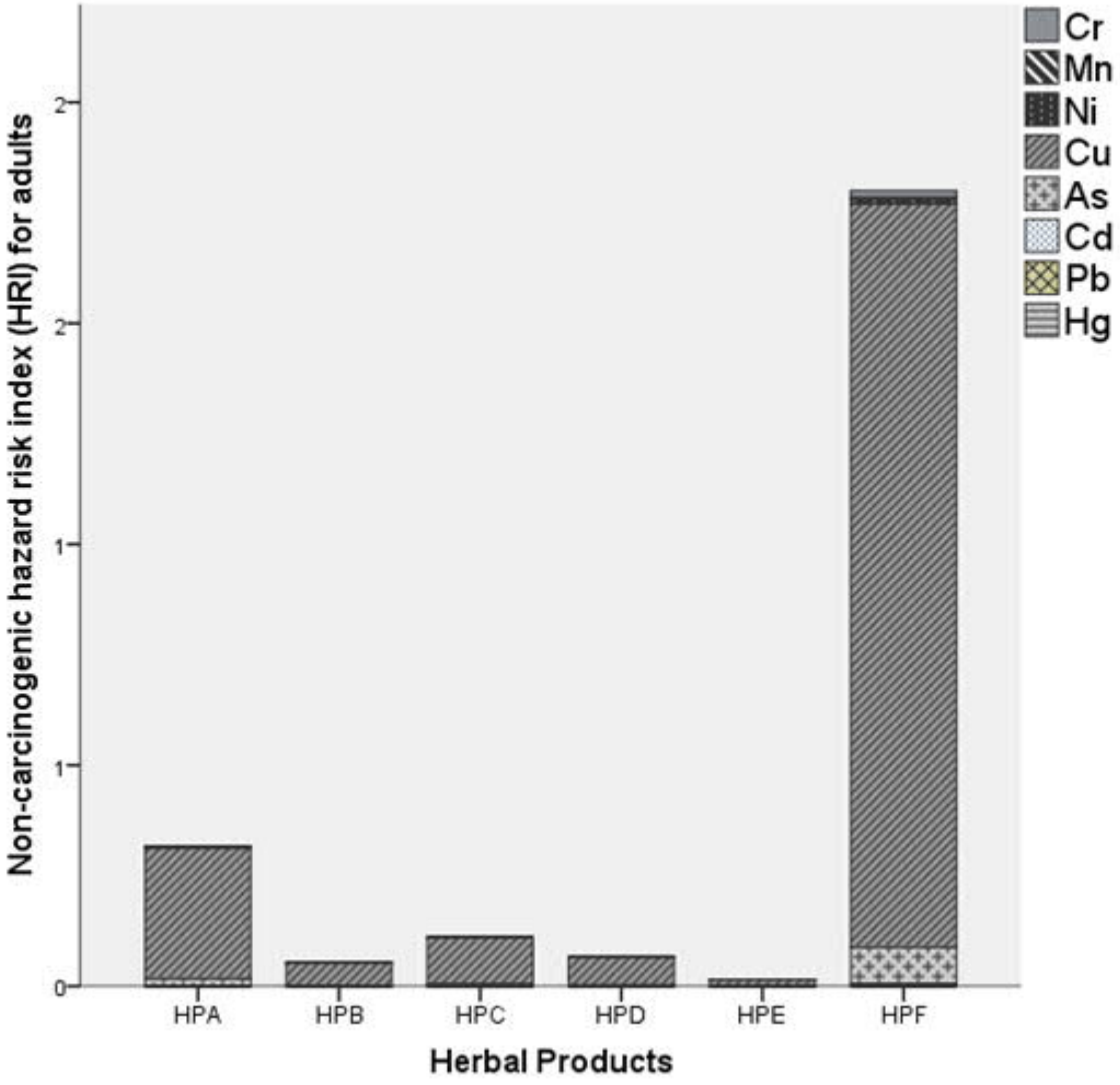

Figure 1: Chronic Hazard Index (HI) for adults.

HPF has HI value for adults greater than 1.

