Chemical and microbial contamination of herbal remedies and their potential health implications: A review

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Abstract
Herbal medicines are generally regarded as safe based on their long-standing use in various cultures. However, there are case reports of serious adverse effects after administration of herbal products. In a lot of cases, the toxicity has been traced to contaminants and adulteration. Assessment of the safety of herbal products, therefore, is the first priority in herbal research. This paper critically reviews a number of publications on the safety of herbal remedies consumed in Nigeria and across the globe. It was observed that most of the herbal remedies contain several chemical and microbial contaminants of priority concern. Even though reported at low concentrations, most times within the threshold limits set by regulatory bodies, continuous consumption may pose serious health challenge as most of these contaminants have ability to bio-accumulate and bio-magnify in the cells/tissues of consumers. Furthermore, there is dearth in information on speciation studies on some of the contaminants; therefore it is proposed that future research should include as a major component speciation studies of the contaminants as the different forms of them exhibit different physico-chemical properties including toxicities. The study concludes by suggesting measures of improving the quality of herbal medicines consumed in Nigeria and gaps that exist in literature.

Keywords aerosols; herbal medicine; chemical contaminant; microbial contaminant; heavy metals; poly aromatic hydrocarbons; pesticide residues.

1 Introduction
The use of herbs as medicine is the oldest form of healthcare known to humanity and has been used in all cultures throughout history (Barnes et al., 2007; Zhang, 2017a, b). Early humans recognized their dependence on nature for a healthy life and since that time, humanity has depended on the diversity of plant resources for food, clothing, shelter, and medicine to cure myriads of ailments. Led by instinct, taste, and experience, primitive men and women treated illnesses by using plants, animal parts, and minerals that were not part of their usual diet. They learned by trial and error to distinguish useful plants with beneficial effects from those
that were toxic or inactive, and also which combinations or processing methods had to be used to gain consistent and optimal results (Zhang and Liu, 2019). World Health Organization (WHO) indicated that 25% of modern medicines are made from plants that were first used traditionally. Examples include atropine, morphine, quinine, ephedrine, warfarin, aspirin, digoxin, vincristine, taxol, and hyoscine (Willow, 2011).

In most African countries including Nigeria, herbal medicine is recognized as an important component of health care system, especially among rural dwellers that constitute about 70% of the population (Esimone et al. 2002). A survey carried out in 1985 by WHO in Nigeria estimated that up to 75% of the population patronised herbal medicine (Omosuyinde, 2003). As a result of the ever increasing cost of orthodox health care services coupled with the side effects of certain synthetic drug therapies, much proportion of patients in the developing countries had resort to alternative herbal health care which they feel is natural, safer, more accessible, and more economical (Carter, 2001). The use of herbal products is not regulated in Nigeria and in many low-income countries and is freely available to everyone. The safety of these herbal medicines is poorly understood (Obi et al., 2006). Herbal medicines are not tested with scientific rigour required for conventional drugs and most manufacturers of these products do not submit proof of safety and efficacy to regulatory bodies before marketing. This calls for proper monitoring by regulatory agencies.

An adverse effect on long term herbal use, adulteration with toxic compounds and contamination by pathogenic microorganisms or natural toxins such as mycotoxins have been reported for herbal products and medicinal plants (Abou-Arab et al., 1999; Igweze et al., 2012; Onwordi et al., 2015; Ayanniyi et al., 2017; Elvis et al., 2019). The concern over quality of the products is mainly due to their potential contamination, considering their natural origin. Practices used in harvesting, handling, storage, production and distribution make medicinal plants subject to contamination. This paper provides a concise review on the available knowledge on chemical and microbial contaminants on herbal extracts, some technical developments in herbal medicine production and associated health implications. The paper recommends policy changes that would guide and improve future research effort especially in areas where much research appears not to have been adequately carried out.

1.1 Definitions of herbal medicines
Herbal medicine, also known as phytomedicine has been defined by WHO as finished labelled medicinal products that contain an active ingredient and can be aerial or underground parts of plants or other plant materials which include in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins, and dry powders of herbs - leaves, bark, roots, rhizomes or other plant parts which may be entire, fragmented powdered, or combinations thereof whether in the crude state or as plant preparations (WHO, 1996; Zhang, 2017a). Herbal medicines have been used to treat many conditions, such as asthma, eczema, premenstrual syndrome, rheumatoid arthritis, migraine, menopausal symptoms, chronic fatigue, and irritable bowel syndrome, among others (WHO, 1996). There is an estimated 750,000 plants on earth (Ahmad et al., 2006); however, relatively speaking, only a very few of the healing herbs have been studied scientifically. And because modern pharmacology looks for one active ingredient and seeks to isolate it to the exclusion of all the others, most of the studies that are done on plants continue to focus on identifying and isolating active ingredients, rather than studying the medicinal properties of whole plants.

Herbs and herbal preparations have been used to treat ailments since pre-historic times and the treatment of various diseases with plant-based medicines has remained an integral part of many cultures across the globe. Such medicines, derived directly or indirectly from plants, constitute over 25% of the pharmaceutical arsenal (Ahmad et al., 2006). Traditional medicine has attracted more attention worldwide since the latter part of the twentieth century.

