The aim of this study was to evaluate the post-market safety and the toxicity of commonly used herbal medicinal products (HMPs) in Kumasi, Ghana. The multidisciplinary study used in-depth qualitative interviews of herbal medicine consumers. Selected HMPs were evaluated for heavy metal and pesticide contamination. Three of the herbal products were further evaluated in a 30-day in vivo sub-chronic toxicity study using OECD 407 continuous dose method in Sprague-Dawley rats.
TOXICOLOGICAL SURVEILLANCE AND SAFETY PROFILE OF COMMONLY USED HERBAL MEDICINAL PRODUCTS IN KUMASI METROPOLIS OF GHANA
Frank Adusei-Mensah

TOXICOLOGICAL SURVEILLANCE AND SAFETY PROFILE OF COMMONLY USED HERBAL MEDICINAL PRODUCTS IN KUMASI METROPOLIS OF GHANA

To be presented by the permission of the Faculty of Health Sciences, University of Eastern Finland for public examination in Medistudia MS300 Auditorium, Kuopio on 17th September 2020, at 12 o’clock noon.

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2020
ABSTRACT

The use of plant-based systems in health care is a globally known practice for centuries. Plants produce secondary metabolites, which compounds have been harnessed for various purposes including control of different human diseases and for the discovery and development of pharmaceutical drugs. Despite the natural source of plant-based medicines and the long historical background, regular surveillance and continuous evaluation are critical for safe administration of plant-based medicine in humans. Safety data on most polyherbal mixtures on the Ghanaian market is lacking. The present study evaluated post-market safety and profiled toxicity of commonly used polyherbal mixtures in the Kumasi metropolis of Ghana.

The multidisciplinary study used in-depth qualitative interviews to obtain field reports of herbal medicine consumers on herbal medicinal products’ (HMPs) safety. Selected HMPs, HPA, HPB, HPC, HPD, HPE and HPF, were evaluated for heavy metal and pesticide contamination. The herbal products were wet-acid digested and the evaluations were done using inductively coupled plasma mass spectrometry (ICP-MS) for metal analysis and cold vapour atomic adsorption spectrometry (CV-AAS) for mercury analysis. Pesticides were extracted, purified and the analysis was carried out with gas chromatography coupled mass spectrometry. The three selected herbal products (HPA, HPB and HPC) were further evaluated in a 30-day in vivo sub-chronic toxicity study using OECD 407 continuous dose method in Sprague-Dawley rats.

Dosage concerns and failure of consumers to report usage and adverse effects to physicians were observed. Occurrence of adverse effects among consumers of HMPs was generally low and not severe. Consumers’ shyness and fear of being condemned by general practitioners (GPs) were identified, as well as the GP’s failure to request for such information during the hospital visits of the consumers. Chronic exposure to the studied HMPs (C, E and F) were observed to pose health risk for adults and children (total hazard index >1) due to heavy metal and pesticide overexposure. Children exposed to HPF had higher health risks than adults due to pesticides and heavy metal overexposure. Children also were at the increased cancer risk (1.01 x 10^{-3} compared to the reference value of 1x10^{-4}). High levels of pirimiphos-methyl were observed in HPE. This predisposes to chronic pirimiphos-methyl exposure and may have impact on health. In 30-day in vivo toxicity study for all the studied products signs of moderate liver, heart, lungs and kidney toxicities were revealed at almost all dose levels. Heavy metal and pesticide contamination may account for the
observed signs of organ toxicities in rats. On the contrary, in HPA and HPC rat groups liver amelioration was indicated by low albumin levels, liver histology sections and by statistically significant low ASAT and low ALAT levels. This observation suggests the presence of component(s) with liver amelioration effects, which finding is supported by literature.

In conclusion, results from the present study revealed that in Ghana there are HMPs available in a market that could pose cancer and organ health risks to consumers especially in long-term exposure. Further research and the need for intervention by relevant regulatory authorities is encouraged for the provision and administration of safe herbal medicinal products in the country.

National Library of Medicine Classification: QV 290, QV 600, QV 602, QV 766, QZ 202, WA 240

Medical Subject Headings: Plants, Medicinal; Plant Preparations; Safety; Consumer Product Safety; Risk Assessment; Long Term Adverse Effects; Product Surveillance, Postmarketing; Carcinogens; Neoplasms; Metals, Heavy; Mercury; Pesticide Residues; Insecticides; Toxicity Tests, Subchronic; Rats; Ghana; Public Health.


Haastatellut kokivat kasvirohdosvalmisteet yleisesti hellävaraisiksi ja turvallisemmiksi kuin perinteiset syntteettiset lääkevalmisteet. Kuluttajat olivat arkoja keskustelemaan kasvirohdosvalmisteiden käytöstä lääkärin kanssa, mikä saattaa olla esteenä niiden asianmukaiselle käytölle. Tutkimuksessa havaittiin, että pitkäaikaisaltistus kolmelle tutkituista ghanalaisista kasvirohdosvalmisteista (HPC, HPE ja HPF) aiheutti potentiaalisen terveysriskin sekä aikuisille että lapsille (kokonaisriski-indeksi >1) johtuen raskasmetalli- ja torjuntaaineellistuksesta. HPF-valmistee on tutkimuksen mukaan aikuisilla suurempi terveysriski johtuen altistuksesta torjuntaaineille ja raskasmetalleille. Myös riski sairastua syöpään on lisääntynyt (1.01 x 10^-3 verrattuna altistukseen viitearvoon 1x10^-4). HPF-
valmisteesta mitattiin korkeita pirimifos-metyyli-torjunta-aineepitoisuksia. Täten
pitkääikaisaltistus HPE-valmisteelle voi aiheuttaa terveysriskin. Kaikkiin kolmeen valmisteeseen
liittyi merkkejä toksisuudesta koe-eläinten maksassa, sydämessä, keuhkoissa ja munuaisissa lähes
kaikissa tutkituissa pitoisuksissa, mikä saattaa johtua tuotteiden sisältämistä raskasmetalleista ja
torjunta-aineista. Toisaalta HPA- ja HPC-koe-eläinten sydämessä alhaiset albumiinitasot, maksan
histologiset leikkeet sekä tilastollisesti merkitsevästi matalat aspartaataminotransferasinsa
(ASAT) ja alaniinaminotransferasinsa (ALAT) tasot viittasivat maksan hyvään toimintaan. Hava
Havainto viittaa kasvirohdosvalmisteiden HPA ja HPC sisältävän maksan kuntoa hoitavia
yhdisteitä, mitä havaintoa tukee myös aikaisempi kirjallisuus.

Nämä tutkimustulokset osoittavat, että Ghanassa on saatavilla kasvirohdosvalmisteita, jotka
saattavat altistaa syövälle tai vaikuttaa elimistöön eri elinten terveyteen epäsuotuisasti varsinkin
pitkääikaisaltistuksessa. Lisää kasvirohdosvalmisteiden turvallisuuteen liittyvää tutkimusta ja
valvontaa tarvitaan, osin myös niiden lisääntyneen suosion sekä maatalouskemikaalien runsaan
käytön vuoksi.

Luokitus: QV 290, QV 600, QV 602, QV 766, QZ 202, WA 240

Yleinen suomalainen ontologia: lääkekasvit; rohdosvalmisteet; myrkyllisyys; turvallisuus;
tuoteturvallisuus; valvonta; riskinarviointi; pitkääikaisvaikutukset; karsinogeenit; raskasmetallit;
elohopea; torjunta-aineet; insektisidit; Ghana; kansanterveys.
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This dissertation is dedicated to my beloved wife, kids, my mum and the entire Adusei-Mensah’s and the Inkum’s families for their love and support throughout the period of execution of this project, especially during the ups and downs. I just want to say ‘thank you for standing by me’.

Time 12:00 noon, Kuopio, 17th September 2020

Frank Adusei-Mensah
The present dissertation is based on the following original publications, referred to in the text by Roman numerals I-IV.


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CONTENTS

ABSTRACT ................................................................................................................................ 7
TIIVISTELMÄ ................................................................................................................................ 9
ACKNOWLEDGEMENT ................................................................................................................ 11
1 INTRODUCTION .................................................................................................................. 25
2 LITERATURE REVIEW ........................................................................................................ 27
  2.1 HEALTH AND HEALTH CONDITIONS .......................................................................... 27
    2.1.1 Epidemiology of Malaria ...................................................................................... 27
    2.1.2 Epidemiology of Diabetes .................................................................................... 29
    2.1.3 Epidemiology of Hypertension ............................................................................. 29
  2.2 PROBLEMS ASSOCIATED WITH CURRENT ANTIMALARIA, ANTIDIABETIC AND ANTIHYPERTENSIVE THERAPIES ........................................................................................ 29
  2.3 PLANTS AS ALTERNATIVE MEDICINES ........................................................................ 30
  2.4. PLANTS IN DRUG DISCOVERY ................................................................................... 30
  2.5 MARKET SIZE OF THE HERBAL INDUSTRY .................................................................. 31
  2.6 HERBAL MEDICINES USAGE AND TRADITION IN GHANA ............................................ 31
  2.7. TRADITIONAL USE OF HERBAL MEDICINES FOR MALARIA, DIABETES AND HYPERTENSION IN GHANA ................................................................. 31
  2.8 HERBAL MEDICINES USAGE AND HEALTH STATUS IN GHANA .................................... 35
  2.9 SAFETY AND REPORTED TOXICITY OF HERBAL MEDICINAL PLANTS ....................... 37
  2.10 HERBAL MEDICINES USAGE AND FERTILITY .................................................................. 37
  2.11 RESIDUAL HEAVY METALS AND HEALTH RISK .............................................................. 37
  2.12 RESIDUAL PESTICIDES AND HEALTH RISK ................................................................. 38
  2.13 ADMINISTRATIVE DISPARITIES BETWEEN HERBAL AND ALLOPATHIC MEDICINE 38
  2.14 REGULATION OF HERBAL MEDICINES IN GHANA ....................................................... 39
  2.15 HEALTH RISK ASSESSMENT AND TERMINOLOGIES .................................................... 39
  2.16 THE USE OF ANIMAL MODELS IN CLINICAL TOXICITY EVALUATION ....................... 40
3 AIMS OF THE STUDY .............................................................................................................. 41
  3.1 SPECIFIC AIMS OF THIS STUDY ................................................................................... 41
4 MATERIALS AND METHODS .............................................................................................. 42
  4.1 SAMPLING METHOD (I) ................................................................................................... 42
  4.2 INTERVIEW TRANSCRIPT ANALYSIS (I) ........................................................................... 42
  4.3 MINI SURVEY AND ANTIMALARIAL HMP SELECTION (II, III, IV) ................................. 43
  4.4 SAMPLE PREPARATION AND GC-MS ANALYSIS (II) ..................................................... 43
  4.5 EXTRACTION AND PURIFICATION OF THE PESTICIDES .............................................. 43
  4.6 MULTI-RESIDUE ANALYSIS WITH GC–MS APPARATUS (II) ....................................... 44
  4.7 WET DI-ACID ACID DIGESTION OF HMP .................................................................... 44
4.8 INDUCTIVELY COUPLED MASS SPECTROMETRIC (ICP-MS) HEAVY METALS AND MINERAL ANALYSIS ................................................................................................................................. 45

4.8.2 Mercury Analysis with Cold Vapour Atomic Adsorption Spectrometer (CV-AAS) ........................................ 45

4.9 HEALTH RISK ASSESSMENTS ........................................................................................................... 45

4.9.1 Estimated Daily Intake (EDI) of the Pesticides and Heavy Metals (II, III) ...................................... 45

4.9.2 Target Hazard Quotient (THQ) for Non-Carcinogenic Risk (II, III) ................................................ 45

4.10 HAZARD INDICES ........................................................................................................................... 46

4.10.1 Chronic Hazard Index (HI) (III) ................................................................................................ 46

4.10.2 Cancer Risk Estimation Index (III) .......................................................................................... 46

4.11 HERBAL PRODUCT PREPARATION FOR THE SUB-CHRONIC STUDY (IV) ................................ 47

4.12 ANIMAL PREPARATION (IV) ......................................................................................................... 47

4.12.1 Housing .................................................................................................................................. 47

4.12.2 Feeding .................................................................................................................................. 47

4.13 RELATIVE ORGAN WEIGHT ANALYSIS .................................................................................. 49

4.14 BIOCHEMICAL ANALYSIS .......................................................................................................... 49

4.15 HEMATOLOGY ............................................................................................................................... 49

4.16 SPERM COUNT, MOTILITY AND MORPHOLOGY ........................................................................ 49

4.17 SAMPLE PREPARATION FOR HISTOLOGY ............................................................................... 49

4.18 STATISTICAL ANALYSIS ............................................................................................................. 50

5 RESULTS AND DISCUSSION ............................................................................................................. 51

5.1 QUALITATIVE STUDY RESULTS (I) ............................................................................................... 51

5.1.1 General Results of the Qualitative Study ................................................................................... 51

5.1.2 Knowledge and Rational Use of Herbal Medicines ................................................................... 52

5.1.3 Concomitant Use of Herbs and Drugs ...................................................................................... 53

5.1.4 Motivation to Use Herbal Medicines ....................................................................................... 53

5.1.6 Users’ Belief and Perception About Herbal and Orthodox Medicines ....................................... 54

5.1.7 Safety Concerns of HMPs ........................................................................................................ 54

5.1.8 Reporting Usage and Safety Issues to General Practitioner ..................................................... 55

5.2 PESTICIDE AND HEAVY METAL EVALUATION (II AND III) ..................................................... 55

5.2.1 Descriptive Statistics of Pesticide and Heavy Metals .................................................................. 55

5.2.2 Safety Evaluation of Pesticides and Heavy Metals (II, III) ......................................................... 56

5.2.3 Acute Health Risk Assessment of Pesticide and Heavy Metals (II and III) .............................. 57

5.2.4 Chronic Health Risk Assessment (II and III) ........................................................................... 59

5.3 IN VIVO 30-DAY REPEATED-DOSE SUB-CHRONIC TOXICITY .................................................. 60

5.3.1 Haematology and Fasting Blood Sugar .................................................................................... 60

5.3.2 Biochemical Study .................................................................................................................. 61