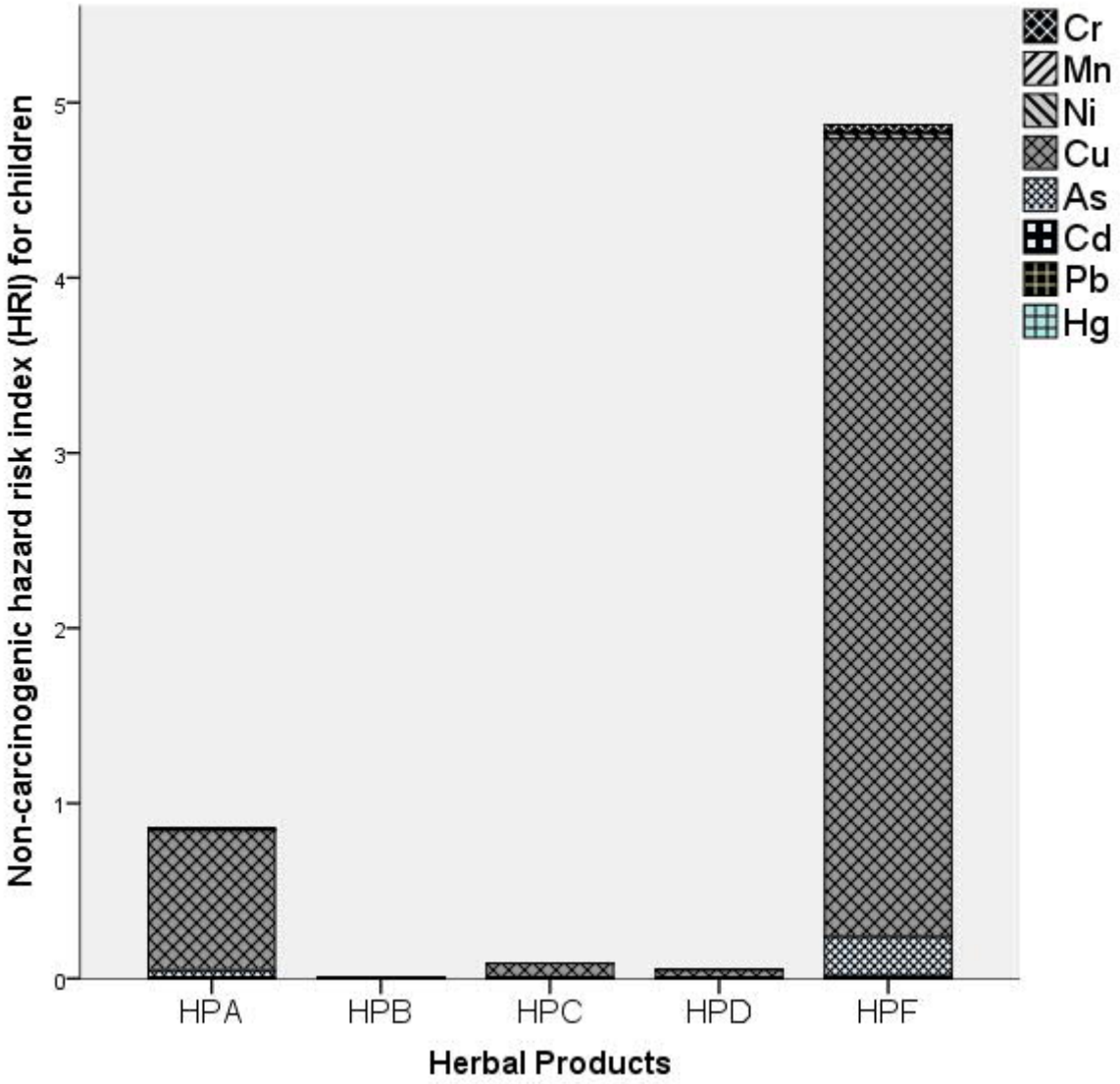

Figure 2: Chronic Hazard Index (HI) for Kids.
HPF has HI value for kids greater than 1