1.2 Potentially hazardous contaminants and residues in herbal medicines
Toxicity in herbal medicine has been traced to contaminants and adulteration. However, some of the plants used in herbal medicines can also be highly toxic. As a whole, herbal medicines can have a risk of adverse effects and drug-drug interactions if not properly assessed. Assessment of the safety of herbal products, therefore, is the first priority in herbal research. There are various approaches to the evaluation of safety of herbal medicines. The toxic effects of herbal preparation may be attributed mainly to the following:

1. Inherent toxicity of plant constituents
2. Manufacturing malpractice and contamination

Evaluation of the toxic effects of plant constituents of herbal formulation requires detailed phytochemical and pharmacological studies. It could however be safe to assume that, based on human experiences in various cultures, the use of toxic plant ingredients has already been largely eliminated and recent reports of toxicity could largely be due to misidentification and overdosing of certain constituents. Some of them are considered as unavoidable contaminants or residues of herbal medicines. Contamination should be avoided and controlled through quality assurance measures such as good agricultural and collection practices (GACP) for medicinal plants, and good manufacturing practices (GMP) for herbal medicines. Chemical and microbiological contaminants can result from the use of human excreta, animal manures and sewage as fertilizers. As noted in the WHO guidelines on GACP for medicinal plants (WHO, 2007), human excreta must not be used as a fertilizer, and animal manures should be thoroughly composted. Toxic elements and other chemical contaminants, including solvents originating from products intended for use in households and industrial chemicals, can be concentrated in composted sewage. Therefore, care should also be exercised with sewage management in agricultural areas.

By far, the majority of potentially hazardous contaminants and residues are found in the herbs and herbal materials. This results in their presence in the products, such as herbal preparations and finished herbal medicines. The level of some contaminants and residues present at the stage of the medicinal plant may change as a result of post-harvest processing (e.g., drying), in herbal preparations such as extracts, and in finished herbal products during the manufacturing process. Table 1 indicates the classification of major contaminants and residues in herbal medicines. It indicates potentially hazardous contaminants and residues that may occur in herbal medicines. The summary table includes information on possible sources of contaminants and residues, as well as the man.

2 Methods
In this study, secondary data from online sources such as Google Scholar, Research Gate and PubMed were explored. Literature reports on the concentrations of chemical and microbial contaminants in herbal products consumed in Nigeria and across the globe were assessed. Major data were extracted and presented for discussion. The concentrations were compared with well-known permissible limits like WHO guidelines, European Union (EU) and United State Environmental Protection Agency (US EPA).

3 Review of Contamination of Herbal Remedies
Tables 2 presents summary of major studies on metal contamination of herbal remedies in Nigeria. Major results from the six geo-political zones are reported. Atomic absorption spectroscopic techniques was used to analyze metals in majority of the studies. Table 3 indicates summary of global outlook of metal contamination of herbal remedies. Studies in countries from Africa, Asia, Europe and South America sub-regions were examined. Majority of the studies used atomic absorption spectroscopic technique which is one of the most popular techniques for determining metals ions in samples. Table 4 shows global outlook of organic contaminants in herbal remedies.
Table 1 Classification of major contaminants and residues in herbal medicines.

<table>
<thead>
<tr>
<th>General Classification</th>
<th>Group</th>
<th>Subgroup</th>
<th>Specific examples</th>
<th>Possible sources</th>
<th>Stage of production at which detection occurred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Contaminants</td>
<td>Toxic and hazardous materials</td>
<td>Toxic metals and non-metals</td>
<td>Lead, cadmium, mercury, chromium (arsenic, nitrite)</td>
<td>Polluted soil and water, during cultivation/growth, manufacturing process</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>POPs</td>
<td>Dioxin, aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, mirex</td>
<td>Polluted air, soil and water, during cultivation/growth</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td></td>
<td>Radionuclide</td>
<td>Cs-134, Cs-137</td>
<td></td>
<td>Air, soil, water during cultivation/growth</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>Biological Contaminants</td>
<td>Microorganisms</td>
<td>Bacteria</td>
<td>Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella species, Shigella species, Escherichia coli</td>
<td>Soil, post-harvest processing, transportation and storage</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yeast, moulds</td>
<td></td>
<td>Post-harvest processing, transportation and storage</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protozoa - amoebae, Helminths -nematode</td>
<td></td>
<td>Soil, excreta; organic farming/cultivation, manufacturing process</td>
<td>1,3,4</td>
</tr>
<tr>
<td></td>
<td>Animals</td>
<td>Parasites</td>
<td>Cockroach and its Parts</td>
<td>Post-harvest processing, transportation and storage</td>
<td>1,2,4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insects</td>
<td>Mouse excreta, earthworms, acarous</td>
<td>Post-harvest processing, transportation and storage</td>
<td>1,2,4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solvents</td>
<td>Organic Solvents</td>
<td>Acetone, methanol, ethanol, butanol</td>
<td>Soil and water, during cultivation/growth, manufacturing process</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insecticides</td>
<td>Carbamate, chlorinated hydrocarbons, organophosphorus</td>
<td>Air, soil, water during cultivation/growth, post-harvest processing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pesticides</td>
<td>2,4-D, 2,4,5-T</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agrochemical Residues</td>
<td>Fungicides</td>
<td>Dithiocarbamate</td>
<td>Air, soil, water during cultivation/growth</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fumigants</td>
<td>Ethylene oxide, phosphine, methyl bromide, sulphur dioxide</td>
<td>Post-harvest processing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disease control Agents</td>
<td>Thiamethoxam</td>
<td>During cultivation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Residual solvents</td>
<td>Organic Solvents</td>
<td>Acetone, methanol, ethanol, butanol</td>
<td>Manufacturing process</td>
<td>3,4</td>
</tr>
</tbody>
</table>

*a Stage of production at which detectable: 1. medicinal plants; 2. herbal materials; 3. herbal preparations; 4. finished herbal products.