5.3.3 Histology Study ....................................................................................................................... 63
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAS</td>
<td>Atomic absorption spectroscopy</td>
</tr>
<tr>
<td>ACT</td>
<td>Artemisinin-based combination therapy</td>
</tr>
<tr>
<td>ADI</td>
<td>Acceptable daily intake</td>
</tr>
<tr>
<td>AFOS</td>
<td>Alkaline phosphatase</td>
</tr>
<tr>
<td>ALAT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>ARfDs</td>
<td>Acute reference doses</td>
</tr>
<tr>
<td>ASAT</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>ATAC 8000®</td>
<td>Automated biochemistry analyzer</td>
</tr>
<tr>
<td>ATn</td>
<td>Average exposure time for non-carcinogens (days)</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood urea nitrogen</td>
</tr>
<tr>
<td>Bwa</td>
<td>Body weight</td>
</tr>
<tr>
<td>C</td>
<td>Concentration</td>
</tr>
<tr>
<td>CA</td>
<td>Canadian upper tolerable daily intake reference limits for finish herbal Products</td>
</tr>
<tr>
<td>CDC</td>
<td>Center for Disease Control</td>
</tr>
<tr>
<td>Chlo</td>
<td>Chlorpyrifos</td>
</tr>
<tr>
<td>CHOL</td>
<td>Total cholesterol</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CR</td>
<td>Cancer risk</td>
</tr>
<tr>
<td>CREA</td>
<td>Creatinine</td>
</tr>
<tr>
<td>Cu(SO₄)₂</td>
<td>Copper sulfate</td>
</tr>
<tr>
<td>DAHD</td>
<td>Daily adult human dose</td>
</tr>
<tr>
<td>DB</td>
<td>Direct bilirubin</td>
</tr>
<tr>
<td>DDT</td>
<td>Dichlorodiphenyltrichloroethane</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetic mellitus</td>
</tr>
<tr>
<td>EDTA</td>
<td>Ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>EDI</td>
<td>Estimated daily intake</td>
</tr>
<tr>
<td>ED</td>
<td>Exposure duration</td>
</tr>
<tr>
<td>EDTot</td>
<td>Total duration of exposure</td>
</tr>
<tr>
<td>EFr</td>
<td>Exposure frequency</td>
</tr>
<tr>
<td>FAO</td>
<td>Food and Agriculture Organization</td>
</tr>
<tr>
<td>FDA</td>
<td>Ghana Food and Drug Authority</td>
</tr>
<tr>
<td>Feni</td>
<td>Fenitrothion</td>
</tr>
<tr>
<td>GC-MS</td>
<td>Gas chromatography coupled mass spectrometry</td>
</tr>
<tr>
<td>GLU</td>
<td>Glucose</td>
</tr>
<tr>
<td>GMP</td>
<td>Good manufacturing practice</td>
</tr>
<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
<tr>
<td>GRA</td>
<td>Granulocyte</td>
</tr>
<tr>
<td>HCl</td>
<td>Hydrochloric acid</td>
</tr>
<tr>
<td>HCT</td>
<td>Hematocrit</td>
</tr>
<tr>
<td>HDL</td>
<td>High-density lipoprotein</td>
</tr>
<tr>
<td>HGB</td>
<td>Haemoglobin</td>
</tr>
<tr>
<td>HI</td>
<td>Hazard index</td>
</tr>
<tr>
<td>HM</td>
<td>Herbal medicinal</td>
</tr>
<tr>
<td>HMP(s)</td>
<td>Herbal medicinal product(s)</td>
</tr>
<tr>
<td>HMs</td>
<td>Herbal medicines</td>
</tr>
<tr>
<td>HNO₃</td>
<td>Nitric acid</td>
</tr>
<tr>
<td>HP(A)</td>
<td>Herbal product ‘A’</td>
</tr>
<tr>
<td>HP(B)</td>
<td>Herbal product ‘B’</td>
</tr>
<tr>
<td>HP(C)</td>
<td>Herbal product ‘C’</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
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<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>HP(D)</td>
<td>Herbal product ‘D’</td>
</tr>
<tr>
<td>HP(E)</td>
<td>Herbal product ‘E’</td>
</tr>
<tr>
<td>HP(F)</td>
<td>Herbal product ‘F’</td>
</tr>
<tr>
<td>HP(s)</td>
<td>Herbal product(s)</td>
</tr>
<tr>
<td>ICP-MS</td>
<td>Inductively Coupled Plasma Mass Spectrometry</td>
</tr>
<tr>
<td>IFR</td>
<td>Intake rate</td>
</tr>
<tr>
<td>IQ</td>
<td>Intelligence quotient</td>
</tr>
<tr>
<td>IRS</td>
<td>Indoor residual spraying</td>
</tr>
<tr>
<td>ITN</td>
<td>Insecticide-treated nets</td>
</tr>
<tr>
<td>IVM</td>
<td>Integrated vector management</td>
</tr>
<tr>
<td>JMPR</td>
<td>Joint meetings on pesticide residues</td>
</tr>
<tr>
<td>KTH</td>
<td>Komfo Anokye Teaching Hospital</td>
</tr>
<tr>
<td>LDL_c</td>
<td>Low density lipoprotein cholesterol</td>
</tr>
<tr>
<td>LYM</td>
<td>Lymphocyte counts</td>
</tr>
<tr>
<td>MCH</td>
<td>Mean corpuscular haemoglobin</td>
</tr>
<tr>
<td>MCHC</td>
<td>Mean corpuscular haemoglobin concentration</td>
</tr>
<tr>
<td>MCV</td>
<td>Mean corpuscular volume</td>
</tr>
<tr>
<td>Mdr</td>
<td>Multidrug resistance</td>
</tr>
<tr>
<td>MgSO₄</td>
<td>Magnesiumsulphate</td>
</tr>
<tr>
<td>MnO₄⁻</td>
<td>Permanganate ion</td>
</tr>
<tr>
<td>MPs</td>
<td>Medicinal plants</td>
</tr>
<tr>
<td>MPV</td>
<td>Mean platelet volume</td>
</tr>
<tr>
<td>MRL</td>
<td>Maximum residual limit</td>
</tr>
<tr>
<td>MXD</td>
<td>Mixed monocytes, basophil and eosinophils</td>
</tr>
<tr>
<td>NaCl</td>
<td>Sodium chloride</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>Sodium carbonate</td>
</tr>
<tr>
<td>ND</td>
<td>Non-detectable</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Ni$_3$(CO)$_4$</td>
<td>Nickel carbonyl</td>
</tr>
<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
</tr>
<tr>
<td>OEHHA</td>
<td>Californian Office of Environmental Health Hazard Assessment</td>
</tr>
<tr>
<td>OPD</td>
<td>Out patient department</td>
</tr>
<tr>
<td>P. falciparum</td>
<td><em>Plasmodium falciparum</em></td>
</tr>
<tr>
<td>Pfcr</td>
<td><em>Plasmodium falciparum</em> chloroquine resistance transporter</td>
</tr>
<tr>
<td>Pfmd</td>
<td><em>Plasmodium falciparum</em> multidrug resistance</td>
</tr>
<tr>
<td>PDW</td>
<td>Platelet distribution width</td>
</tr>
<tr>
<td>P-LCR</td>
<td>Platelet larger cell ratio</td>
</tr>
<tr>
<td>PLT</td>
<td>Platelet count</td>
</tr>
<tr>
<td>p-HMPs</td>
<td>Polyherbal medicinal products</td>
</tr>
<tr>
<td>PM</td>
<td>Pirimiphos-methyl</td>
</tr>
<tr>
<td>PSA</td>
<td>Primary and secondary amine exchanger</td>
</tr>
<tr>
<td>QGIS</td>
<td>Quantum geographical information system</td>
</tr>
<tr>
<td>QuEChERS</td>
<td>Quick, Easy, Cheap, Effective, Rugged, and Safe</td>
</tr>
<tr>
<td>RBC</td>
<td>Red blood cell</td>
</tr>
<tr>
<td>RQDA</td>
<td>R package for computer-assisted qualitative data analysis</td>
</tr>
<tr>
<td>SDGs</td>
<td>Sustainable development goals</td>
</tr>
<tr>
<td>TB</td>
<td>Total bilirubin</td>
</tr>
<tr>
<td>TCR</td>
<td>Total cancer risk</td>
</tr>
<tr>
<td>TG</td>
<td>Triglyceride</td>
</tr>
<tr>
<td>THQ</td>
<td>Target hazard quotient</td>
</tr>
<tr>
<td>TI</td>
<td>Tolerable intake</td>
</tr>
<tr>
<td>TP</td>
<td>Total Protein</td>
</tr>
<tr>
<td>UCCIRB</td>
<td>University of Cape Coast Institutional Review Board</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>US EPA</td>
<td>United States of America Environmental Protection Agency</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>USD</td>
<td>United States Dollar</td>
</tr>
<tr>
<td>V. amygdalina</td>
<td>Vernonia amygdalina</td>
</tr>
<tr>
<td>V. grandifolia</td>
<td>Vitex grandifolia</td>
</tr>
<tr>
<td>VGA</td>
<td>Vapour generation accessory</td>
</tr>
<tr>
<td>VLDL_c</td>
<td>Very low-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cell</td>
</tr>
</tbody>
</table>
INTRODUCTION

The practice of using herbal medicines (HMs) for preventive, curative and for chronic disease management is a globally known and dates back in centuries. According to the European Commission herbal medicinal products are defined as any medicinal product, exclusively containing one or more herbal substances as active ingredients, one or more herbal preparations, or a combination of the two (European Commission, 2004). Similarly, the Finnish Medicines Agency (FIMEA) also defines herbal medicinal products as medicinal products that contain herbal substances, herbal preparations or a combination of these as their active agents (FIMEA, 2004). Furthermore, herbal medicinal product has been defined by Ghana Food and Drugs Authority as any finished labeled medicinal product that contains active ingredients, aerial or underground parts of the plant or other plant material or combination used for the purposes of treatment or prevention of a disease or altering normal physiological function, permanently or temporarily in any way in humans (FDA, 2013). There has been increasing demand for plant-based medicines in recent years. The increasing resistance to pharmaceutical medicines, lack of definitive and cost-effective therapies for some diseases (Lantto, 2017) less accessibility and affordability of pharmaceutical medicines in parts of developing and underdeveloped countries have increased dependency on plant-based medicines. Currently, over 4 billion of the current global population and close to 20 million Ghanaians are using such systems for their primary health care needs (Drew and Myers, 1997, WHO, 2007a, WHO 2014, Forster et al., 2006, Mahady, 2001).

Prior to the inception of conventional health care system in Ghana, herbalists and village healers were the primary care givers, offering herbal remedies to patients (WHO, 2018). In Ghana, herbal medicinal products (HMPs) are considered as drugs and they are advertised as having curative ability for treating numerous diseases. In addition, most producers of HMPs in Ghana take for themselves herbal doctors’ title. HMPs are therefore under the jurisdiction of the Ghana Food and Drug Authority (FDA) that regulates production, registration and distribution of food and drugs in the country. The regulation authorities are making effort to regulate and integrate HMPs into the mainstream health care (Agyei-Baffour et al., 2017). However, herbal medicines are poorly regulated in the country, many HMPs still enter the Ghanaian market without registration and safety data. There is also lack of regular safety and efficacy monitoring and standardized dosage limits. Adherence to good manufacturing practice (GMP) is insufficient.

Following the history of longtime usage and huge patronization of herbal medicines they are generally perceived to be safe, but plants with inherent adverse toxic health effects have been reported (Eswarappa et al., 2003). Also, natural and anthropogenic factors increase the health risk. Mineral mining and the increasing use of pesticides exposes medicinal plants to heavy metal and pesticide contamination and health risk. Adverse health risks due to overexposure to minerals and heavy metals including mercury (Hg), lead (Pb), cadmium (Cd), arsenic (As), copper (Cr) and pesticides have been well documented (Nkansah et al., 2016, Byard et al., 2017).

A previous study has identified medicinal plant materials on the Kumasi market to be heavy metal contaminated (Nkansah et al., 2016). However, data on post-market safety of most finished polyherbal medicinal products on the Ghanaian market are lacking. In addition, most cases of adverse health effects associated with the use of HMPs go unreported in Ghana resulting in a
paucity of data in this area of health care. There is therefore a need for a post-market surveillance study to ascertain the extent and to toxicologically profile the safety of hugely patronized herbal medicinal products in the Kumasi metropolis, Ghana.

Figure 1. Schematic health risk cycle of herbal medicinal products. MP=Medicinal plants, HMP=Herbal medicinal product.
2 LITERATURE REVIEW

2.1 HEALTH AND HEALTH CONDITIONS

Health is defined by the World Health Organization (WHO) as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” (WHO, 1948). The search for good health is the quest of public health institutions around the world and indeed, it forms the core objective of WHO. Good health is however influenced by a wide range of factors including social, economic, physical environment and the person’s genetic characteristics and behavioral factors. These factors interrelate, and if they are not well managed can result in either infectious and/or non-infectious health conditions (diseases) including malaria, diabetes, hypertension, and cancers.

2.1.1 Epidemiology of Malaria

Malaria, the life-threatening disease, is caused by the plasmodium parasite. The parasite is transmitted from an infected person, the (host), to hitherto uninfected person through the bite of a female anopheles mosquito (vector) (Gouagna et al., 2004). Tropical climate favors the breeding of the vector, as a result, the prevalence of the disease is higher in Africa, Asia and southern America than in the temperate regions. Globally, malaria affects over 200 million people annually (Naß and Efferth, 2019) and most of these cases emanates from African and Asian countries. The disease is endemic in sub-Saharan Africa including Ghana and it is the single most common cause of mortality and morbidity among children and pregnant women, (Ahorlu et al., 2007, Febir et al., 2016). In Ghana, malaria constituted 10 839 392 cases, 35% of all out-patient morbidity cases in 2014 (Ghana Health Service, 2015).

Control of malaria includes the use of preventive approach through insecticide-treated nets (ITN), indoor residual spraying (IRS), and other components recommended in the World Health Organization’s integrated vector management (IVM) approach (Beier et al., 2008, Bhatt et al., 2015). Four different species of plasmodium parasites cause malaria in humans namely Plasmodium falciparum, Plasmodium malariae, Plasmodium ovale and Plasmodium vivax. Biochemically, the plasmodium parasite undergoes a complex life cycle involving the host organism and the vector (White, 2004). The organism undergoes two phases of life cycle, sexual and asexual phases in the vector mosquitoes and the vertebrate hosts, respectively. In the host, the hepatocytes and the red blood cells of the host organism are used for the replication of the parasite resulting in lysis of the host cells. The nature and severity of the erythrocytic and the hepatocytic lysis is dependent on the plasmodium species causing the infection. P. falciparum causes severe malaria morbidity with a high degree of mortality than all other known forms of human malaria (World Health Organization, 2000).

Certain stages in the plasmodium’s life cycle have served as targets for antimalarial drug discovery and development both in the past and in the continuum of drug discovery (Combrinck et al., 2013), (Figure 2). The complex and the ever-evolving nature of the plasmodium organism has led to the development of resistance strains to most of previously known regimes rendering the therapies ineffective. For instance, chloroquine resistance was associated with point mutations in the pfcrt...
*Plasmodium falciparum* chloroquine resistance transporter) gene of the parasites’ vacuole transmembrane protein, which reduce the accumulation of the drug and its effect on hemoglobin catabolism in the trophozoites’ vacuole (Sidhu et al., 2002, Fidock et al., 2000). Quinone resistance has been associated with the mutations in the *pfmdr1* (*Plasmodium falciparum* multidrug resistance 1) gene, which is a homologue of the *mdr* ( multidrug resistance) gene (Sidhu et al., 2005). Using combination therapy is a means to overcome malaria resistance development by simultaneously targeting multiple pathways with several different drug molecules. Due to widespread resistant to the pharmaceutical therapies, chloroquine, sulfadoxine-pyrimethamine and amodiaquine, WHO recommended the use of artemisinin-based combination therapies as the first line drug for uncomplicated malaria caused by *P. falciparum* (WHO, 2001). Artemisinin-based combination therapy (ACT) regimes (Kimbi et al., 2014, Naß and Efferth, 2019) was introduced to boost therapeutic success in the control of malaria at the same time to reduce the chances of resistance development. However, development of ACT resistance strains has been reported in certain parts of Africa and Asia (Ouji et al., 2018) due to the emergence of multi-drug resistant (MDR) strains (Wongsrichanalai et al., 2002). There is therefore urgent need for crucial efforts to identify alternative antimalarial therapies.

![Figure 2. Life cycle of *P. falciparum* according to Enomoto et al., 2012.](image)

In the human phase, the degree of hepatocyte and erythrocyte rupturing (schizont stage) depends on the infection, and it is a key for the disease developing from the mild stage into the complicated or severe stage (Slater, 1993, Pett et al., 2019). Artemisinin adversely affects mitochondria’s energy metabolism (Hou et al., 2019). Amodiaquine, artesunate, lumefantrine, mefloquine and quinine are believed to influence heme catabolism at the erythrocytic stage of the parasite life cycle (Combrinck et al., 2013).
2.1.2 Epidemiology of Diabetes

Diabetic mellitus (DM) is a non-communicable metabolic and/or hormonal disease that is usually described by persistent hyperglycemia, as a result of defects in insulin secretion by pancreatic \( \beta \)-cells, and reduced sensitivity of cell surface receptors to insulin or both (Zimmett et al., 2001). Globally, over 380 million people are living with the disease (Doherty et al., 2014, Adeghate et al., 2006, Guariguata et al., 2014). It is believed that most people with diabetes live in low- and middle-income countries. In 2011, 4.1% of the Ghanaian population were reported to be living with the disease (Guariguata et al., 2014). Several treatments have been developed for DM including intramuscularly injected insulin and orally delivered antihyperglycemic agents such as sulfonylureas, glucosidase inhibitors, metformin and thiazolidinedione. These oral agents may stimulate the release of insulin from the pancreatic \( \beta \)-islet cells, increase receptor sensitivity to insulin and reduce glucose absorption rate from the intestines (Fryer et al., 2002, Chitturi and George 2002, Adinortey et al., 2019). But they are mostly faced with drug related adverse health effects. For instance, the sulfonylurea carbutamide was associated with significant liver toxicity (Chitturi and George, 2002), patients administered with sulfonylurea experienced vanishing bile duct syndrome or even die from liver failure (Clarke et al., 1974, Van et al., 1992). Metformin has been associated with acute cholestatic hepatitis and bland cholestasis while troglitazone-induced liver injury has also been reported (Chitturi and George, 2002). There is therefore a continuous search for safer alternative therapies for the prevention and control of DM.