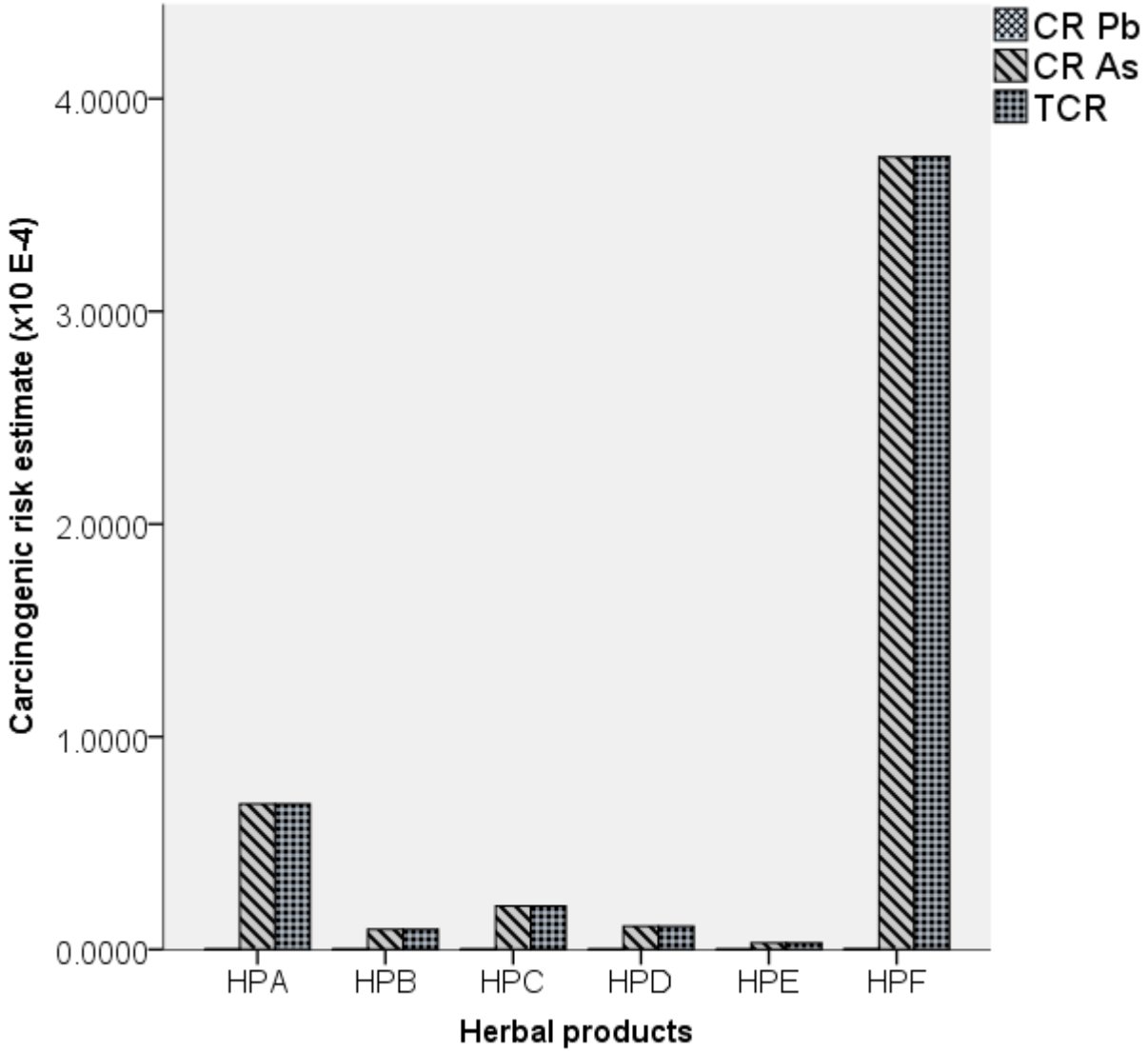

Figure 3: Estimated cancer risk (CR) for the herbal medicinal products HPA-F

The cancer risk (CR) values for herbal products A-F are all within the acceptable limit. The total cancer risk (TCR) as a result of the sum total of the individual cancer risk present by the carcinogenic metals per herbal preparation were also within the acceptable limit. It was observed that, the contribution of carcinogenic risk from As was much higher than contribution of CR from Pb in all the herbal products.

CR is for cancer risk. Total CR is for total cancer risk per herbal preparation which is the sum total of the risk from As and Pb in the herbal product.