Source: (WHO, 2007)
### Table 2 Summary of studies on metal contaminants in herbal remedies in Nigeria.

<table>
<thead>
<tr>
<th>S/N</th>
<th>Reference Numbers</th>
<th>Geopolitical zone</th>
<th>Metals Analysed</th>
<th>Major Results: liquid (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ayanniyi et al., 2017</td>
<td>North-Central</td>
<td>Cd, Pb, and Fe</td>
<td>Cd: 0.003-0.3; Pb: BDL-0.067; Fe: 0.083-0.27; majority of the samples contained Cd and Pb in concentrations significantly lower than the permissible limits.</td>
</tr>
<tr>
<td>2</td>
<td>Odoh and Ajiboye, 2019</td>
<td>North-East</td>
<td>Cr, Zn, Fe, Pb, Ni, Co and Cd</td>
<td>Cr: 2.35-21.7; Zn: 16.0-24.1; Fe: 61.9-230; Pb:6.44-25.1, Ni:4.72-15.5, Co: 0.64-5.61; Cd: BDL</td>
</tr>
<tr>
<td>3</td>
<td>Umar et al., 2016; Ibrahim et al., 2018; Iwuwa and Mohammed, 2018</td>
<td>North-West</td>
<td>Cd, Cr, Co, Cu, Fe, Mn, Ni, Pb and Zn, Ca, Hg</td>
<td>Cd: 0.0045-0.1601; Cr: 0.0418-0.2092; Co: 0.0038-1.64; Cu: 0.0547-0.2465; Fe: 0.1197-876, Mn: 0.0123-7.72; Ni: 0.0073-1.72; Pb: BDL-11.8; Zn: BDL-0.2444; Ca: 743-19927; Hg: BDL</td>
</tr>
<tr>
<td>4</td>
<td>Obi et al., 2006; Elvis et al. 2019; Nwoko and Mgbeahuruige, 2011; Ekeanyanwu et al., 2013; Onyemelukwe et al., 2019; Iwuozor, 2019</td>
<td>South-East</td>
<td>Cd, Cu, Fe, Ni, Se, Zn, Pb, Hg, Cr, Mn,</td>
<td>98-100% of samples analysed contained elevated amount of heavy metals compared to FAO/WHO Standard</td>
</tr>
<tr>
<td>5</td>
<td>Igweze et al., 2012; MacDonald et al., 2014; Vaikosen and Alade, 2017; Igweze et al., 2019; Ayobami and Sylvester, 2019; Ayobami, 2019</td>
<td>South-South</td>
<td>As, Cd, Cr, Co, Pb and Ni</td>
<td>Percentage violation of WHO/EU guidelines for the metals were: As: 0%, Cd: 58.3%, Cr: 4.16%; Co: 0%; Pb: 54.1%, Ni: 54.1%</td>
</tr>
<tr>
<td>6</td>
<td>Onwordi et al., 2015; Offor et al., 2014; Jimoh et al., 2015; MacDonald et al. , 2015; Adie and Adekunle, 2017; Akintelu et al., 2019; Rufai et al., 2019</td>
<td>South-West</td>
<td>Cr, Ni, Cu, Zn, Cd, Mn, Hg</td>
<td>Cu: 0.04-9.44; Zn: 0.94-35.4; Pb: ND-33.8; Cr, Ni, Mn, and Hg were not detected</td>
</tr>
<tr>
<td>Region</td>
<td>Country</td>
<td>Concentration Ranges (ppm)</td>
<td>Reference Numbers</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>---------------</td>
<td>--------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>Nigeria</td>
<td>As: &lt; 0.005, Hg: BDL, Pb: 0.00057-33.80, Cd: 0.00059-3.08, Co: 0.00058-0.216, Mn: 0.0123-7.72-0.9, Ni: 0.000274-54.00, Cr: 0.00066-21.681</td>
<td>Obi et al., 2006; Igweze et al., 2012; Onwordi et al., 2015; Odoh and Ajiboye, 2019; Umar et al., 2016; Ibrahim et al., 2018; Jimoh et al., 2015; Laar and Odonkor, 2012.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ghana</td>
<td>As: 0.001-0.0012, Hg: &lt; 0.001, Pb: 0.0056-17.650, Cd: 0.002-14.050</td>
<td>Laar and Odonkor, 2012.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kenya</td>
<td>Pb: 0.02-22.08, Mn: 0.05-233.84, Cr: 0.02-7.31</td>
<td>Ngari et al., 2013.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>South Africa</td>
<td>Cd: 0.0045-0.1601, Cr: 0.0418-237.00, Co: 0.0038-0.0760, Mn: 0.0123-248.69, Ni: 0.0073-30.00, Pb: 0.185-0.0927</td>
<td>Okern et al., 2014.</td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>Saudi Arabia</td>
<td>Pb: 0.06-1.528, Hg: 0.026 - 0.102, Cd: 0.016-0.025</td>
<td>Alwakeel, 2008</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vietnam</td>
<td>Cr: 0.804-5.042, As: 0.173-15.162, Se: 0.038-1.168, Cd: 0.050-0.252, Hg: 0.024-0.508, Pb: 1.108-6.242</td>
<td>Kim et al., 2010.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Iran</td>
<td>As: 0.246-0.293, Pb: 0.254-52.74, Cd: 0.031-1.75</td>
<td>Mostafa et al., 2011; Zahra et al., 2013</td>
<td></td>
</tr>
<tr>
<td></td>
<td>India</td>
<td>Hg: BDL, As: 0.08-0.46, Pb: 0.002-2.64-0.0260, Co: 0.02-0.0088-0.23-0.0881, Cd: BDL -0.02-0.0010 Cr: 0.036 -4.93-0.0185, Ni: 0.06 ± 0.0120-1.07 ± 0.0057, Mn: 0.036-6.13 ± 0.0176</td>
<td>Rao and Galib, 2011; Kishan et al., 2014; Karayil and Bhavani, 2014</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malaysia</td>
<td>Pb: &lt;1 , Mn: 1.394±18.545, Cd: 0.105 ±0.314, Ni: BDL-54.5</td>
<td>Kong et al., 2018; Adelinesuyien et al., 2013</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lebanon</td>
<td>Pb: 1.1 -33.80, Cd: BDL -1.70, Mn: 23.00 -458.00, As: BDL-10.80, Cr: 3.1-55.00</td>
<td>Samira et al., 2013.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pakistan</td>
<td>Pb: 5.780 -6.696, Ni: 3.196 -3.621, Cd: 0.025-0.086, Cr: 3.400-4.276</td>
<td>Khan et al., 2013.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UAE</td>
<td>Cd: 0.1-1.11, Pb: 1.00-23.52</td>
<td>Rania et al., 2015.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Palestine</td>
<td>Cd: 64.01, Pb: 0.3210</td>
<td>Abuallah et al., 2019.</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>Poland</td>
<td>Mn: 3.03-129.01, Cd: 0.024-0.153, Ni: 1.30-2.71, Cr: 0.270 -1.721, Pb: 0.441-0.751</td>
<td>Krejpecio et al., 2007; Suchacz and Wesolowski, 2012.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serbia</td>
<td>Fe: 137.53-423.32, Cu, Zn and Mn ranges from: 8.91 to 62.20</td>
<td>Kostić et al., 2011.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Argentina</td>
<td>Heavy metals Present</td>
<td>Gomez et al., 2007.</td>
<td></td>
</tr>
<tr>
<td>South America</td>
<td>Brazil</td>
<td>Heavy Metals: 0.02-540, Pb: 3.37-0.25 to 7.03-0.51 (greater than ones previously published in literature)</td>
<td>Leal et al., 2013; Marina, 2009</td>
<td></td>
</tr>
</tbody>
</table>
Table 4 Concentrations of selected organic contaminants including PAHs in some countries across the globe.