2.1.3 Epidemiology of Hypertension

Like diabetes the burden of hypertension and all forms of heart disease has drastically increased in Ghana in recent years. In the year 2013, 644 134 outpatient cases of hypertension were reported in Ghana compared to 497 845 cases in the previous year and 195 655 cases in 1992, which signifies over 300% increase in two decades (Ghana Health Service, 2015). In rural Ghanaian communities, traditional remedies including herbal medicines are commonly used to treat hypertension or to alleviate side effects of other antihypertensive medications (Nyaaba et al., 2019) due to adverse health problems associated with the current therapies (Chitturi and George, 2002) and lack of affordability, accessibility and availability.

2.2 PROBLEMS ASSOCIATED WITH CURRENT ANTIMALARIA, ANTIDIABETIC AND ANTIHYPERTENSIVE THERAPIES

Malaria resistance strains to ACT have been emerged in Cambodia, and over 30 other dihydroartemisinin–piperaquine combination therapy resistant cases were reported in Southeast Asia (Tse et al., 2019). Primaquine is still useful in treating the liver stage parasites of \( P. \) \( vivax \) malaria. In areas with low resistance to chloroquine it is the first line drug for \( P. \) \( vivax \) and \( P. \) \( ovale \). Toxicity issues, resistance development, delivery, availability, accessibility and affordability are known problems associated with pharmaceutical drugs. One major problem of the ACT for most populace in developing counties is the cost structure with a price of 1.35-2.40 US dollars (USD) per adult treatment course, being about 10-30 times more expensive than pharmaceutical antimalarial drugs (Bosman and Mendis, 2007). ACTs are less affordable to many low-income countries’ patients where substantial proportion of the population live below 1.9 USD per day.
In remote parts of Ghana and other developing countries, there is limited access of most pharmaceutical therapies probably due to logistical issues and poor road network. Patients travel long distances to receive care, leading to reduction in healthcare usability and pharmaceutical drug usage (Sulemana and Dinye, 2014). For instance, in 1990 over 70% of the Ghanaian populace lived over 8 km from the nearest health care provider (Ministry of Health, 1998, Sulemana and Dinye, 2014). Logistic and poor road network serve as barriers to healthcare and quality drug accessibility in rural areas of developing countries.

Against several diseases organ and system toxicity is a major challenge to pharmaceutical therapies all over the world (Peters et al., 2007). Adverse drug effects including genotoxicity, nephrotoxicity and hepatotoxicity remain a dogged concern of many commonly prescription drugs in clinical practice (Chitturi and George, 2002). For example, the insulin-sensitizing agent, troglitazone, was withdrawn from the market after being implicated in several deaths or referrals for liver transplantation (Bloomgarden, 2001, Kohlroser et al., 2000). The known antidiabetics and antihypertensives have contributed in providing better care for the patients and saving millions of lives. However, continuous research into new and alternative therapies are needed due to patient-related and therapy-related factors.

2.3 PLANTS AS ALTERNATIVE MEDICINES

The tradition of using plants for food and for health purposes is as old as human existence on earth. Substantial amount of work has been associated with diets rich in vegetables and fruits with prevention, delay onset and control of different kinds of health problems (Estruch et al., 2013, Zamora-Ros et al., 2010). Therapies of plant origin have served cheaper, more environmentally friendly and easily accessible means of health care (McCurdy and Scully, 2005). Plant phenols and flavanones provide good antioxidants, anti-inflammatory and anti-clastogenic agents impeding the onset and progression of cancers (Putri and Fatmawati, 2019, Xu et al., 2019, Anantharaju et al., 2017, Lantto, 2017). Leaves of Solanum surattense have been used as anti-oxidative, anti-apoptotic and hepatoprotective agents and are traditionally used in Saudi Arabia to treat liver illnesses and cancers (Parvez et al., 2019). Plant extracts including β-sitosterols of Cassia auriculata have been used for their antidiabetic properties (Noor et al., 2013). Molecules of plant origin have proven as potential agents for the management and treatment of both chronic and infectious diseases both in traditional medicine and in scientific systems (Adinortey et al., 2019, Tack et al., 2019, Parvez et al., 2019).

2.4. PLANTS IN DRUG DISCOVERY

Compounds of plant origin have served as an important resource in drug discovery for various health conditions. Despite the recent interest in molecular modelling, drug design and development techniques, molecules of natural origin remain an important source of new drugs and lead compounds for drugs discovery (Newman et al., 2003). It was reported that, between 1981-2014, an average of 50% of all novel therapeutic agents approved globally had scaffolds (lead compounds) originating from natural product(s) including herbal products (Newman and Cragg, 2016). During 1940-2014 about ¾ of anticancer, 65% of antihypertensive and 70% of antimigraine therapeutic agents approved globally had natural origin (Newman et al., 2003, Butler, 2004). Novel antimalaria chemotherapies that have been successful in controlling malaria have been discovered
from plants. Quinine has been obtained from *Cinchona* species. Artemisinin and its synthetic
derivatives (artesunate, artemether or arteether), used in ACT combination therapy, were derived
from Chinese traditional medicinal plant *Artemisia annua* (Kirby, 1997).

2.5 MARKET SIZE OF THE HERBAL INDUSTRY

Herbal medicinal industry is fast-growing and widespread with an estimation of 80% of the
developing world and over 65% of the developed world’s population using herbal medicines.
Patients’ annual expenditure on traditional systems including herbal medicines in the USA from
200 million USD in 1988 to 5.1 billion USD in 1997 (Eisenberg et al., 1998). In 2001, the global
market of the herbal industry was 16-20 billion USD per annum, of which 7 billion USD was from
the European Community (Mahady, 2001, WHO, 2002). The global market grew over 300% from
16-20 billion USD per annum to 60 billion USD per annum in less than a decade (Tilburt and
Kaptchuk, 2008). An estimated 100 million Europeans uses traditional and complementary
systems, 20 million of this number use it regularly (WHO, 2013).

2.6 HERBAL MEDICINES USAGE AND TRADITION IN GHANA

In Ghana, herbal products are freely marketed on different public scenes and media platforms
with little regulation and control. Most registered and unregistered herbal HMPs enter the
Ghanaian market without pre-market safety and toxicity data. There have also been cases of
undocumented reports of adverse effects associated with HMPs’ consumption in Ghana, but data
is lacking in this area of health care.

Affordability, easy accessibility and year-round availability to the rural population makes HMs a
reliable source for the treatment of common ailments. HMs have deep-rooted tradition in Ghana
which dates to the pre-colonial era. The advancement in technological innovations in the last
decade is gradually transforming the herbal industry in Ghana. Such innovations and the HMs’
ability to control a wide spectrum of diseases have had positive impact on the industry resulting
in substantial increase in patronage during recent years (Abdullahi, 2011, Adusei-Mensah and
Inkum, 2015). Patronage of HMs is believed to be higher among patients with malaria and chronic
diseases than among the general population in Ghana (Yarney et al., 2013, Sewani-Rusike and
Mammen, 2014).

2.7. TRADITIONAL USE OF HERBAL MEDICINES FOR MALARIA, DIABETES
AND HYPERTENSION IN GHANA

Herbs have been used for centuries both for food and for treating health conditions without a clear
distinction between when it is meant as food and when it is meant for treatment (Petrovska, 2012).
The use of herbal medicines in Ghana is extensive but highly diverse due to phytogeographical
distribution and cultural diversity. In the treatment of uncomplicated malaria, herbal medicines
have played a critical role in Ghana (Febir et al., 2016) without widespread reported resistance
development against these medications (HMs). Herbal anti-malarial medications are either used
solely or in combination with pharmaceutical medicines for malaria treatment in Ghana (Febir et
al., 2016, Willcox and Bodeker, 2004). HMs are also used to treat or manage all forms of illnesses
in the country including diabetes (Adinortey et al., 2019), hypertension (Nyaaba et al., 2019), stroke
and fevers (Boadu and Asase, 2017). Through continuous research, indigenous herbal medicines can lead to the discovery of new bioactive agents with minimal chances at resistance development, improved quality on efficacy and safety. One major challenge is that, despite the increase in the patronage of traditional medicines, scientific, evidence-based safety and efficacy data on multiherbal mixtures are rather limited.

Table 1A. Ethno-medicinal use of the constituents of antimalaria HMPs

<table>
<thead>
<tr>
<th>Scientific name and family name</th>
<th>Herbal product and form</th>
<th>Common ethnomedicinal use</th>
<th>Documented safety</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bombax buonopozense</em> Family <em>Bombacaceae</em></td>
<td>Antimalaria HPA (decoction)</td>
<td>Used to treat sleeping sickness. Ethanol extract of the stem bark has antitrypanosomal activities. Leave infusion is used as anti-diabetic, anti-oxidative and anti-aging agents in Ghana</td>
<td>Data lacking. It is believed to bioconcentrate copper and zinc metals.</td>
<td>(Boadu and Asase, 2017, Ngwuluka, 2012, Mann et al., 2011, Mustapha et al., 2014).</td>
</tr>
<tr>
<td><em>Cola gigantean</em></td>
<td>Antimalaria HPA (decoction)</td>
<td>Stem barks are used in folklore medicine for inflammation, bacterial infections and heart diseases.</td>
<td>Safety and toxicity data are limited.</td>
<td>(Agyare et al., 2012, Sonibare et al. 2009).</td>
</tr>
<tr>
<td><em>Solanum torvum</em> Family <em>Solanaceae</em></td>
<td>Antimalaria HPA (decoction)</td>
<td>Leaves and the unripe fruits are used to treat tuberculosis and cancer. Fruit is used to treat diabetes, epilepsy, parasitic infections and to reduce oxidative stress on the liver. The plant is also used in Ghana to treat malaria, tuberculosis, and preventing nephrotoxicity.</td>
<td>Safety data limited. Do not significantly affect semen quality in rats.</td>
<td>(Mohan et al., 2010, Abdul et al., 2008, Nguta et al., 2015, Nguta et al., 2016, Challal et al., 2014, Ramamurthy et al., 2016, Asase et al., 2010).</td>
</tr>
<tr>
<td><em>Spathodea campulanata</em> Family <em>Bignoniaceae</em></td>
<td>Antimalaria HPA (decoction)</td>
<td>The plant is used for malaria, cancer and for healing of wounds. Bacterial infections, HIV management, poor blood circulation, gastro-intestinal diseases.</td>
<td>It caused reversible hepatoxic effect in rats.</td>
<td>(Makinde et al., 1988, Mbosso et al., 2016, Agyare et al., 2009, Ilodigwe et al., 2010).</td>
</tr>
<tr>
<td><em>Vernonia amygdalina</em> Family <em>Asteraceae</em></td>
<td>Antimalaria HPA, anti-diabetics HPD and HPE (decoctions)</td>
<td>Leaf extract of <em>V. amygdalina</em> have been reported to affect multiple stages of <em>Plasmodium</em> life cycle, leukemia and prostate cancer and as hepatoprotective agents. Leaf and root decoction for type II diabetes management in Ghana.</td>
<td>Reported to have chromosomal aberrations effect.</td>
<td>(Boadu and Asase, 2017, Busia 2007, Abay et al., 2015, Yedjou et al., 2018, Okwuzu, et al., 2017).</td>
</tr>
<tr>
<td><em>Azadirachta indica</em> Family <em>Meliaceae</em></td>
<td>Antimalaria HPA (decoction)</td>
<td>Different parts of the plant (Leaves, flowers and seeds) are used to treat malaria, cancer, ulcer and diabetes in Ghana, dengue fever, chicken pox and dermal complications.</td>
<td>Reported to have a reversible adverse effect on mammalian reproduction.</td>
<td>(Busia 2007, Saleem, et al., 2018, Bedri et al., 2013, Lucantoni et al., 2010, Boeke et al., 2004).</td>
</tr>
<tr>
<td><em>Cymbopagon citatus</em></td>
<td>Antimalaria HPA (decoction)</td>
<td>Leaf infusion has been used in folklore medicine to treat fever and malaria, inflammatory conditions, antifungal infestations and epilepsy.</td>
<td>Oil extracts showed gastric and hepatic toxicities in higher concentrations.</td>
<td>(Chukwuocha, et al., 2016, Dike, et al., 2012, Francisco et al., 2013, Fandohan et al., 2008).</td>
</tr>
<tr>
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<tr>
<td><strong>Moringa oleifera</strong>&lt;br&gt;Family Moringaceae</td>
<td>Antimalaria HPB (decoction)</td>
<td>The plant is used for treating malaria. Leaf decoction for treating diabetes, cancer and inflammatory diseases. It has α-amylase and α-glucosidase inhibitory activity and are useful in lowering blood glucose level.</td>
<td>Reported to be safe with no reported toxicity cases in humans.</td>
<td>(Busia 2007, Prabhu et al., 2011, Jaja-Chimedza et al., 2017, Stohs and Hartman, 2015).</td>
</tr>
<tr>
<td><strong>Ocimum viride</strong>&lt;br&gt;Family Lamiaceae</td>
<td>Antimalaria HPB (decoction)</td>
<td><em>Ocimum</em> viride have insecticidal and insect repellent and anticancer activity. Ethanol extract of <em>O. viride</em> aerial parts showed apoptosis properties.</td>
<td>Higher doses and chronic administration of (4000mg/kg) showed signs of liver toxicity,</td>
<td>(Owusu, 2000, Bhagat, et al., 2018, Sharma et al., 2010).</td>
</tr>
<tr>
<td><strong>Tetrapleura tetraptera</strong></td>
<td>Antimalaria HPB (decoction)</td>
<td>It is used in West Africa for the treatment of malaria, diabetes, hypertension, inflammation, ulcer and for the management of epilepsy and childhood convulsions.</td>
<td>Ethanol extract of the plant bark showed hepatoprotective effect in mice treated with carbon tetrachloride (CCl4). Neurologic toxicity effect in mice has been reported.</td>
<td>(Ngwoke et al., 2018, Anyanwu et al., 2015, Madubunyi and Asuzu 1996).</td>
</tr>
<tr>
<td><strong>Phyllanthus fraternus</strong>&lt;br&gt;</td>
<td>Antimalaria HPC (decoction)</td>
<td>Used in Indian Ayurveda and Siddha medicine to treat jaundice, the aerial part have hepatoprotective activity. The plant also has anti-DNA polymerase activity of the hepatitis virus. Leaf decoction is used in traditional antidiabetic medications in Ghana.</td>
<td>Believed to have high safety index.</td>
<td>(Busia 2007, Rajasubramaniam and Saradhi, 1997, Ahmed, et al., 2002, Sailaja and Setty, 2006, Gopi and Setty, 2010, Adesina et al., 2019).</td>
</tr>
<tr>
<td><strong>Vitex grandifolia</strong>&lt;br&gt;</td>
<td>Antimalaria HPC (decoction)</td>
<td>The stem bark is used for malaria, yellow fever, filarial and dengue vector control due to its larvicidal activity. In traditional medicine, the leaves of <em>V. grandifolia</em> is used to treat diabetes <em>mellitus</em> and as a diuretic in the treatment of high blood pressure.</td>
<td>Prolonged exposure of <em>V. grandifolia</em> is reported to have toxic effects in Sprague-Dawley rats,</td>
<td>(Owolabi et al., 2010, Azokou et al., 2013).</td>
</tr>
</tbody>
</table>