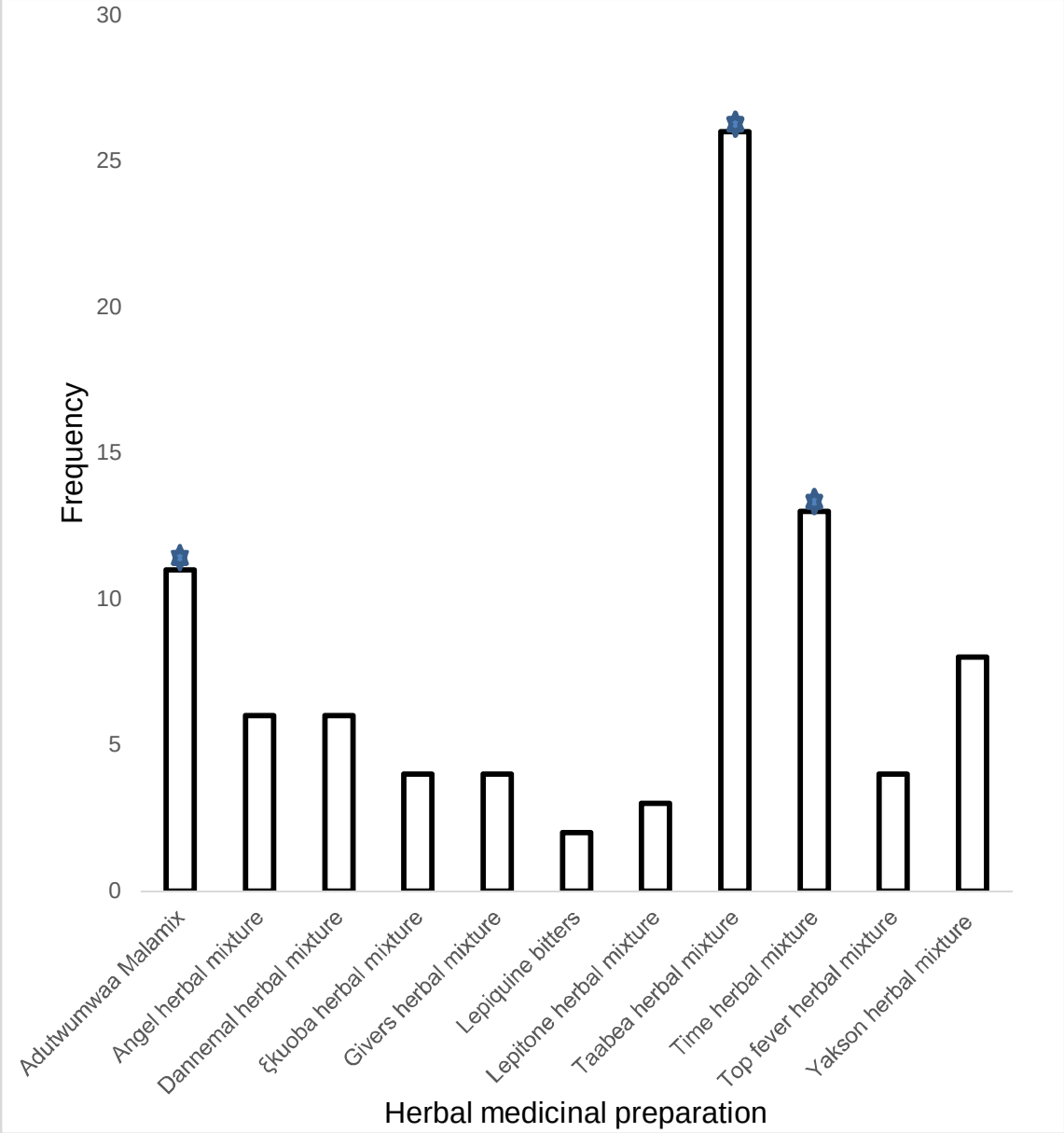

Figure 4A: Commonly patronized antimalarial herbal medicinal preparations among surveyed participants in the Kumasi metropolis of Ghana. The bars with the star represent the top-three most patronized antimalarial herbal medicinal products selected for the study.