<table>
<thead>
<tr>
<th>Country</th>
<th>PAHs and pesticide residues</th>
<th>Results</th>
<th>Reference Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>16 EPA Priority PAHs</td>
<td>(Σ16PAHs) in the tea samples ranged from 323 to 8800 μg/kg with the highest PPAHs found in a black tea.</td>
<td>Lin et al., 2005.</td>
</tr>
<tr>
<td>China</td>
<td>15 out of the 16 EPA Priority PAHs</td>
<td>The levels of total PAHs varied from 28.9 μg/kg in poria to 206.7 μg/kg in pinellia. The highest level was found for Naphthalene in pinellia tuber (140.6 μg/kg) and phenanthrene in panax (80.8 μg/kg).</td>
<td>Lingfeng et al., 2015</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>8 out of the 16 EPA Priority PAHs - naphthalene, fluoranthene, pyrene, methylanthracene, triphenylene, benzo[a]anthracene, benzo[a]pyrene, and coronene were determined</td>
<td>They were all detected</td>
<td>Ondrej et al., 2012</td>
</tr>
<tr>
<td>India</td>
<td>Heavy metals and Pesticide Residues</td>
<td>Heavy metals and pesticide residue were found below detection limits in all the samples.</td>
<td>Rao and Galib, 2011</td>
</tr>
<tr>
<td>Nigeria</td>
<td>16 EPA Priority PAHs</td>
<td>Σ16PAHs): 5.2–913.1, 38.7–593.1, and 38.0–1406.4 μg/kg for tea-, coffee-, and cocoa-based food drinks, respectively.</td>
<td>Chukwuindu et al., 2015</td>
</tr>
<tr>
<td>Nigeria</td>
<td>USEPA-16 PAHs</td>
<td>The estimated cancer risk from this study in an adult was 5.07 x 10^{-9} mg/kg/day over an average lifetime of 70 years.</td>
<td>Orisakwe et al., 2015</td>
</tr>
<tr>
<td>Nigeria</td>
<td>Pesticides</td>
<td>chloride and the phosphate – 141.8 mg/kg and 4.6–40.2 mg/kg, respectively; PCBs: Detected</td>
<td>Bello et al., 2016</td>
</tr>
<tr>
<td>Nigeria</td>
<td>16+1 US-EPA Priority PAHs</td>
<td>Σ16PAHs): 1.63±0.33–73.53±6.07 μg/kg, 4.71±0.23–79.61±7.02 μg/kg, and 12.52± 0.15–26.89±0.68 μg/kg, for green, herbal and black tea samples, respectively.</td>
<td>Benson et al., 2018</td>
</tr>
<tr>
<td>Nigeria</td>
<td>16 EPA Priority PAHs</td>
<td>The cancer risk estimated values in this study were below the risk level of 1x10^{-6} set by USEPA to cause cancer.</td>
<td>Ayobami, 2019; Akintelu et al., 2019</td>
</tr>
<tr>
<td>Poland</td>
<td>16 EPA Priority PAHs</td>
<td>The highest benzo(a)pyrene and Σ4PAHs contents (209±42 μg/kg and 756±151μg/kg, respectively) were found for black tea leaves. The transfer of Σ4PAHs from black tea to tea infusions was 0.48%, while it was 1.55–1.72% for red, white and green teas.</td>
<td>Zachara et al., 2017</td>
</tr>
<tr>
<td>Poland</td>
<td>16 EPA Priority PAHs</td>
<td>Σ16PAHs): 41.5 to 2910.2 μg/kg in dried teas and from 52.9 to 2226.0 μg/L in infusions.</td>
<td>Ciernniak et al., 2019</td>
</tr>
<tr>
<td>Syria</td>
<td>16 EPA Priority PAHs</td>
<td>Σ16PAHs): 47 to 890 mg kg^{-1}</td>
<td>Krajian and Ôdeh, 2013</td>
</tr>
</tbody>
</table>
Table 5 indicates some principal toxic effects of heavy metals. Some metal like Arsenic and Cadmium impacts acute effects while metal like Lead impacts chronic effects.