33
Table 2. Ethno-medicinal use of the constituents of studied antidiabetic HMPs

<table>
<thead>
<tr>
<th>Scientific name and family name</th>
<th>Herbal product and form</th>
<th>Common ethnomedicinal use</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Carica papaya</strong></td>
<td>Antidiabetic HPD</td>
<td>Traditionally used for antidiabetic and antihyperlipidaemic effects. As an antidiabetic, it works by restoring pancreatic islet cell function.</td>
<td>Reported in literature to be sub-chronically safe.</td>
<td>(Afzan et al., 2012, Ismail et al., 2014, Omonkhua et al., 2013, Adinortey et al., 2019).</td>
</tr>
<tr>
<td><strong>Musa paradisiaca</strong></td>
<td>Antidiabetic HPD</td>
<td>The plant is used as an anticancer and an antibacterial agent against multi-drug resistant nosocomial infection-causing pathogens. The unripe banana and the latex from the inflorescence are used traditionally to treat gastroduodenal ulcers.</td>
<td>Flower bud ethanol extract had toxic effects on <em>Artemia salina</em> shrimp larvae. The unripe fruit powder has been reported to be safe in rats.</td>
<td>(Rampe and Tombuku, 2016, Tekha, et al., 2016, Costa et al., 1997, Vijayakumar et al., 2017, Karuppiah and Mustaffa, 2013).</td>
</tr>
<tr>
<td><strong>Momordica charantia</strong> Family Cucurbitaceae</td>
<td>Anti-diabetic HPE</td>
<td>The leaves, whole plant and fruit infusion is used in Ghana as antidiabetic agent. It believed to enhance insulin secretion by regenerating pancreatic β-cells. It also has antiviral and antineoplastic activities.</td>
<td>Liver toxicity and reduced fertility have been reported in rodents. Hypoglycemic coma and convulsion have been reported in humans.</td>
<td>(Boadu and Asase, 2017, Ooi et al., 2012, Ma et al., 2017, Raman and Lau, 1996, Jilka et al., 1983, Basch, et al., 2003).</td>
</tr>
<tr>
<td><strong>Strophanthus hispidus</strong> Family Apocynaceae</td>
<td>Anti-diabetic HPE</td>
<td>Roots and leaves are used in African traditional medicine for diabetes. Stem bark is used for asthma treatment.</td>
<td>It contains cyanogenic glycosides that causes cardiac arrest.</td>
<td>(Fraser, 1872, Ojiako and Igwe, 2009, Sonibare and Oblie, 2008).</td>
</tr>
<tr>
<td><strong>Lippia multiflora</strong> Family Verbenaceae</td>
<td>Anti-diabetic HPE</td>
<td>Whole plant decoction is used against liver disease, hypertension, malaria, asthma, nervousness, ulcer, epilepsy, bucco-anal and digestive candidoses.</td>
<td>Its leaf extracts and essential oils have been reported to be safe.</td>
<td>(Péllissier et al., 1994, Gandonou et al., 2017, Folashade and Omorogbe, 2012).</td>
</tr>
</tbody>
</table>
Table 3. Ethno-medicinal use of the constituents of studied antihypertensive HMP

<table>
<thead>
<tr>
<th>Scientific name and family name</th>
<th>Herbal product and form</th>
<th>Common ethnomedicinal use</th>
<th>Documented safety</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Citrus aurantifolia</em> Family Rutaceae</td>
<td>Antihypertensive HPF (decoction)</td>
<td>Its essential oil contains citral b which has β-glucuronidase inhibitory activity for diabetic control. Traditionally, it is used as an appetite stimulant, for cold and cough, for sore throat and as a digestive stimulant.</td>
<td>Sub-chronic study showed moderate toxicity and oxidative stress in mice.</td>
<td>(Arbo et al., 2009, Saleem et al., 2003, Apraj et al., 2011).</td>
</tr>
<tr>
<td><em>Allium sativum</em> (garlic) Family Amaryllidaceae</td>
<td>Antihypertensive HPF (decoction)</td>
<td>Garlic is used for cancer, inflammation, wound-healing, asthma, malaria, diabetes, anemia, jaundice and epilepsy. It has hypotensive activity and are used for a variety of cardiovascular conditions including lowering blood pressure and cholesterol levels.</td>
<td>Garlic extract causes toxic effects that affected growth, biochemical parameters and histologic structures.</td>
<td>(Fehri et al., 1991, Tesfaye and Mengesha, 2015, Tabassum and Ahmad, 2011)</td>
</tr>
<tr>
<td>Honey</td>
<td>Antihypertensive HPF (decoction)</td>
<td>Honey is used in traditional remedy for treating microbial infections of antibiotic resistance strains including Staphylococcus aureus, Helicobacter pylori, and Acinetobacter baumannii. It is useful in the treatment of infected wounds and ulcers, arthritis, bladder infections, cholesterol lowering, skin and urinary tract infections.</td>
<td>No serious adverse effects have been reported in literature.</td>
<td>(Saranraj et al., 2016, Mohtashami et al., 2015).</td>
</tr>
</tbody>
</table>

2.8 HERBAL MEDICINES USAGE AND HEALTH STATUS IN GHANA

Though doctor-patient and nurse-patient ratios in Ghana have significantly improved in the last decades (Ghana Health Service, 2015), they are still below the recommended level by WHO (Sulemana and Dinye, 2014, Muhammed et al., 2013). Hospital waiting times and specialists’ waiting times are still longer than recommended. In the rural communities of Ghana, where modern healthcare resources are scarcely distributed, many patients travel long distances to seek treatment. In addition, most village dwellers have low income jobs to support their households, which limits their accessibility and usability of the conventional healthcare facilities. Most medicinal plants or herbal products are either within the catchment areas or are brought into the catchment areas at affordable prices. The products are also available all-year-round. As a result, most Ghanaians use traditional medicinal products (including herbal medications) for their primary health needs. Like the Ayurveda of the Indians and the Chinese Traditional Medicine, herbal medicines form a fabric of health care delivery in Ghana. Over 17 million (over 70%) of the adult population rely on herbal and traditional medicines for their basic health needs (Ekor, 2014). Recent reports suggest that Ghana is above average in most health parameters including 61% decline in the under-five-year mortality rate between 1980 and 2014 (Tette et al., 2016a) and improved life expectancy (Boachie, 2017).
Figure 3. Pictorial map of Ghana showing the geographical regions and vegetative cover. Map developed by Ahianyo Cornelius using QGIS Software with Transverse Mercator (Miezah, et al., 2015).
2.9 SAFETY AND REPORTED TOXICITY OF HERBAL MEDICINAL PLANTS

Most cases of adverse health problems associated with the use of HMPs go unreported in Ghana (Yarney et al., 2013) and the true quantum of such incidences remains unknown. Lack of interest of researchers and publishers could have compounded the problem of undocumented adverse reactions associated with some herbal preparations in Ghana. The herbal industry has been faced with concerns about pesticides, microbial contamination and adulteration with pharmaceutical therapies. Those who adulterate do so with the intention of increasing the efficacy and usually without clinical data on compatibility and drug-herb interactions. Several herbal medicines consumers in Ghana purchase the herbal medicines over-the-counter from open markets and from the sales van without a prescription thereby increasing the patients’ health risk.

Previous research has identified some adverse reactions associated with the use of medicinal herbs. Aristolochic acid from Aristolochia species has been reported for being carcinogenic, mutagenic, hepatotoxic and causes severe toxic effects on kidney (Ekor, 2014, Chen et al., 2012). Products containing Ephedra sinica have been associated with severe cardiovascular and central nervous system (CNS) problems (Hackman et al., 2006, Hallas et al., 2008, Chen et al., 2010), neurotoxicity, hepatotoxicity and temporal blindness (Skoulidis et al., 2005, Schoepfer et al., 2007). Pyrrolizidine-containing alkaloids from Tussilago farfara have been associated with hepatotoxicity, hepat-veno occlusion and cancers (Edgar et al., 2011). Kava (Piper methysticum) is traditionally used in medications for its CNS depressant and its anxiolytic activity, but severe liver damage has been attributed to its use (CDC 2002).

2.10 HERBAL MEDICINES USAGE AND FERTILITY

Childlessness is a reproductive health problem affecting many couples globally (Tabong and Adongo, 2013). Infertility of newly married couples is on the increase in Ghana (Fiander, 1990, Donkor and Sandall, 2009) and finding the cause is a concern to all public health practitioners and health care providers. The use of herbal products for disease control and as food supplements for aphrodisiac, for weight loss and for other purposes has increased in recent years in Ghana (Aziato and Antwi, 2016, Adusei-Mensah and Inkum 2015). This has been witnessed in an era of increasing infertility in the country (Tabong and Adongo, 2013).

2.11 RESIDUAL HEAVY METALS AND HEALTH RISK

The presence of contaminants, adulterants and inherent toxic compounds in herbal medicines has been associated with adverse events of herbal medicines administration (Mosiluzzaman and Choudhary, 2008). Heavy metals are defined as naturally occurring metallic elements which have relatively high atomic weights and a density of at least 5 times greater than that of water (≥5 g/cm³) (Tchounwou et al., 2012). Essential trace metals form key components of several key enzymes that play important roles in various vital physiological processes (Tchounwou et al., 2012). Cobalt (Co), copper (Cu), chromium (Cr), iron (Fe), magnesium (Mg), manganese (Mn), molybdenum (Mo), nickel (Ni), selenium (Se) and zinc (Zn) are essential metal nutrients required in small quantities for various biochemical and physiological functions (WHO 2004, Tchounwou et al., 2012). Excessive amount of the trace metals or their lack in the human system have been linked to various adverse effects and human diseases. Chromium (Cr(IV)) and copper have narrow concentration
range for beneficial effect, and outside this narrow range leads to toxic effects (Tchounwou et al., 2008, Achadu et al., 2016).

Vanadium (V) and manganese are essential for proper enzyme functioning, but oxidized vanadium such as vanadium pentoxide ($V_2O_5$) is carcinogenic in animals and when inhaled, causes DNA damage (Tchounwou et al., 2012). Despite the known importance of manganese, iron and nickel in the body, permanganate ion ($MnO_4^-$) is a known liver and kidney poison and ingesting more than 0.5 grams of iron a day can induce cardiac collapse and death (Tchounwou et al., 2012). Nickel carbonyl ($Ni(CO)_4$), is known to cause extreme toxicity in human causing respiratory failure, brain damage and death (Budavari et al., 1996, Goyer, 1991). A high dose of copper sulfate ($Cu(SO_4)_2$) have been reported to cause major organ damage and death.

### 2.12 Residual Pesticides and Health Risk

Pesticides are defined by the Food and Agriculture Organization (FAO) as any substance or mixture of substances intended for preventing, destroying, or controlling any pest. Pesticides provide an efficient, economic, labour and life-saving means for pest control in both agriculture and public health sectors (Cooper and Dobson, 2007, Damalas and Eleftherohorinos, 2011). Despite the enormous benefits of pesticides, their extensive use presents health risk to humans and they are of great concern (Skovgaard et al., 2017). Data on global health impacts of pesticides are limited, but a lot can be learnt from the few reported data. For instance, the impact of preventable pesticide ingestion has been estimated to have caused 186 000 deaths and 4 420 000 disability adjusted life years in 2002 (Gyewali et al., 2017). It has been reported that over 98% of sprayed insecticides and 95% of herbicides reach non-targeted destinations including other ecologically important species, air, water and soil thereby polluting the environment and causing health risk (Tsimbiri et al., 2015). Excess and run-off pesticides seep into the soil and are washed into water bodies contaminating them. Pesticides with long half-life stay long in the environment and end up in the tissues of plants including herbal medicinal plants and into humans via the food chain.

Intake of certain pesticides in amounts above their safe levels can lead to acute or chronic poisoning, coma and death (Skovgaard et al., 2017, Sumi et al., 2008). Reduced intelligence quotient (IQ) power (Isling et al., 2014), cancer, (Ames and Gold, 1997) and neurological problems are some of the health problems associated with chronic exposure to some pesticides (Skovgaard et al., 2017). The use of aldrin, camphechlor, chlorecone, dieldrin, endrin, dichlorodiphenyltrichloroethane (DDT), heptachlor and mirex is prohibited or severely restricted by the Stockholm convention (United Nations, 2001). But according to recent reports, some of these banned hazardous pesticides are still being used in many countries including Ghana (Ghana Environmental Protection Agency, 2008).

### 2.13 Administrative Disparities Between Herbal and Allopathic Medicine

Medications, both pharmaceutical and herbal, are aimed at curing or treating infirmities and improving the health of consumers. In most countries the latter is less regulated. In Ghana, there is a high probability that the herbal medicinal plant identified by an herbalist will reach the market. This is due to lack of toxicity studies and strict regulatory policies (Adusei-Mensah and Inkum, 2015). Herbal medicines might reach the market with limited or no data on safety, dosage limits,
efficacy, drug-herb interactions and expiry dates for safe administration. The rush of new HMPs entering the Ghanaian market and the growing usage of HMPs in Ghana raise public health concern and require regular post-market surveillance studies to ensure public safety.

2.14 REGULATION OF HERBAL MEDICINES IN GHANA

Herbal products containing plant materials from two or more different medicinal plants are considered polyherbal products. Most of the herbal products on the Ghanaian market are polyherbal comprising of several herbs in a single preparation (Zhang et al., 2014). The producers assert that several herbs are necessary for a holistic effect and for improved efficacy (Zhang et al., 2014). A multi-herbal product may benefit from positive synergy where the efficacy of a component may be potentiated by the presence of other component(s). There could also be a negative synergy where there is an increased toxic effect compared with the known effects on the individual herbal plants. In Ghana, most toxicity and safety data on herbal medicines available are either on specific herbal plant or some compounds present in these plants. Data on the potential toxicity and safety of many multi-herbal preparations available on the market have not been well established (Ntchapda et al., 2014, Rosidah et al., 2009, Dhanavathy and Jayakumar, 2017).

The herbal medicine section of the Ghana Food and Drug Authority has the responsibility of evaluating and registering herbal medicines and food supplements in the country (Ghana Food and Drugs Authority, 2019). Despite the effort by the FDA, some HMPs still enter the market without FDA’s registration. The FDA has not been able to carry out regular post-market surveillance on HMPs on the market due to the sheer size and the diverse nature of the herbal market and the attitude of some manufacturers.