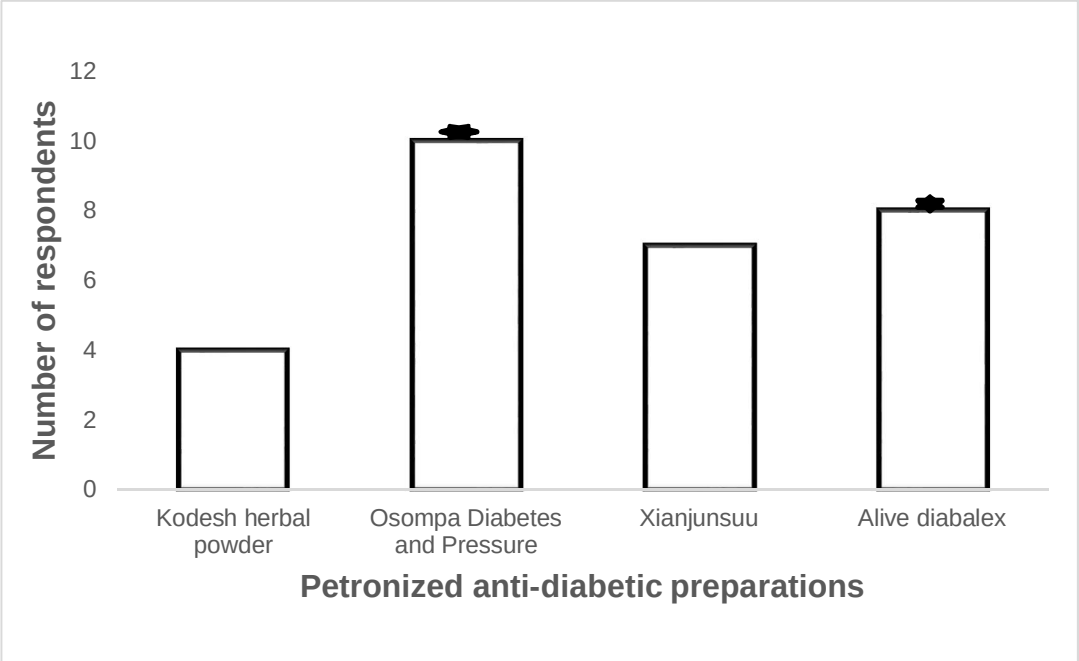

Figure 4B: Commonly patronized antidiabetic herbal medicinal preparations among surveyed participants in the Kumasi metropolis of Ghana. The bars with the star represent the top-two most patronized antidiabetic herbal medicinal products selected for the study. Number of diabetic respondents was 29.

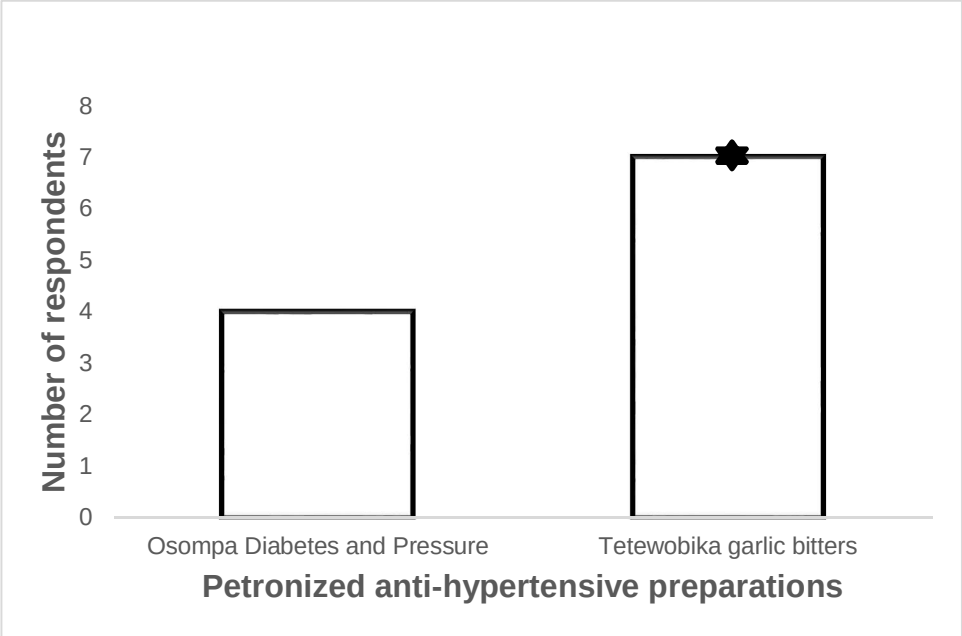

Figure 4C: Commonly patronized antihypertensive herbal medicinal preparations among surveyed participants in the Kumasi metropolis of Ghana. The number of respondents for antihypertensive herbal preparations was 11. The bar with the star represents the top-one most patronized antihypertensive herbal medicinal product selected for the study. The second most patronized product 'Osompa' diabetes and pressure' is used for the treatment of both diabetes and pressure and has already been short-listed as an anti-diabetic preparation in this study.