<table>
<thead>
<tr>
<th>Heavy metals</th>
<th>Principal toxic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
<td>Lung cancer and skin diseases</td>
</tr>
<tr>
<td>Cadmium</td>
<td>Kidney damage, lung cancer and bone disorder</td>
</tr>
<tr>
<td>Chromium</td>
<td>Respiratory effects, allergic dermatitis, kidney and liver damage</td>
</tr>
<tr>
<td>Lead</td>
<td>Neurological effects, hematopoietic system damage and reproductive effects</td>
</tr>
<tr>
<td>Mercury</td>
<td>Neurological effects and kidney damage</td>
</tr>
<tr>
<td>Manganese</td>
<td>Central nervous system effects</td>
</tr>
<tr>
<td>Zinc</td>
<td>Gastrointestinal disturbances and anaemia</td>
</tr>
</tbody>
</table>

Sources: Martin and Griswold (2009) and Singh et al. (2011).

4 Discussion
4.1 Review of metal contamination in herbal remedies
From Table 2, it is obvious that a number of cases of heavy metal contamination of herbal remedies have been reported in Nigeria. The presence of toxins especially heavy metals may results from many sources ranging from bio-availability in herbs grown in contaminated soils to the herbal drug manufacture processes. Heavy metals are metallic, naturally occurring compounds that have higher densities compared to other metals - at least five times the density of water (Zumdal, 2007). Heavy metals are toxic to humans. Even small doses can have serious consequences. The quality and safety of herbal medicines are major concerns worldwide due to increasing heavy metal contamination resulting from anthropogenic activities. Metals are widely distributed throughout nature and occur freely in soil and water. Heavy metals in herbal preparations may not be a result of accidental contamination but may be introduced for supposed therapeutic properties; for example, mercury was used to treat syphilis until the introduction of penicillin, while arsenic-derived compounds are still used for treatment of some forms of malignancy (Shaban et al., 2016). Among the heavy metals mercury, lead, arsenic and cadmium are toxic metals and have mutagenic effects even at very low concentration (Sathiavelu et al., 2012).

In Nigeria, the consumption of herbs either as supplements or remedies cuts across all ages and social groups and most often a combination of these products are consumed simultaneously. There is no documented implication of this practice and as such it has become imperative to evaluate the acute and chronic toxicity profiles of these herbal supplements with a view to ascertaining degree of violations of standard recommended guidelines of WHO, EU and US EPA. Most papers reviewed have shown contamination of herbal products with heavy metals. The results of the research carried out by Igweze et al. (2012) as shown in Table 2, revealed that almost all the capsules and soft get preparations were contaminated with heavy metals, with some of them exceeding WHO, EU and US EPA limits. The presence of these metals in the preparations could lead to chronic toxicity and interactions with conventional medicine. In a similar research in Nnewi and Owerri, Nigeria (Obi et al., 2006), the levels of potential toxic metals in ready-to-use herbal products purchased from the open market were studied. The result showed that 100% of the samples contained elevated amounts of heavy metals (Obi et al., 2006). The study suggested that the public health hazards from ingestion of herbal medicines should be identified and disclosed by in-depth risk assessment studies.
However, on a contrary, Jimoh et al. (2015) analyzed heavy metal contamination of some poly-herbal products from Lagos state. All metals were either below detection limit or within recommended WHO/FAO permissible limits. This may be due to the fact that most of the poly-herbal products have been screened and certified by NAFDAC. A similar study in Imo State, Nigeria (Ekeayanwu et al., 2013) also indicated that all metals determined were within the limits.

A study carried out to examine potential toxic metal contamination of local medicinal plants and extracts sold in Ibadan, Nigeria showed that the concentrations of cadmium, chromium and nickel in all samples were below detection limits (Adie and Adekunle, 2017). However, all ethanol extracts and one out of four water extracts contained lead. Lead is one of the highly toxic environmental pollutants that is ubiquitous in the environment. It can complex with various bio-molecules which adversely affect their functions. Lead exposure may have an adverse effect on the blood, nervous, immune, renal, skeletal, muscular, reproductive, and cardiovascular systems causing poor muscle coordination, gastrointestinal symptoms, brain and kidneys damage, hearing and vision impairments, and reproductive defects (Edebi and Alade, 2011; Johnson, 1998). Consumption of these products poses a serious health risk; hence, there is need for continuous monitoring of herbal drugs sold in the market to ensure safety and efficacy of these remedies.