2.15 HEALTH RISK ASSESSMENT AND TERMINOLOGIES

Adverse effect, an important factor in patient safety, induced by administration of a medication or by exposure to a chemical can be indicated by an untoward result such as illness or death. Defined by WHO it is a change in morphology, physiology, growth, development or life span of an organism, which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influences (WHO, 2007). In the field of patient safety, the conformance of the herbal medicinal product to internationally recommended reference measures such as maximum residue limit (MRL), acceptable daily intake (ADI) and tolerable intake (TI) is crucial. ADI is defined by WHO as the estimated maximum amount of an agent, expressed on a body mass basis to which an individual in a (sub)population may be exposed daily over his or her lifetime without appreciable health risk (Hamner, et al., 2013, WHO, 2007). WHO defines maximum residue limit (MRL) as the maximum concentration of a pesticide residue (expressed as mg/ kg) recommended by the Codex Alimentarius Commission to be legally permitted in food commodities and animal feeds and used by analogy for herbal medicines (WHO, 2007). For safe administration, the contaminants’ short-term intake ought to not exceed the acute reference doses (ARfDs), and the agent’s long-term intake should be limits as recommended by FAO/WHO (2007a).
2.16 THE USE OF ANIMAL MODELS IN CLINICAL TOXICITY EVALUATION

The use of experimental animal models in health research is known practice (Dano, et al., 2000). Due to ethical restraints in using human subjects, animal subjects have served as translation models in understanding disease etiology, safety and toxicity of therapeutic substances. Rodents including mice have therefore been used in pre-clinical toxicity evaluation and post-market safety surveillance of drugs meant for humans (Sharpless and DePinho, 2006). Successful translation of data including toxicity and efficacy from animal studies into humans have been reported (Mannava et al., 2013, Barkley-Levenson and Crabbe, 2012, Dickson and Chen, 2011, Ittner et al., 2015, Wojcikowski and Gobe, 2014). Rats have been used to empirically assess the post-market safety and toxicity of herbal medications for humans use (Sarhadynejad et al., 2016, Wang et al., 2012). Rodents are believed to possess certain characteristics that makes them good substitutes for human studies. Despite the structural differences, the rodents are believed to be genetically similar animals to humans (Nolan et al., 2006, Nilsson et al., 2001) and have the ability to mimic human pathophysiological states (Wang et al., 2010, Sharpless and DePinho, 2006). Scientists believed that, most disease genes in humans are conserved between rodents and humans making rodents an excellent model for human pathology studies (Shimoyama et al., 2015, Iannaccone and Jacob, 2009).
3    AIMS OF THE STUDY

The primary goal of this study was to evaluate the post-market safety and to profile the toxicity of commonly used herbal medicinal products (HMPs) in the Kumasi metropolis of Ghana. This is aimed at ascertaining whether these HMPs are within internationally acceptable toxicity levels and safe for human consumption.

The research question was: Are herbal medicinal products sold and consumed in Kumasi metropolis safe for use, and what are their possible adverse health effects following sub-chronic administration?

3.1 THE SPECIFIC AIMS OF THIS STUDY WERE:

1. To determine the reported safety of herbal medicinal products used by the populace in Kumasi metropolis of Ghana through users’ self-reports. (I)
2. To profile residual pesticides present in the selected herbal preparations used by the target population and to estimate the health risk associated with such exposure. (II)
3. To profile residual heavy metals present in the selected herbal preparations and to estimate the health risk associated with such exposure. (III)
4. To determine the sub-chronic toxicity of the selected herbal medicinal preparations used by the populace in Kumasi metropolis using Sprague-Dawley rat model. (IV)
4 MATERIALS AND METHODS

4.1 SAMPLING METHOD (I)

Figure 4. Study design. Pre-study feasibility interviews were carried out on 10 participants (informants) prior to the main study to fine-tune the interview guide. Transcripts of the pre-study trials were not added to the main study. In the main study, face-to-face in-depth interviews were conducted on 37 information-rich users of HMPs (age ≥ 18 years). Interviews were conducted with the help of an interview guideline and described in detail in Study I.

4.2 INTERVIEW TRANSCRIPT ANALYSIS (I)

The biometric data comprising of the age, occupation, educational level and other closed-ended questions in the study transcript were analyzed with IBM’s SPSS version 21 using frequency descriptive statistical analyses. Qualitative thematic analysis approach with RQDA (R package for computer-assisted qualitative data analysis) RQDA version 3.4.4 on R-studio 1.0.153 platform was used to analyze the qualitative data. Braun and Clarke’s six steps to thematic analysis process were followed (Braun and Clarke, 2006). The analysis steps have been described in Study I.
4.3 MINI SURVEY AND ANTIMALARIAL HMP SELECTION (II, III, IV)

Mini survey was carried out among randomly selected herbal medicines consumers and pharmacy shops that sell herbal medicines to their wholesale, retail and final customer clients. The list was compiled and tallied. The top 3 antimalarial herbal preparations, top 2 antidiabetic preparations and the top 1 anti-hypertensive herbal products emerged from survey were sampled out for further investigation as described in Studies II, III and IV.

4.4 SAMPLE PREPARATION AND GC-MS ANALYSIS (II)

Six herbal products comprising the most patronized the top-3 antimalarial herbal products, top-2 antidiabetic products and the top-1 anti-hypertensive herbal product were extracted and purified using QuEChERS (Quick, Easy, Cheap, Effective, Rugged, and Safe) sample preparation method for GC-MS multi-residue pesticide analysis. The procedure described by Kimaru and Nguyen, 2014 was applied. Pesticide Standards for 33 different pesticides with known concentrations were prepared as external standards. The samples were injected into the GC-MS and the pesticides present in the samples were quantitatively determined.

4.5 EXTRACTION AND PURIFICATION OF THE PESTICIDES

Quick, Easy, Cheap, Effective, Rugged, and Safe (QuEChERS) method was used for the pesticides. In brief, 10 mL of the herbal product was extracted with 45 mL of analytical grade of n-hexane – ethylacetate system (7:3) through solvent-solvent extraction. The organic phase (supernatant) was collected. The collected organic phase was dehydrated with 2 g of anhydrous MgSO₄ and 0.5 g of NaCl (MgSO₄: NaCl 4:1). The extract was concentrated into 2 mL using rotary evaporator (Büchi rotary evaporator, R-200, Singhla Scientific, India) at 35 °C. It was reconstituted in 7:3 n-hexane:ethylacetate system to 10 mL. Purification was done with 2 g of Florisil Sigma, 2 g of anhydrous MgSO₄ and primary secondary amine (PSA) sorbent and centrifuged for 5 minutes as shown in figure 5.
4.6 MULTI-RESIDUE ANALYSIS WITH GC–MS APPARATUS (II)

The herbal medicinal product (HMP) samples were analysed on Varian Saturn Ion Trap 2000 bench top GC-MS system equipped with Varian CP 8400 Autosampler. The detector was set at 10 volts and sample rate at 10.00 Hz. GC separation was performed on a DB-5MS capillary column (30 m × 0.25 mm i.d., film thickness 0.25 µm) with the following operating conditions: initial oven temperature 120 °C for 3 min, then a 5 °C min⁻¹ ramp to 290 °C and held for 10 min, carrier gas was He with constant flow at 1.0 mL min⁻¹, injection volume 1 µl (splitless), the temperature for inlet, ion source and MS transfer line was 250, 230 and 290 °C, respectively, and total run time was 32.967 min. A total of 33 external standards were used and detected pesticides were quantified using calibration curve and peak area.

4.7 WET DI-ACID ACID DIGESTION OF HMP

All used chemicals were of analytical grade. Digestion was done to release the metals in the herbal preparations from their metal complexes. A total of 5 ml of the liquid herbal product was placed in a glass beaker, 10 mL of nitric acid (HNO₃) was added and 2 mL of perchloric acid (HClO₄) was added. The beaker was covered with a watching glass lid and placed in a fume cupboard.
overnight. The mixture was heated in a hood at 250 °C for overnight until the mixture began to emit white smoke and the colour of the mixture became colourless. The mixture was cooled to room temperature in a desiccator and a volume of 3 mL of hydrochloric acid (HCl) solution (6 N) was added. The mixture was reheated again on a hot plate until a white smoke started to arise and cooled to room temperature in a desiccator. Then 1 mL HCl solution (6 N) was added to the solution. The resulting mixture was transferred to a 50 mL flat bottom flask containing deionized water and was filled to the 50 mL with deionized water.

4.8 INDUCTIVELY COUPLED MASS SPECTROMETRIC (ICP-MS) HEAVY METALS AND MINERAL ANALYSIS

Aliquots of the digested samples were taken for Inductively Coupled Mass Spectrometric analysis (ICP-MS) (Agilent ICP-MS 7700x (Agilent Technologies, Inc. Hachioji-shi, Tokyo, Japan)). The analysis was carried out to quantitatively measure the Pb, As, Cd, Cr, Cu, Ni, and Mn content in the HMPs using Agilent ICP-MS 7700x instrument and standard method for metal analysis. Standard calibration solutions of analytical grade and blank were run prior to sample injection. The ICP-MS has high detection power (Kamunda et al., 2016) and the obtained results were in parts per billion (ppb). The instrument conditions and quality control settings are described in detail in Study (III).

4.8.2 Mercury Analysis with Cold Vapour Atomic Adsorption Spectrometer (CV-AAS)

The analysis and quantification of mercury in the HMPs was carried out using Varian Atomic Absorption Spectrometer AA240FS (Varian Inc, California, USA) equipped with cold vapour generation accessory (VGA-77). The cold vapour technique, the instrument conditions and quality control for Hg analysis are described in detail in Study (III).

4.9 HEALTH RISK ASSESSMENTS

4.9.1 Estimated Daily Intake (EDI) of the Pesticides and Heavy Metals (II, III).

The estimated daily intake (EDI) of the heavy metals (Cr, Mn, Ni, Cu, As, Cd, Pb and Hg) in the studied HMPs was determined by the following equation (Singh, et al., 2010, Ou et al., 2016).

$$\text{EDI} = \frac{E_D \times C}{W_{ab}} \quad \text{(Equation 1)}$$

Where EDI is the estimated daily intake of the heavy metal, C is the determined heavy metal content in the HMP, $E_D$ is the daily dosage of the HMP and $W_{ab}$ is the Ghanaian average body weight (65 kg adults, 24 kg children) (Ou et al., 2016, Biritwum et al., 2005)

4.9.2 Target Hazard Quotient (THQ) for Non-Carcinogenic Risk (II, III)

Non-carcinogenic risk estimation of heavy metal consumption due to HMP administration was determined using target hazard quotient (THQ) values. THQ is measured as a ratio of the determined dose of a contaminant exposed to and a safe reference limit. Exposure beyond the reference limit is considered harmful.
Where \( EFr \) is the exposure frequency (365 days/year). Length of exposure (EDtot) was set to 65 years as the average for Ghanaian males and females based on the average life expectancy in Ghana (WHO 2014). For HPA-HPE dose as stated on the product bottles starts from the age of 12 years (ie ED is 65-12 = 53 years) and for HPF from the age of 6 years (ie ED is 65-6 = 59 years). Adults are 18 years and over (ED is 65-18 = 47 years). IFR is the herbal product (HP) ingestion rate (g/person/day). Dosages as indicated on the product bottles, (kg/person/day). C is the concentration of the contaminant metal/pesticide in the HMP (mg/kg), RiDo is the oral reference dose ((µg /g/day), ATn is the average time (in days). BWa is the adult body weight (65 kg).

### Table 4. International oral reference dose values (RfDo) for the heavy metals

<table>
<thead>
<tr>
<th>Contaminant</th>
<th>Cr(VI)</th>
<th>Mn</th>
<th>Ni</th>
<th>Cu</th>
<th>As</th>
<th>Cd</th>
<th>Pb</th>
<th>Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>RfDo (mg kg(^{-1})day(^{-1}))</td>
<td>0.02</td>
<td>0.14</td>
<td>0.02</td>
<td>0.001</td>
<td>0.003</td>
<td>0.001</td>
<td>0.004</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Estimation of annual exposure frequency parameters for the evaluation based on dosage instructions were the following: HPA (antimalaria product, 35 days/year), HPB (antimalaria product, 105 days/year), HPC (antimalaria product, 200 days /year), HPD (antidiabetic and antihypertensive product, 365 days/year), HPE (antidiabetic product, 365 days/year) and HPF (antihypertensive product, 365 days/year). Malaria disease incidence density of 5 infections per person per year was considered for Sub-Saharan African and for this study (Koram et al., 2002). Also, dosage instructions given for the products were used. Antidiabetic or hypertensive drugs were used as stated on the products or throughout the year due to the chronic nature of the disease.

### 4.10 HAZARD INDICES

#### 4.10.1 Chronic Hazard Index (HI) (III)

The chronic hazard index (HI) of a herbal product is the sum of more than one hazard quotient of multiple toxicants in the HP. Exposure to two or more pollutants may result in additive and/or interactive effects. As a result, the THQs is summed across constituents to generate a hazard index (HI) for an oral dosage pathway combination to estimate the long-term combined effect.

\[
HI = \sum^{n'} THQ1 + THQ2 \ldots THQn \quad \text{(Equation 3)}
\]

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

#### 4.10.2 Cancer Risk Estimation Index (III)

Prediction of increased cancer risk due to chronic exposure to carcinogenic substances in the products was estimated using equations 4 and 5.
CR = CSF × EDI  \hspace{1cm} \text{(Equation 4)}

TCR = \sum_{i=1}^{n} CR_i + CR_2 \ldots CR_n \hspace{1cm} \text{(Equation 5)}

In the equation CSF is the oral carcinogenic slope factor and for Pb it is 0.0085 (mg/kg/day)$^{-1}$ set by Californian Office of Environmental Health Hazard Assessment (OEHHA, 2009) for As CSF is 1.5 (mg/kg/day)$^{-1}$ set by US EPA (USA EPA 2007). CR and TCR describe cancer risk and total cancer risk, respectively. EDI is the estimated daily intake of the pesticide or the 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), (Kamunda, et al., 2016, Ekhator et al., 2017).

4.11 HERBAL PRODUCT PREPARATION FOR THE SUB-CHRONIC STUDY (IV)

The daily dosages of the three antimalaria products for adult humans were noted in this study as a volume (mL) per 65 kg adult human body weight. The corresponding weight equivalent in the rats based on the average rat weight were prepared as the minimum dose for the rats represented as HPA (1), HPB (1) and HPC (1). Five times and ten times the minimum doses were the middle (HPA (5), HPB (5) and HPC (5)) and the highest doses (HPA (10), HPB (10) and HPC (10)), respectively. Composition and properties of the studied HMPs are shown in Table 5.

4.12 ANIMAL PREPARATION (IV)

Forty young healthy adult male Sprague-Dawley rats (10-12 weeks old) were used for the study. Rats were randomly assigned to ten groups of four rats each (n = 4). Each group was assigned a cage and all the rats were kept for 10 days to allow for acclimatization before the main study. The rats were dosed with the herbal products daily via oral gavage route for 30 days. The handling, dose preparation and administration and treatment are described in detail in the original study IV and in OECD 407.

4.12.1 Housing

In brief, the experimental animal room was kept at room temperature 22 °C (±3 °C). Relative humidity was at least 30% and not exceeding 70%. Artificial lighting was used with a cycle of 12 hours light and 12 hours dark.