Table 3 indicate summary of global outlook of metal contamination of herbal remedies. Studies from African, Asia, Europe and South American sub-regions were presented. Heavy metal contamination is a global challenge because herbal product contamination with heavy metals have also been reported from other African countries, Asia, Europe and South America (Okem et al., 2014; Rania et al., 2015; Krejpcio et al., 2007; Marina, 2009). Both developed and developing countries have shown high levels of potentially toxic heavy metals in products available to the public (Onwordi et al., 2015; Rania et al., 2015). The presence of selected pathogenic microorganisms and selected elemental levels of herbal materials used in management of oral health in Nairobi, Kenya; have been investigated. The herbal materials were found to be contaminated with aluminium, chromium, manganese, iron, copper, zinc and lead at various concentrations which were unsafe for human consumption (Ngari et al., 2013). In a research conducted to assess the safety of herbs available in the Kumasi central market in Ghana with regards to heavy metal contamination, a total of 15 medicinal herbs were randomly collected and the results showed that most of the metal concentrations in the herbs were within the WHO maximum permissible limits (Nkansah et al., 2016). This was not the case in a similar study conducted in Ghana by Affum et al. (2013) where the level of arsenic in ready-to-use aqueous-based anti-malaria herbal medicine were reported higher than WHO permissible levels. In a similar study conducted in United Arab Emirates, a total of 81 samples of seven herbs were purchased from the local market in Dubai and analysed for their cadmium, lead, copper, iron, and zinc contents. The metals were present in varying concentrations in the herbal samples with most of the analysed herbs containing unsafe levels of heavy metals that exceeded the WHO permissible limits (Rania et al., 2015).

Toxic metal testing was performed on 121 natural health products (including Ayurvedic, traditional Chinese, and various marine-source products) as well as 49 routinely prescribed pharmaceutical preparations in Ontario and Alberta, Canada. Testing was also performed on several batches of one prenatal supplement, with multiple samples tested within each batch. Results were compared to existing toxicant regulatory limits. Toxic metal contamination was found in many supplements and pharmaceuticals. Levels exceeding established limits were only found in a small percentage of the products tested. Some of the products demonstrated contamination levels above preferred daily end-points for mercury, cadmium, lead, arsenic or aluminium. Natural health products manufactured in China generally had higher levels of mercury and aluminium (Stephen et al., 2012).
The levels of potassium, calcium, iron, zinc, copper, manganese, arsenic, cadmium, chromium, and lead in commonly used medicinal herbs and their infusions by Lebanese were analyzed by EDXRFS and AAS techniques, respectively. The levels of manganese, chromium, lead and arsenic in herbal infusions were found to be higher in soaked than boiled preparations and correlated with iron, while zinc and copper levels were higher in boiled infusions. Cluster analysis indicated metals were most probably in plants due to wastes disposal and irrigation with contaminated wastes and/or from atmospheric waste particulates (Rania et al., 2015). Several Pakistani plants are known to be of potential therapeutic value and are used in traditional herbal medicine system of the country. Ten of the most popular routinely used medicinal plants (Achyranthes aspera, Alternanthera pungens, Brassica campestris, Cannabis sativa, Convolvulus arvensis, Hordeum vulgare, Justicia adhatoda, Parthenium hysterophorus, Ricinus communis, Withania somnifera), belonging to Haripur basin were studied first time for their trace (zinc, copper, chromium, nickel, cobalt, cadmium, lead, manganese and iron) and major (potassium, sodium, calcium and magnesium) elemental composition. Although all the plants were found to accumulate good quantities of iron, potassium, sodium, calcium and magnesium; their trace heavy metal contents were high according to the international safety standards for human consumption (Khan et al., 2013). In a similar research in Pakistan, all other metals analyzed were below permissible level except chromium.

In a study conducted to investigate the toxic metal content (lead, arsenic, cadmium and mercury) of 52 frequently prescribed herbal medicines and to identify herbal medicines that exceed the Korea Food and Drug Administration (KFDA) maximum limits, a total of 3534 samples, including 1966 domestic samples and 1568 imported samples, were analyzed using an Inductively Coupled Plasma-Mass Spectrometer (ICP-MS) (Donggyu et al., 2015), the total amount of lead, arsenic, cadmium and mercury were significantly different between domestic (0.63 mg kg$^{-1}$) and imported (0.81 mg kg$^{-1}$) medicines. Among the 52 kinds of samples, 4 kinds of herbs required quality control for lead and 12 kinds of herbs required quality control for cadmium. No sample contained arsenic and mercury above the limits.

4.2 Review of organic contamination of herbal remedies

4.2.1 Pesticides
Research has shown that herbal remedies are contaminated not only with heavy metals but also with organic pollutants such as pesticides residues and PAHs (Table 4). Pesticide residues are any specified substance in food, agricultural commodities or animal feed resulting from the use of a pesticide. The term includes any derivatives of a pesticide, such as conversion products, metabolites, reaction products and impurities considered to be of toxicological significance. Medicinal plant materials may contain pesticide residues, which accumulate as a result of agricultural practices, such as spraying, treatment of soils during cultivation and administration of fumigants during storage. Bello et al. (2016) in a research carried out in Northwest Nigeria reported the presence of Poly-Chlorinated Biphenyls (PCBs) in selected herbal remedies. Chloride and phosphate were found to be in the concentration ranges of between 141.8mg/kg and 4.6 - 40.2 mg/kg, respectively. The congeners 2,2′,5,5′-tetrachlorobiphenyl and 2,2′,3,4,4′,5,5′-heptachlorobiphenyl were not detected in any of the samples; the highest concentration of PCBs was recorded for 2,3,3′,4,4′,5-hexachlorobiphenyl in one sample. Other three congeners were detected at varied concentrations in different percentages. Most other pesticides had very short residual actions. Therefore it was suggested that, where the length of exposure to pesticides is unknown, the herbal materials should be tested for the presence of organically bound chlorine and phosphorus as a preliminary screening method (WHO, 2007).