4.12.2 Feeding

The animals were fed with unlimited standard rodent feed and clean water throughout the acclimatization and experimental periods.
Table 5. Composition and properties of the studied HMPs

<table>
<thead>
<tr>
<th>Herbal medicinal product (HMP)</th>
<th>Abbreviation</th>
<th>Reported ingredients</th>
<th>Nature of the herbal product</th>
<th>Origin of the herbal product</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbal product ‘B’ Taabea Herbal Mixture</td>
<td>HPB</td>
<td>Ocimum viride, Azadirachta indica, Paullinia pinnata, Tetrapleura tetraptera, Theobroma cacao, Cymbopagon citatus, Moringa oleifera</td>
<td>Registered herbal medicine, Goldenrod orange colour decoction.</td>
<td>Taabea Company Ltd, Kumasi.</td>
<td>Indicated to treat malaria, loss of appetite, general body pains.</td>
</tr>
<tr>
<td>Herbal product ‘C’ Adutwumwaa Malamix</td>
<td>HPC</td>
<td>Anthocheista nobilis, Vitex grandifolia, Phyllanthus fraternus</td>
<td>Registered herbal medicine, dark brown decoction.</td>
<td>Adutwumwaa Herbal Industries Ltd, Kumasi.</td>
<td>Indicated to treat malaria.</td>
</tr>
<tr>
<td>Herbal product ‘D’ Osompa D.P.</td>
<td>HPD</td>
<td>Carica papaya, Vernonia amygdalina, Musa paradisiaca</td>
<td>Registered herbal medicine, Chocolate brown decoction.</td>
<td>Osompa Herbal Center, Accra.</td>
<td>For diabetes, high blood pressure and weight loss. Lowers blood sugar and cleans the body system.</td>
</tr>
<tr>
<td>Herbal product ‘F’ Tetewobika garlic bitters “The natural herbal medicine for strength and vitality”</td>
<td>HPF</td>
<td>Citrus aurantifolia, allium sativum, Honey.</td>
<td>Registered herbal medicine, Chocolate brown decoction with visible solid granules.</td>
<td>Tetewobika Herbal Center Ltd, Accra.</td>
<td>For the management of asthma, high blood pressure, diabetes, body pains and menstrual pains.</td>
</tr>
</tbody>
</table>

NB: None of the products indicated the proportions or amounts of the ingredients present in the respective products.
4.13 RELATIVE ORGAN WEIGHT ANALYSIS

The rats were weighed weekly during the study period and on the 30<sup>th</sup> day prior to sacrifice. On the 30<sup>th</sup> day the rats were sacrificed by chloroform. The liver, heart, lung, kidney, spleen and testes were removed and washed, dried with filter paper and weighed. The organ weights relative to the body weights were calculated using the equation below.

\[
\text{Relative organ weight} = \frac{\text{Weight of the organ (g)}}{\text{Weight of the animal (g)}} \times 100
\]  
(Equation 6)

4.14 BIOCHEMICAL ANALYSIS

For the biochemical analysis the rats were fasted for 12 hours, were chloroformed and 5 ml of blood was collected via cardiac puncture. Gel separator sample tubes without anticoagulant were used. The samples were centrifuged at 3000 rpm for 15 min. The sera were separated, stored at -20°C and used for evaluation of biochemical parameters. The analysis was done in an automated biochemistry analyser (ATAC 8000, Elan Diagnostics, CA, USA). The biochemical parameters were bilirubin (both direct bilirubin (DB) and total bilirubin (TB)), alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), alkaline phosphatase (AFOS), total protein (TP), albumin (ALB), globulin (GLO), blood urea nitrogen (BUN), creatinine (CREA), glucose (GLU), low density lipoprotein (LDL), very low density lipoprotein (VLDL), high density lipoprotein (HDL), triglyceride (TG) and cholesterol (CHOL).

4.15 HEMATOLOGY

Blood samples were collected into sample tubes containing sodium EDTA (1% sodium EDTA in normal saline), centrifuged at 3000 rpm for 20 min as described above. Red blood cell (RBC), white blood cell (WBC), granulocyte (GRA), lymphocyte (LYM) and platelet (PLT) counts, haemoglobin (HGB), hematocrit (HCT), mean corpuscular haemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC), platelet distribution width (PDW), mean platelet volume (MPV), thrombocytocrit (PCT) and platelet larger cell ratio (P-LCR) were determined.

4.16 SPERM COUNT, MOTILITY AND MORPHOLOGY

Briefly, small portion of cauda epididymis was cut and crushed in 1 mL of 37°C neutral buffer solution of sodium carbonate (NaHCO<sub>3</sub>) to make a homogeneous mixture. Nigrosine stain (in a volume of 2-3 drops) was added into the mixture and 10 µL of the homogenate sample was pipetted on a prewarmed slide. A minimum of 10 fields were observed for sperm counting and to evaluate quality under the high-power of light microscopy at 40X magnification.

4.17 SAMPLE PREPARATION FOR HISTOLOGY

The liver, heart, kidney, spleen, lungs and testis were taken and fixed in 10% formalin in neutral sodium carbonate (NaHCO<sub>3</sub>) buffer (%/%). Sections of the fixed liver, heart, kidney, spleen, lungs and testis prepared for histological examination were dehydrated, paraffinized into paraffin
blocks and embedded according to standard sampling and trimming procedures. About 4–10 µm thick sections were prepared, stained with haematoxylin and eosin and mounted in neutral DPX medium. Observing the slides was done under a light microscope.

**4.18 STATISTICAL ANALYSIS**

Results were analysed using one-way Analysis of Variance (one-way ANOVA) at 95% confidence interval and Turkeys post hoc test. Statistically significant differences were set at p < 0.05 for all tests. GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA) for Windows and IBM’s SPSS version 21 were used to perform all statistical analysis and the findings were presented in charts and tables.

Ethical clearance for the data collection was issued by the UCCIRB (ethical approval number: UCCIRB/EXT/2017/07).
5 RESULTS AND DISCUSSION

In the present study the safety of the herbal medicinal products was investigated from different perspectives. Insight into the efficacy and safety of commonly used herbal medicinal products (HMPs) was obtained from the users and the follow-up studies. The data will be useful in consumer education, further studies and possibly policy development to enhance safe and rational use of HMPs.

5.1 QUALITATIVE STUDY RESULTS (I)

5.1.1 General Results of the Qualitative Study

The consumer interviews included seven major themes. The themes were substandard medication, cost, knowledge on herbal medicines, efficacy, belief and perception about HMs, reporting adverse effect to general practitioner and safety of HMs. In brief, herbal medicinal products were routinely used among respondents and often over an extended period. Over 70% of the interview participants had used HMPs for 2 or more years, and 73% of these individuals use the HMPs routinely with or without pharmaceutical medicine for their primary health needs. Experienced efficacy reported by the informants was high (60%). Close to 21% believed HMPs were expensive and not cost effective, but most participants believed the HMPs are less expensive and cost effective. Concerns about the fast-growing number of HMPs on the market, substandard medications, false claims by vendors and dosage mis-appropriation practices were high among informants. Adverse health effects associated with HMP usage were generally not severe. Voluntary reporting of HMP usage and adverse effect to the general practitioner was very low.
5.1.2 Knowledge and Rational Use of Herbal Medicines

In this study, it was observed that most participants’ knowledge about herb-drug, herb-herb and herb-food interactions was generally low, which affects safe use of the products. The observation and the unsafe practices correlate well with the findings of Dawood et al., (2017) who reported that lack of consumers’ knowledge was associated with inappropriate practices in using medicines. This observation could be due to the lack of adequate information on the product data sheets. Many consumers buy their herbal products from over-the-counter facilities outside professional care providers where professional guidance might not be available. Also, the available information was sometimes regarded ambiguous and misleading. The users felt that there was lack of scientific evidence. Similar findings have been reported by Monera-Peduka et al.,
(2016), and Raynor et al., (2011) in the United Kingdom study. Due to the perceived bias and unjustified labeling information there was apparent lack of trust in the labels on the herbal products.

5.1.3 Concomitant Use of Herbs and Drugs

Data on combined use of herbs and drugs have been divisive. Zhang (2011) reported that patients combining herbal and antipsychotic drugs had significantly better improved health outcomes compared to antipsychotic drugs users. However, a small fraction of the study group combining herbal medicines and antipsychotic drugs was reported to have worse outcomes than antipsychotic drugs group (Zhang, 2011). In the present study, concomitant herb-drug use among the informants without knowledge about the compatibility of the combined drugs was high. Similar findings have been previously reported in other parts of Ghana (Ameade et al., 2018). Informants practicing such combination without professional guidance were at increased risk for undesirable drug-herb interaction. A possible reason observed was that a sizeable number of informants believed that orthodox medicine has immediate but short-lived effect while the efficacy of HM is slow but long-lasting. As a result, they administer HMs after pharmaceutical medical treatment to completely cure their sickness. “I usually take herbal medications after pharmaceutical medicine to complete the treatment; cure it” (H33). This observation correlates with previous studies (Mcintyre et al., 2015, Aziato and Antwi, 2016). Some consumers used HMPs after pharmaceutical drugs in order to reduce or manage the side effects of pharmaceutical medicines.

5.1.4 Motivation to Use Herbal Medicines

Different factors were identified as motivators in using HMPs. Some interviewees have previously reported that advertisement of herbal medicines in Ghana is very low (Aziato and Antwi, 2016). In the present study, however, it was observed that most participants were introduced into using herbal medicines via media advertisement. In Uganda a major motivating factor for pregnant women to use herbal medicines was the perception that they are effective (Nyeko et al.,2016). In South Germany younger residents having low educational level, with poor health and low socio-economic status were reported to be positively associated with HMP use (Du et al., 2014). Usually, HMPs are not prescribed by physicians in Ghana, patients rely hugely on advertisements and recommendations from family, friends, and previous users. “I rely on people’s experiences and recommendations after using such medications” H7. About 40 % of informants were first introduced into using herbal medicinal products through radio advertisement, 27% through friends and 13.5% through family members. Most informants listen to radio advertisements for health information. As a result, radio channel could serve as a means for public health education and health promotion exercises that targets HMP consumers. Other motivating factors identified include recommendations by the HMP vendors, when they are advertising their herbal products. The belief that HMPs are non-chemicals and are without side effects was also identified. This belief has also been reported previously by Aziato and Antwi (2016) as a motivator to HMPs usage.
5.1.5 Assessing Cost and Cost-Effectiveness of HMPs

Available data on cost of HMPs is divisive (James et al., 2018). In the present study, close to 50% participants believed that HMs are expensive, sometimes more expensive than pharmaceutical medicines. A similar trend was identified in Australia by McIntyre and colleagues (2015). This finding contradicts WHO position on HMs, which considers the use of HMs to be an affordable means of treatment (WHO, 2007). The reason could be the subsidization of essential medicines in Ghana by international donors, and the free provision of pharmaceutical medicines that are covered by the Ghana Health Insurance Scheme (GHIS). The scheme provides free pharmaceutical medicines to patients under its coverage. The HMPs in Ghana do not benefit from any of these policies and might be seen expensive by users of these products.

5.1.6 Users’ Belief and Perception About Herbal and Orthodox Medicines

In the present study, a class of informants had the belief that some sicknesses can only be managed or treated with herbal medicines. Some of the respondents used HMPs to relieve the side effects emanating from pharmaceutical medications administration. This practice is built on the perception that herbal medicines are safer alternatives of health care. These factors correlate well with the previous studies especially concerning chronic disease management (Kristoffersen et al., 2019). According Wagner et al., (1999) perceived seriousness of the illness and safety of herbal medicines were associated with higher number of visits to alternative medicine practitioners compared to physician visits in the USA in 1990. Different beliefs and perceptions towards herbal medicines, pharmaceutical drugs and or disease states have been previously reported by Peprah et al. (2019).

5.1.7 Safety Concerns of HMPs

Consumers had concerns about adulterated and sub-standard HMPs on the Ghanaian market. The concerns of the consumers are justifiable. The adulteration practices are widespread and there are methodological difficulties in detecting the adulterants in HMPs. In the country HMPs are less regulated. The consumers who were aware of fake HMPs on the market expressed efficacy of herbal medicines with caution.

Adulteration of HMPs refers to the addition of extraneous, improper, or inferior ingredients that should not be present in the herbal product (Xu et al., 2019). Adulteration and fake medications are global health challenge (Roger and Boateng, 2007, Ambroise-Thomas, 2012, Sato, 2014). According to Xu et al. (2019), substantial number of Traditional Chinese Medicines (TCMs) including herbal medicines were adulterated with undeclared drugs and non-drug substances. In Ghana anti-malaria herbal products have been adulterated with chloroquine in (Wilmot et al., 2017). Fake medicines represent close to 50% of the pharmaceutical medicines on the market of many African countries, the same could be said about HMPs (Ambroise-Thomas, 2012). Fake medicines lead to increased deaths, disease complications and development of drug resistant strains. It therefore poses a major public health challenge and require concerted effort to control it.

Another area of concern was the perception that HMPs are natural, non-chemical and as a result they are safe. This finding correlates well with previous studies (James et al., 2018, Ahwinahwi
Poisonous medicinal plants that have been documented in literature (Watt and Breyer-Brandwijk, 1962, Muenscher, 1939, Chopea, 1949) and natural is not synonymous to safety. Some users had experienced adverse health effects ranging from mild to moderately severe health conditions. Common among such side effects were constipation, nausea, headache and dizziness, kidney disease confirmed by the medical doctor and hypertension. The findings support the evidence that, though HMPs are natural and generally safe, they could still cause adverse health problems (Ernst, 1998).

5.1.8 Reporting Usage and Safety Issues to General Practitioner

It was observed that HMP consumers find it difficult to voluntarily report HMPs usage and side effects to the primary care physician during their hospital visits. This observation conforms to previous findings by McIntyre et al., (2015) and was also reported in a systematic review by James et al., (2018). It was reported that over 50% of alternative medicine consumers in Sub-Saharan Africa fails to report their alternative medicine use to their health care providers. Factors such as fear of receiving improper care, healthcare providers’ negative attitude and a lack of enquiry about the used traditional, complementary and alternative medicines were identified (James et al., 2018). In the present study three reasons were found to be responsible for the reporting constrains between HM consumers and physicians. The first is “shyness”, the second is fear and “feeling of being condemned by the physician”. The third was the physicians’ failure to ask for such information from the patient. Physicians could create a friendly atmosphere and initiate discussions on this topic during hospital visitations by patients and guide HMPs consumers on the safe use of their herbal preparations.

5.2 PESTICIDE AND HEAVY METAL EVALUATION (II AND III)

5.2.1 Descriptive Statistics of Pesticide and Heavy Metals

Organophosphates were the most common class of pesticides identified in the products. Chlorpyrifos was identified in all the six products with concentration range of 0.002 mg/kg to 0.042 mg/kg. Higher levels of pirimiphos-methyl were identified ranging from 0.008 mg/kg to 0.082 mg/kg in the samples. Heavy metals ranged from non-detectable (ND) to 9.171 mg/kg. The metal with the highest concentrations was Mn (1.755 mg/kg to 9.171 mg/kg) (II, III). The heavy metal concentrations were relative higher than the pesticide contents in the samples (table 1 study II, table 1 study III).

All the metal concentrations did not correlate well with the pesticides in the HMPs. This observation generally suggests different accumulation paths for these classes of compounds. The herbal materials are obtained by local farmers and herbalists either wild or cultivated. The detected pesticides are locally applied during plant cultivation or post-harvest pest control. Mineral elements and heavy metals result from natural processes, mining activities and other anthropogenic sources. Pirimiphos-methyl pesticide and heavy metals in the samples have likely different sources due to the strong reverse correlation observed (table 6). However, strong correlations were observed among most of the metals except mercury (Hg) and lead (Pb) during Pearson’s two tailed pairwise correlation analysis. This finding suggests that, Cr, Mn, Cu, As and Cd in the samples might have originated and/or accumulated from a common source in the
medicinal plants. Natural sources like rock weathering and anthropogenic factors including mining activities and farming practices might have a role in the origin of the observed heavy metals or pesticides. The identification of chlorpyrifos in all and pirimiphos-methyl in most of the studied HMPs correlates with the findings of a previous multinational study (Ingenbleek et al., 2019). The identification of these organophosphorus pesticides in different foods and herbal products in the Sub-Saharan region suggest their diverse use in the region.

Table 6. Pearson’s two-tailed correlation of metals and pesticides in the HMPs

<table>
<thead>
<tr>
<th></th>
<th>Cr</th>
<th>Mn</th>
<th>Ni</th>
<th>Cu</th>
<th>As</th>
<th>Cd</th>
<th>Pb</th>
<th>Hg</th>
<th>Chlo</th>
<th>Feni</th>
<th>PM</th>
</tr>
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<td>Cr</td>
<td>1.0</td>
<td>.77</td>
<td>.92</td>
<td>.96</td>
<td>.97</td>
<td>.93</td>
<td>.87</td>
<td>.06</td>
<td>.38</td>
<td>b</td>
<td>-1.0</td>
</tr>
<tr>
<td>Mn</td>
<td>.77</td>
<td>1.0</td>
<td>.86</td>
<td>.85</td>
<td>.84</td>
<td>.88</td>
<td>.65</td>
<td>-2.1</td>
<td>.54</td>
<td>b</td>
<td>-1.0</td>
</tr>
<tr>
<td>Ni</td>
<td>.92</td>
<td>.86</td>
<td>1.0</td>
<td>.96</td>
<td>.92</td>
<td>.94</td>
<td>.54</td>
<td>.05</td>
<td>.62</td>
<td>b</td>
<td>-1.0</td>
</tr>
<tr>
<td>Cu</td>
<td>.96</td>
<td>.85</td>
<td>.96</td>
<td>1.0</td>
<td>.96</td>
<td>.99</td>
<td>.72</td>
<td>.20</td>
<td>.61</td>
<td>b</td>
<td>-1.0</td>
</tr>
<tr>
<td>As</td>
<td>.97</td>
<td>.84</td>
<td>.92</td>
<td>.96</td>
<td>1.0</td>
<td>.93</td>
<td>.83</td>
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<td>.51</td>
<td>b</td>
<td>-1.0</td>
</tr>
<tr>
<td>Cd</td>
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<td>.94</td>
<td>.99</td>
<td>.93</td>
<td>1.0</td>
<td>.79</td>
<td>.20</td>
<td>.62</td>
<td>b</td>
<td>-1.0</td>
</tr>
<tr>
<td>Pb</td>
<td>.67</td>
<td>.65</td>
<td>.54</td>
<td>.72</td>
<td>.63</td>
<td>.79</td>
<td>1.0</td>
<td>.30</td>
<td>.29</td>
<td>b</td>
<td>-1.0</td>
</tr>
<tr>
<td>Hg</td>
<td>.06</td>
<td>-.21</td>
<td>.05</td>
<td>.20</td>
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<td>.30</td>
<td>1.0</td>
<td>.50</td>
<td>b</td>
<td>b</td>
</tr>
<tr>
<td>Chlo</td>
<td>.38</td>
<td>.54</td>
<td>.62</td>
<td>.61</td>
<td>.51</td>
<td>.62</td>
<td>.29</td>
<td>.50</td>
<td>1.0</td>
<td>b</td>
<td>b</td>
</tr>
<tr>
<td>Feni</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td>b</td>
</tr>
<tr>
<td>PM</td>
<td>-1.0</td>
<td>-1.0</td>
<td>-1.0</td>
<td>-1.0</td>
<td>-1.0</td>
<td>-1.0</td>
<td>-1.0</td>
<td>-1.0</td>
<td>-1.0</td>
<td>b</td>
<td>1</td>
</tr>
</tbody>
</table>

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).
. b Cannot be computed because at least one of the variables is constant.

Chlo = chlorpyrifos, Feni = fenitrothion, PM = pirimiphos-methyl

5.2.2 Safety Evaluation of Pesticides and Heavy Metals (II, III)

Trace essential minerals including Mn, Cu, Cr and Ni are needed in micro quantities for normal physiological activities. Exposure to excess amounts above their permissible levels may pose serious adverse health risk. Not much physiological importance has been associated with As, Cd, Hg and Pb. The levels of Cr, Mn, Ni, Cu, As in all the studied HMPs(A-F), Pb in HPA and HPB, and pirimiphos-methyl in HPE (0.085 mg/kg) were above their respective international maximum residual limits (MRL) (Studies II, III). Based on the USA, EPA and WHO standards these products are considered unsafe to be on the market and they are not allowed to entry into countries that use these standards. Ghana has not MRL standards of its own. The heavy metal contamination...
observed in the present study correlates well with the study by Nkansah et al., (2016). They discovered that certain medicinal plant materials on the Kumasi market had high levels of heavy metals in raw medicinal plant materials. They reported 0.44–0.89 mg/kg for Pb and 0.11–0.53 mg/kg for Cd. In the present study 0.02338– 0.13969 mg/kg Pb and 0.00181– 0.06 mg/kg Cd was identified in the final products. The low content of these metals compared to the raw materials suggest that the materials might have been contaminated prior to processing. Anthropogenic sources like the use of As and Hg for gold and mining for other mineral ores (Kamunda et al., 2016), irrigation with polluted water and agrochemicals are possible sources for heavy metal contamination (Singh et al., 2010).

The concentrations of the identified pesticides were mostly within the MRL safe limit and do not pose adverse health risk to the public. In addition, globally banned pesticides including aldrin, dieldrin, allethrin and gamma chlordane, which are also banned in Ghana, were identified qualitatively in 50% of the samples. Presence of banned pesticides in Ghanaian plant materials has been recently reported by Affum and colleagues as well (2018). These observations suggest continual use of these pesticides in the country and thus concerted effort by authorities will be required to bring it under control.

5.2.3 Acute Health Risk Assessment of Pesticide and Heavy Metals (II and III).

The estimated daily intakes (EDIs) of the heavy metals and pesticides for both adults and children were mostly within the oral reference dose limits for HPB-HPE (table 7A and 7B). However, the daily intakes of Cu of HPA, As and Cr of HPF for children (table 7B) as well as As of adults for HPF (table 7A) were all above the daily reference dose. This indicates that the daily administration of HPB-HPE may not pose acute health risk to the patient if administered in accordance to the dosage instructions. The current observation supports the findings of Tschinkel et al., (2020) on the Brazilians’ herbal medicinal concoctions.

The daily administration of HPF poses Cr and As overexposure health risk to children and As overexposure to adults. Furthermore, HPA poses children to overexposure to Cu. In addition, from the consumer interview study (study I), we observed that many consumers do not administer their products in accordance to the dosage instructions. This class of consumers therefore put themselves at a greater health risk. Heavy metal contamination of herbal medicines is major global concern requiring regular monitoring to protect the health of the public.
Table 7A. Estimated daily intakes (EDI) of the heavy metals and pesticides (adult) (mg/kg/day)

<table>
<thead>
<tr>
<th>Sample</th>
<th>HPA</th>
<th>HPB</th>
<th>HPC</th>
<th>HPD</th>
<th>HPE</th>
<th>HPF</th>
<th>CA</th>
<th>WA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cr</td>
<td>4.77x10^{-5}</td>
<td>8.35x10^{-6}</td>
<td>1.47x10^{-5}</td>
<td>8.99x10^{-6}</td>
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<td>3.07x10^{-4}</td>
<td>3.33x10^{-4}</td>
<td>8.33x10^{-4}</td>
</tr>
<tr>
<td>Mn</td>
<td>1.19x10^{-4}</td>
<td>2.05x10^{-5}</td>
<td>4.67x10^{-5}</td>
<td>1.66x10^{-5}</td>
<td>6.54x10^{-6}</td>
<td>5.19x10^{-4}</td>
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<td>4.33x10^{-3}</td>
</tr>
<tr>
<td>Ni</td>
<td>3.18x10^{-5}</td>
<td>5.84x10^{-6}</td>
<td>1.45x10^{-5}</td>
<td>6.75x10^{-6}</td>
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<td>2.22x10^{-4}</td>
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<td>2.33x10^{-2}</td>
</tr>
<tr>
<td>Cu</td>
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<td>1.05x10^{-4}</td>
<td>6.20x10^{-5}</td>
<td>1.36x10^{-5}</td>
<td>1.68x10^{-3}</td>
<td>NA</td>
<td>5.0x10^{-2}</td>
</tr>
<tr>
<td>As</td>
<td>4.56x10^{-5}</td>
<td>6.32x10^{-6}</td>
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<td>7.30x10^{-6}</td>
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<td>3.33x10^{-4}</td>
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<tr>
<td>Cd</td>
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<td>3.33x10^{-4}</td>
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</tr>
<tr>
<td>Hg</td>
<td>ND</td>
<td>3.08x10^{-10}</td>
<td>ND</td>
<td>1.98x10^{-8}</td>
<td>ND</td>
<td>ND</td>
<td>3.33x10^{-4}</td>
<td>1.67x10^{-4}</td>
</tr>
<tr>
<td>Chlo</td>
<td>3.91x10^{-5}</td>
<td>6.15x10^{-5}</td>
<td>5x10^{-4}</td>
<td>2.68x10^{-4}</td>
<td>3.88x10^{-5}</td>
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<td>Feni</td>
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<td>ND</td>
<td>ND</td>
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<td>NA</td>
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<td>PM</td>
<td>ND</td>
<td>ND</td>
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<td>ND</td>
<td>6.36x10^{-4}</td>
<td>ND</td>
<td>NA</td>
<td>1x10^{-2}</td>
</tr>
</tbody>
</table>

CA = Canadian upper tolerable daily intake reference limits for herbal products (HPs) in mg/kg/day (Kosalec et al., 2009), WA = WHO/FAO upper tolerable daily intake reference limits for HPs (mg/kg/day) (Sekwati-Monang, et al., 2016). HP(A-F) = herbal products A-F. NA = reference not available. ND = not detectable. Chlo = chlorpyrifos, Feni = fenitrothion and PM = pirimiphos-methyl. Figures above the reference level are shown in bold.
Table 7B. Estimated daily intakes (EDI) of the heavy metals and pesticides for children (mg/kg/day)

<table>
<thead>
<tr>
<th>Sample</th>
<th>HPA</th>
<th>HPB</th>
<th>HPC</th>
<th>HPD</th>
<th>HPE</th>
<th>HPF</th>
<th>CA</th>
<th>WA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cr</td>
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<td>4.48 x10^{-5}</td>
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</tr>
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</tr>
<tr>
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<td>1.68 x10^{-4}</td>
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</tr>
<tr>
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<td>4.12 x10^{-6}</td>
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</tr>
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<td>1.15 x10^{-4}</td>
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<td>8.33 x10^{-10}</td>
<td>ND</td>
<td>5.36 x10^{-8}</td>
<td>ND</td>
<td>ND</td>
<td>3.33 x10^{-4}</td>
<td>1.67 x10^{-4}</td>
</tr>
<tr>
<td>Chlo</td>
<td>1.06 x10^{-4}</td>
<td>1.67 x10^{-4}</td>
<td>1.36 x10^{-3}</td>
<td>7.25 x10^{-4}</td>
<td>1.05 x10^{-4}</td>
<td>8.69 x10^{-3}</td>
<td>NA</td>
<td>5.0 x10^{-2}</td>
</tr>
<tr>
<td>Feni</td>
<td>ND</td>
<td>8.33 x10^{-4}</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>NA</td>
<td>3 x10^{-1}</td>
</tr>
<tr>
<td>PM</td>
<td>ND</td>
<td>ND</td>
<td>2.58 x10^{-4}</td>
<td>ND</td>
<td>1.72 x10^{-3}</td>
<td>ND</td>
<td>NA</td>
<td>1 x10^{-2}</td>
</tr>
</tbody>
</table>

CA = Canadian upper tolerable daily intake reference limits for herbal products (HP) in mg/kg/day (Kosalec et al., 2009), WA = WHO/FAO upper tolerable daily intake reference limits for HPs (mg/kg/day) (Sekwati-Monang, et al., 2016). HP(A-F) = herbal products A-F. NA = reference not available ND = not detectable, Chlo = chlorpyrifos, Feni = fenitrothion and PM = pirimiphos-methyl. Figures above the reference level are shown in bold.

5.2.4 Chronic Health Risk Assessment (II and III).

Non-carcinogenic chronic hazard index of heavy metals and pesticides

The total non-carcinogenic chronic hazard index (HI) per herbal product is the sum of the individual targeted hazard quotient (THQ) of all contaminants (pesticides and heavy metals) per HMP. If the estimated HI value is ≥ 1, there is a potential health risk to the exposed population over an extended exposure period. HI <1 indicates that the exposed population is unlikely to experience adverse health risk in their lifetime. The available estimated HI for HPC, HPE and HPF for both adults and children were greater than 1 (table 8). This finding shows that long-term consumption of HPC, HPE and HPF may pose health risk to the public due to heavy metal and pesticide contamination. Increased heavy metal health risk through herbal medicines exposure have been well documented in literature (Ingenbleek et al., 2019, Tschinkel et al., 2020, Nkansah et al., 2016). Health risk associated to overexposure to metals and pesticides have been well documented in literature. For instance, respiratory paralysis has been associated with pirimiphos-methyl over exposure (Rajini and Krishnakumari, 1988, Akoto et al., 2016). Cd, Pb, As and Cr have been linked with lung and kidney cancers, hypertension and cardiovascular diseases, diabetes, kidney and heart failure (Bagraie and Aghili, 2019, Turdean 2011, Elevli and Ozturk 2019, Habibollahi et al., 2019, Cui et al., 2004). In addition, it was observed that children who consume HPF have higher cancer risk with total cancer risk (TCR) of 1.01x10^{-3} to develop adverse health...
effects due to pesticides and heavy metal over exposure than their adult counterparts with TCR of $3.73 \times 10^{-4}$ (table 8).

<table>
<thead>
<tr>
<th>HMP</th>
<th>TCR Adults</th>
<th>TCR Children</th>
<th>HI Adults</th>
<th>HI Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPA</td>
<td>$6.85 \times 10^{-5}$</td>
<td>$1.85 \times 10^{-5}$</td>
<td>0.34</td>
<td>0.88</td>
</tr>
<tr>
<td>HPB</td>
<td>$9.48 \times 10^{-5}$</td>
<td>$2.57 \times 10^{-5}$</td>
<td>0.71</td>
<td>0.71</td>
</tr>
<tr>
<td>HPC</td>
<td>$2.04 \times 10^{-5}$</td>
<td>$5.54 \times 10^{-5}$</td>
<td>1.03</td>
<td>1.09</td>
</tr>
<tr>
<td>HPD</td>
<td>$1.1 \times 10^{-5}$</td>
<td>$2.97 \times 10^{-5}$</td>
<td>0.78</td>
<td>0.79</td>
</tr>
<tr>
<td>HPE</td>
<td>$3.02 \times 10^{-6}$</td>
<td>$8.19 \times 10^{-6}$</td>
<td>1.75</td>
<td>6.62</td>
</tr>
<tr>
<td>HPF</td>
<td>$3.73 \times 10^{-4}$</td>
<td>$1.01 \times 10^{-3}$</td>
<td>2.15</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

Figures showing cancer risk TCR and HI above acceptable level are bolded.

**Total carcinogenic chronic hazard index of heavy metals and pesticides**

Total carcinogenic risk (TCR) assessment for the carcinogenic pesticides and heavy metal components present in the HMPs were carried out to assess the increased risk to cancer due to the consumption of the HMPs. TCR is dependent upon many factors including the carcinogens present, the exposure route and the duration of exposure. The oral exposure route of exposure and the oral route slope factors were used for the TCR estimation. TCR values lower than $1 \times 10^{-6}$ are considered as negligible, above $1 \times 10^{-4}$ unacceptable and between $1 \times 10^{-6}$ and $1 \times 10^{-4}$ are considered acceptable range (Ullah, et al., 2017). In this study the TCR values were acceptable for both adults and children except for HPF. For adults TCR value of HPF was $3.73 \times 10^{-4}$ and for children $1.01 \times 10^{-3}$ compared to the reference value $1 \times 10^{-4}$ (Table 8). Children and adults consuming HPF therefore have increased risk to cancer during a chronic exposure. Most of the observed cancer risks in this study originated from Cd and As exposure.

**5.3 IN VIVO 30-DAY REPEATED-DOSE SUB-CHRONIC TOXICITY**

**5.3.1 Haematology and Fasting Blood Sugar.**

In the present study, the red blood cells and total white blood cells were slightly elevated in some study groups, but none of the hematological parameters were significantly different from the control rats (Tables B1-B3 of study IV). This observation is similar to that of Asare et al. (2012).

The fasting blood sugar levels of HPB(1) and HPB(10) were significantly higher when compared with the control group. The observation suggests that the exposed rats were predisposed to diabetes. It could be inferred that consumers to the HPB are predisposed to hyperglycemia and increased diabetes risk.
Figure 7a. Biochemical parameters. F_Gluc = Fasting blood glucose (mg/dL), LDL_c = low density lipoprotein cholesterol (mg/dL), VLDL_c = very low density lipoprotein cholesterol (mg/dL), HDL = high density lipoprotein cholesterol (mg/dL), Ind_Bili = indirect bilirubin (µmol/L), Tot_Bili = total bilirubin (µmol/L), D_Bili = direct bilirubin (µmol/L), Urea (µmol/L).
Figure 7b. Biochemical parameters. Sperm concentration (Sperm_C) in (10^6/ml), Globulin (g/dL), Albumin (g/dL), total protein (g/dL), Alanine aminotransferase (ALT) (IU), aspartate amino transferase (ASAT) (IU), Alkaline phosphatase (AFOS) (IU), creatine (µmol/L).