4.2.2 Polycyclic Aromatic Hydrocarbons (PAHs)
Polycyclic Aromatic Hydrocarbons (PAHs) constitute a large class of organic compounds characterized by a structure made up of carbon and hydrogen atoms forming two or more fused aromatic rings without any
heteroatom or substituent. The compounds containing five or more aromatic rings are known as heavy PAHs, whereas those containing less than five rings are named light PAHs. Both kinds of PAHs are non-polar compounds showing high lipophilic nature. Therefore, heavy PAHs are more stable and toxic than the other group.

Poly-Aromatic Hydrocarbons (PAHs) are ubiquitous environmental contaminants which are widespread in the air bonded to particulate matter (Soceanu et al., 2011). Although PAHs show hydrophobic properties (especially heavy PAHs), they are also found in water. These compounds are produced during a variety of combustion and pyrolysis processes from anthropogenic and natural sources. A high amount of PAHs are emitted from processing coal, during incomplete combustion of organic matter (e.g. wood and fossil fuels), from motor vehicle exhaust and cigarettes (Soceanu et al., 2011). Forest fires, volcanoes or hydrothermal processes are natural emission sources of PAHs (Silva et al., 2011). The largest concern associated with exposure to PAHs is cancer risk, because many PAHs are highly carcinogenic and mutagenic in laboratory animals and have been implicated in breast, lung, and colon cancers in humans (ACGIH, 2005). PAHs are metabolized to dihydrodiols by hydrocarbon hydroxylases present in the liver, and dihydrodiols and their epoxide derivatives bind to DNA and proteins, starting mutagenic processes in the cells (Wang et al., 2010). Various recent epidemiological studies have revealed an association between dietary exposure to PAHs and increased risks of some human cancers (Diggs et al., 2011). Also, many PAHs exert teratogenic and immunotoxic effects (Reynaud and Deschaux, 2006). Thus, exposure to PAHs is a significant public health problem.

This group of organic contaminants have been detected at different concentrations in various foods and herbal medicines, including edible oils, olive oil, vegetables oils, fruits and vegetables, coffee, tea leaves, tea infusions, beverages, seafood, smoked fish, smoked meat, moked cheese, milk, honey, foodstuffs, dried foods, cooked foods, food supplements, and herbal products (IPCS, 2010). Few studies have been performed that investigated the levels of PAHs in raw medicinal herbs.

Ishizaki et al. (2011) analyzed 15 PAHs in five teas and 29 medicinal herbs. The total concentration of the 15 PAHs ranged from 6.5 to 1112.1 mg/kg. The total concentration of 15 PAHs was found to be maximum (1112.1 mg/kg) in eucommia bark. Yu et al. (2012) investigated 16 PAHs as representative contaminants in nine Chinese medicinal herbs to ensure food safety from this source. The total levels of PAHs varied from 98.2 mg/kg (cassia seed) to 2245 mg/kg (eucommia bark). Among the PAHs, the phenanthrene concentration was maximum in liquorice root (631.3 mg/kg), indigo wood leaf (551.0 mg/kg), rose flower (435.2 mg/kg) and eucommia bark (432.3 mg/kg). Krajian and Odeh (2013) determined the levels of 16 EPA-PAHs in the leaves and flowers of 10 medicinal plants. The sum of the 16 PAHs in the investigated medicinal plants ranged from 47 to 890 mg/kg, where the highest PAHs were found in plant samples of Sage.

Similar studies in Nigeria, have reported the presence of PAHs of priority concern in green herbal, black tea samples, coffee and cocoa based food drinks at varying concentrations (Chukwujindu et al., 2015; Benson et al., 2018; Zumdal, 2007; Edebi and Alade, 2011). The estimated cancer risk from exposure to PAHs arising from consumption of Chinese teas were calculated to be less than the U.S. EPA cancer risk range of $1 \times 10^{-6}$ to $1 \times 10^{-4}$ (Orisakwe et al., 2015). The study suggests that consumption of Chinese teas may not be one of the factors responsible for the increased rate of cancer in Nigeria. In all of the studies, low molecular weights PAHs were found as the dominant contaminants.

4.3 Review of microbial contaminants in herbal remedies

Herbs and herbal materials normally carry a large number of bacteria and moulds, often originating in soil or derived from manure. While a large range of bacteria and fungi form the naturally occurring microflora of medicinal plants, aerobic spore-forming bacteria frequently predominate (WHO, 2007). Current practices of
harvesting, production, transportation and storage may cause additional contamination and microbial growth. Proliferation of microorganisms may result from failure to control the moisture levels of herbal medicines during transportation and storage, as well as from failure to control the temperatures of liquid forms and finished herbal products.