Treatment-related responses were observed in all the three herbal preparations for ASAT enzyme. Significantly low ASAT activity was observed in HPA(1), HPA(5) and HPC at all dose levels (Figure 7b). Hepatocellular protective activity by a component of the polyherbal mixture could result in the observed lowered ASAT activity. Previously, one of the active medicinal plant components of HPC, *Phyllanthus fraternus* (Table I, IV), have been reported to possess liver ameliorative activity (Sailaja and Setty, 2006, Rajasubramaniam and Saradhi, 1997, Ahmed et al., 2002, Gopi and Setty, 2010). *Phyllanthus fraternus* is used in anti-jaundice medications traditionally.

This hepatoprotection observation was enforced with a dose-dependent reduction in ALAT levels in HPA and HPC dose groups though none was statistically significant. However, signs of liver toxicities were observed in the histology slides of almost all dose groups of the herbal products. Our observation supports the results reported by Tetteh and colleagues (2017), where any dose-related biochemical changes in the rats in the HPC study group were not identified. In addition HPA(5) induced a low albumin globulin ratio and a statistically significant low albumin levels when compared to the control group (P= 0.016). The low albumin and the albumin/globulin ratio indicate a sign of impeded synthetic function of the liver. The ASAT levels, especially induced by HPA and HPC, decreased. Since the polyherbal mixtures had two to seven different medicinal plant components, antagonizing effects by certain components cannot be underestimated.

Furthermore, *Vitex grandifolia*, a component of HPC has been reported to have toxic effects in Sprague-Dawley albino rats (Owolabi et al., 2010). The findings in the present study suggest that
the polyherbal mixtures A and C have plant component(s) that have hepatic ameliorating impact on toxic effect of another component present in the polyherbal mixture. The anti-hepatotoxic property correlates with previous findings (Upur et al. 2009, Wilmont et al., 2017). Both protective (Sailaja and Setty, 2006, Madubunyi and Asuzu, 1996, Fandohan et al., 2008, Mohan et al., 2010) and toxic (Owolabi et al., 2010) effects of certain herbal components have been reported.

5.3.3 Histology Study

Table 9. Histology results with observed signs of toxicity

<table>
<thead>
<tr>
<th>HMP</th>
<th>Liver</th>
<th>Kidney</th>
<th>Heart</th>
<th>Lung</th>
<th>Spleen</th>
<th>Testis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPA(1)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPA(5)</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPA(10)</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPB(1)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPB(5)</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPB(10)</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPC(1)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPC(5)</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPC(10)</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

(-) No signs of toxicity, mild (+), moderate (++), and above moderate (+++) toxicity of the histology study

Liver histology

The liver histology study on rats administered with HPA, HPB and HPC showed liver toxicity with signs including necrosis in HPA(1) (table 9, Fig. 5E, IV), intracytoplasmic fat globules in HPB(5) (Fig. 5F) and HPA(10) (Fig. 5G) treated groups. The observation contradicts the previous findings of Ojiako & Nwanjo, (2006). Furthermore, liver sections from HPB(5) and HPB(10) treated rats revealed fatty liver conformation. Similarly, foci of foamy hepatocytes was observed in HPC(5) treated rats, (Fig. 5I, IV). Other signs of hepatotoxicity including vessel congestion, foci of fatty changes and of foamy hepatocytes were also observed in some dose groups. Due to the observed heavy metal contamination in all the studied herbal products (III) the metals' contribution to the current liver toxicity results cannot be ignored (Baghaie and Aghili, 2019, Turdean, 2011). This observation opposes the results of a previous clinical trial carried out by Tetteh et al. (2017), where HPC was reported to be safe and without any adverse effects. In the present study the presence of component(s) with possible opposing harmful effects (Owolabi et al., 2010) or contamination with Cr, As, Cd and Pb heavy metals identified (III) might have overshadowed or thwarted the health benefits resulting in the hepatotoxic effects observed. In other studies the signs of liver toxicity in the liver histology sections have been detected to
contradict or overshadow the liver amelioration properties of *Vernonia amygdalina* present in HPA (Adesanoye and Farombi, 2010), and *Anthocleista nobilis* and *Phyllanthus fraternus* in HPC (Madubunyi and Asuzu 1996, Lata et al., 2014).

**Kidney histology function test**

The study group administered with HPC(1) had significantly lower relative kidney weight compared to the respective control group. There was no dose-response relationship in the middle and the highest dose groups, however. Kidney sections from the rats showed mild to moderate signs of toxic effects for most of the treated groups when compared to the control. All HPA, HPB and HPC dose groups except HPB(1) showed renal tubules and collecting ducts with mild congestion within their stroma and within the glomeruli (Fig. 5, IV). In addition, there were foci of chronic inflammatory change in the highest dose group of HPC. Signs including mild congestion with foci of chronic inflammatory change were observed in the kidney sections of HPC(10) treated group (Fig. 5T, IV). The inflammation was mild and the influence on hematologic anti-inflammatory response was not statistically significant (IV). The non-significant toxic effect is in line with the previous studies carried out with *Carica papaya*, a component of HPA (Afzan et al., 2012).

**Heart histology**

The heart sections had signs of toxicity in all the studied HMP groups, except in the group HPB(1) (table 9) with congested heart vessels observed in all HPA (Figure 5V-X, IV) and HPC treated groups (Figure 5Ab-Ad, IV). Haemorrhage, amorphous exudates and intensely congested vessels were observed in the heart of rats that received HPB(10).

**Lungs histology**

Signs of mild to moderate toxicity were observed in all dose levels of the three antimalarial polyherbal mixtures (table 9, Fig. 6, IV). Signs of chronic inflammation and foci of sloughed tissues within the airway were observed in HPA(1, 5 and 10) treated rats (IV). In addition the alveolar spaces in HPA(5 and 10) groups were obscured by debris and chronic inflammatory cells (IV). Non-specific chronic inflammation, thickened alveolus and congestion within the lung parenchyma were observed in HPB(1, 5, 10) groups. Furthermore, foci of sloughing within the airways were also observed in the lungs of the rats treated with HPB(5 and 10). Moreover, the lung sections of the rats that received HPC (all dose levels) showed alveolus with signs of moderate chronic inflammation, foci of sloughing and groups of chronic inflammatory cells filling alveolar spaces. These observations indicate that all the polyherbal mixtures had component(s) or foreign contaminants with lung toxicity effects.

**Spleen histology**

Any significant changes were not detected in the histology of the spleens when the study rats were compared to the control group (Figure 6K-T, IV). The finding is supported by literature (Ugbogu et al., 2018, Adesanoye and Farombi, 2010).
Testis histology

The sperm count decreased with increasing herbal dosage in all the three groups studied, but there was no statistical difference compared to the control group. Sperm morphological study showed no significant difference between the treated groups and the control group. Sections from testis of the control rats and from the study rats receiving different doses of HPA, HPB and HPC showed normal architecture with seminiferous tubules. They contained cells at all stages of spermatogenesis without any evidence of inflammation or adverse drug effect (Figure 6U-Ad, IV). Based on the results, it could be inferred that sub-chronic administration of HPA, HPB and HPC may not significantly affect fertility, but in chronic administration the effect might differ. Our results do not support previous studies on *Momordica charantia*, present in HPE, that the plant has antifertility effect on male and female rats (Tumkiratiwong et al., 2014, Adewale et al., 2014). In the present study no signs of adverse effects on sperm quality and quantity were detected.
6 SUMMARY AND CONCLUSIONS

The use of traditional and plant-based system of health care is a practice known globally for centuries. Plants produce secondary metabolites as a physiologically defensive mechanism against pests, diseases, pathogenic organisms and as an adaptation to stressful conditions. These metabolites have been harnessed to control disease vectors and to treat human and veterinary diseases. These plant compounds have also served as leads for the discovery and development of different pharmaceutical drugs. Growing trend of multidrug resistant pathogens, complex diseases as well as economic and easy accessibility of plant-based products have led millions of people to resort to traditional and plant-based medicines all over the world. Though globally used, policies and understanding of plant-based medicines varies between countries. Plant-based medicines are poorly regulated and less monitored for safety and efficacy in most developing and underdeveloped countries. In the present study, we evaluated the post-market safety and profiled the toxicity of commonly used polyherbal medicinal products (p-HMPs) in the Kumasi Metropolis of Ghana. This study has given a comprehensive understanding of safety of HMPs from different perspectives.

The interview study revealed that dosage malpractices were common among consumers. The knowledge of the consumers about possible side effects of HMPs was low, which contributed to consumers irrational use and dosage malpractices. Consumers acknowledged the circulation of fake, ineffective and possible adulterated HMPs. From the study it was observed that the efficacy and safety of the HMP is affected by factors including medicinal plant cultivation practices, the medicinal plant used in the mixture, the manufacturer, and distribution conditions. HMPs were reported to be generally safe; most side effects experienced by informants were generally not severe. Most informants however failed to report side effects and/or HMP usage to their general practitioners. Common reasons identified were the consumers’ shyness and fear of being condemned by general practitioners (GPs) and the GP’s failure to request for such information during the consumers’ hospital visitations.

In addition to the consumer interviews six Ghanaian polyherbal products, three antimalarial herbal products (HP(s)) (HPA, HPB and HPC), two antidiabetic HP(s) (HPD and HPE), and one antihypertensive HP (HPF) were evaluated. The study revealed that chronic exposure to HPC, HPE and HPF may pose health risk for adults and children due to heavy metal and pesticide overexposure (total hazard index >1). Respiratory paralysis (Rajini and Krishnakumari, 1988), kidney cancer (Turdean 2011), hypertension, cardiovascular diseases, lung cancer, and diabetes (Elevli and Ozturk, 2019, Habibollahi et al., 2019) have been associated with the overexposed pesticides and/or metals in this study. In addition, children exposed to HPF have higher risk to develop adverse health effects due to pesticides and heavy metal over exposure than adults. It was observed that these children have increased risk to cancer with TCR value of 1.01x10^{-3} compared to the reference TCR value of 1x10^{-4}. The data from the present study also suggest that chronic consumption of HPE may predispose to pirimiphos-methyl exposure and thus to possible health hazard. Similarly, some banned pesticides including aldrin, dieldrin and chlordane were identified in 50% of the studied herbal preparations, which suggests continual use of these pesticides in the country.
The polyherbal products HPA, HPB and HPC were further evaluated in *in-vivo* sub-chronic toxicity study in Sprague-Dawley rats. The results showed no signs of serious impairment to sperm count and sperm quality in the rats. Rats exposed to HPB were predisposed to hyperglycemia with increased diabetic risk. The organ histology sections of the highest dose groups of all the three polyherbal antimalarial products, HPA, HPB and HPC showed signs of mild to moderately severe heart, liver, lungs and kidney toxicities. Despite signs of hepatotoxic effect caused by all the studied products, the hepatic enzyme analysis of HPA and HPC rat groups revealed liver ameliorating property. The analysis revealed low ALAT and significantly low ASAT levels. HPA and HPC have components with liver ameliorating activity, which finding is supported by literature.

Pesticide and heavy metal contamination observed in all the studied polyherbal mixtures may impact either wholly or partly to the lung, liver, kidney and the heart toxicity. All the herbal mixtures were contaminated with As, Cr and Ni. Pb contamination was observed in HPA and HPB products. It has been well documented that exposure to high levels of Cr and As increases lung cancer risk (Habibollahi et al., 2019, Elevli and Ozturk, 2019). In addition, overexposure to and bioaccumulation of high level of As and Cd have been associated with heart failure, hypertension, cardiovascular diseases and diabetes (Elevli and Ozturk, 2019, Baghaie and Aghili, 2019). Furthermore, overexposure to Cd and Pb have been linked with kidney failure and kidney cancer (Baghaie and Aghili, 2019, Turdean 2011).

In conclusion, according to consumers’ reports, the herbal products are generally safe and effective. Dosage misappropriations and unsafe practices were common among informants. Consumers had concerns about sub-standard and possible adulterated HMPs. Most informants had the opinion not to report HMPs usage and side effects to general practitioners. The six studied HMPs were contaminated with heavy metals and HPE was contaminated with chlorpyrifos-methyl pesticide. Furthermore, HPC, HPE and HPF were identified to pose non-carcinogenic health risk to adults and children. Also, children exposed to HPF were observed to have higher health risk than adults and increased risk to cancer during chronic exposure. In addition, the 30-day *in-vivo* sub-chronic evaluation of HPA, HPB and HPC showed signs of mild to moderate liver, heart, lung and kidney toxicities in rats.

The results from this study could be applied for health promotion and for educating HMP consumers for the safe and rational use of polyherbal products. The results are useful for producers and cultivators in order to implement good cultivation and manufacturing practices. Over 40% of informants were introduced into HMs usage via radio advertisements. Radio broadcasting could be used for education and health promotion exercises of consumers. The obtained data will contribute for the reduction of the safety data gap, will increase scientific knowledge and discourse, and will direct other studies in further. The outcome also provide justification for clear-cut policies on herbal medicines and for the continuous need to review of existing regulatory requirements by regulatory authorities. This is necessary when protecting public health and ensuring that all herbal medicines approved for sale are safe and of suitable quality.

Further investigation on large-scale post-market surveillance should be conducted throughout the country for proper documentation of safety and efficacy of all HMPs on the market. The present study failed to associate experienced side effects by consumers of any specific HMPs due to
confounding factors including the practice of administering multiple HMPs concurrently (polypharmacy) during the occurrence of adverse effect. Prospective long-term investigation on population level and follow-up of the consumers of HPA-HPF products will be needed. These investigations are necessary in order to reveal incidences of organ disfunctions, cancers and other health problems caused by pesticide and heavy metal contamination. Investigation of chronic toxicity of HPA-HPF products in animal models and the use of modern technologies are recommended.

Based on the results from this study the following conclusions can be drawn

1. HMs were generally reported to be safe and effective and the experienced side effects were mostly not severe based on observed signs by consumers.

2. Consumers failed to report side effects and usage of HMs to general practitioners (GPs) due to factors including shyness and the feeling of being condemned by GPs and the doctors’ failure to request for such information.

3. Patients’ safety in using HMPs rest on all stakeholders including the consumers, policy makers, physicians and the HMPs producers.

4. Chronic exposure to the studied HPC, HPE and HPF products was associated with non-carcinogenic health risk for adults and children. Children exposed to HPF had higher health risk than adults and an increased risk to cancer due to heavy metal and pesticide contamination.

5. All the studied antimalarial products (HPA, HPB and HPC) had the potential to cause major organ-system damage in rats.

6. Patients should use the established health care system for their healthcare needs for severe malaria, and for diabetes and hypertension. The detected contaminants in the studied HMPs may potentially exacerbate problems associated with severe malaria, diabetes and hypertension during long-term management and expose to chronic organ adverse effects. Short-term exposure of the studied HMPs was not identified to pose significant health risk to the consumers.

7. Herbal products consumption has become part of the culture in Ghana. Regulatory assessments for approval of sale of herbal products should direct specific concern to the assessment of heavy metals and pesticides in the products. Authorities and producers need to ensure that only products of high quality with no or only with allowed amounts of contaminants are sold to consumers to protect patient safety. Better labeling of herbal products indicated with possible adverse health effects and herb-drug interactions will be needed in order to improve patient safety.
REFERENCES


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The aim of this study was to evaluate
the post-market safety and the toxicity
of commonly used herbal medicinal
products (HMPs) in Kumasi, Ghana.
The multidisciplinary study used in-depth
qualitative interviews of herbal medicine
consumers. Selected HMPs were evaluated
for heavy metal and pesticide contamination.
Three of the herbal products were further
evaluated in a 30-day in vivo sub-chronic
toxicity study using OECD 407 continuous
dose method in Sprague-Dawley rats.