The presence of Escherichia coli, Salmonella spp. and moulds may indicate poor quality of production and harvesting practices (WHO, 2007). Microbial contamination may also occur through handling by personnel who are infected with pathogenic bacteria during harvest/collection, post-harvest processing and the manufacturing process (WHO, 2007). This should be controlled by implementing best practice guidelines such as GACP and GMP.

A good number of studies reported the presence microorganisms in herbal remedies. *Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella typhi* was reported to be present in some herbal products consumed in Nairobi, Kenya (Ngari et al., 2013). Adelinesuyien et al. (2013) and Alwakeel (2008) also reported cases of microbial contaminant in herbal products consumed in Malaysia and Saudi Arabia respectively. Also, Microbial load of some medicinal plants sold in local markets of Benin, Nigeria was reported to contain *P. aeruginosa* and *B. subtilis* among others (Idu et al., 2011). In Kaduna Nigeria, studies indicated presence of pathogenic *S. typhi* in 65.7% of herbal products analysed and E. coli in 58.7% of the samples analyzed (Abba et al., 2009). Evaluation of microbial quality of plant materials in Belgrade indicated the presence of *E. coli*, Bacillus and Clostridia species (Stevic et al., 2012). When evaluation of microbial and fungal contaminations of herbal products was carried out in Ghana (Ahene et al., 2011), aflatoxins, nitrobacteria and *P. aeruginosa* among others were found to be present. In South Africa, studies have shown that herbal products are heavily contaminated with bacteria (Adeleye et al., 2005). Consumers of these products are in no doubt at risk of infection with pathogenic microbes.

World Health Organization (WHO) stipulates that Salmonella and Shigella species must not be present in herbal medicines intended for internal use at any stage. Other microorganisms should be tested for and should comply with limits set out in regional, national or international pharmacopoeias (WHO, 2007). However, in some of the papers reviewed, *E. coli*, *Salmonella* spp, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and other microorganisms were present in varying amounts and this has profound and severe implications for public health. Drug samples in which microbial load is higher than WHO norms may be harmful as they can produce toxic substance like aflatoxins which may cause harm to the human heath instead of curing the disease. There are innumerable reports of mycotoxin contamination of herbal drugs (Aziz et al. 1998; Kumar and Roy, 1993; Refai, 1988). The risk of mycotoxin production especially aflatoxin should be considered in the process of the herbal preparation because of the proven mutagenic, carcinogenic, teratogenic, neurotoxic, nephrotoxic and immunosuppressive activities of these microbes (Refai, 1988; Scimea, 1995).

### 4.4 Metal speciation studies

The need to distinguish between chemical forms of an element is crucial in food, environmental, and pharmaceutical sectors. In the past, measuring the total amount of an element was sufficient. Unfortunately, the effect of an element extends far beyond its absolute amount. Different forms of an element can exhibit very different physio-chemical properties, including varying toxicities. The process of separation and quantification of different chemical forms of an element, more specifically termed speciation analysis, can determine an element’s various chemical forms, and thus deliver a better understanding of the environmental or health related impact associated with a particular sample.

Whether an element is toxic or not is determined by many factors including route of exposure, dose, site of accumulation, nutritional status, detoxification biochemistry, and the particular form or species in which the element exists within the body (Stephen et al., 2012). Different species of elements have the potential to
display distinct toxicity patterns. For example, hexavalent chromium (chromium-VI) is highly toxic and carcinogenic while trivalent chromium (chromium-III) is an essential metal involved in lipid and carbohydrate metabolism.

Similarly, inorganic and organic arsenic are both naturally occurring compounds that display different toxicities. While certain inorganic arsenic species are classified as human carcinogens, some forms of organic arsenic, such as arsenobetaine (which accumulates in some aquatic organisms such as shrimp) are relatively nontoxic. Specific forms of some elements also have the potential to be converted within the body to different forms, which changes their properties and potential toxicity.

5 Health Implication of Contamination of Herbal Medicine

5.1 Heavy metals
Table 5 presents some major adverse health effects arising from toxic metals to humans. All metals are toxic at higher concentrations, excessive levels can be damaging to the organisms including humans (Chronopoulos et al., 1997). Toxicological problems associated with the use of herbal medicines are complex but have been regularly associated with serious adverse fatalities ranging from cardiovascular problems to psychiatric to neurological effects to liver toxicity or malfunction to hematologic and renal toxicity (Ernst, 2003). Among the heavy metals, mercury, lead, arsenic and cadmium are toxic metals and have mutagenic effects even at very low concentration. Several cases of human disease, malfunction and malformation of organs due to metal toxicity have been reported. Along with human beings, animals and plants are also affected by toxic levels of heavy metals (Sathiavelu et al., 2012; Ibrahim et al., 2006) (See Table 5).

5.2 Pesticide residues
Pesticide exposure is linked with various diseases including cancer, hormone disruption, asthma, allergies, and hypersensitivity (Van et al., 2010). A line of evidence also exists for the negative impacts of pesticide exposure leading to birth defects, reduced birth weight, foetal death, etc. (Baldi et al., 2010; Meenakshi et al., 2012; Wickerham et al., 2012). On the basis of scientific evidence, the real, predicted, and perceived risks that pesticides pose to human health and the environment are fully justified. Depending on their method of action, certain pesticides, such as those determined to be xenoestrogens (organochlorines, organophosphates, and carbamates), will have increased effects based on the developmental stage of individuals when exposure occurs (Inigo-Nunez et al., 2010). The risk of health hazards due to pesticide exposure depends not only on how toxic the ingredients are but also on the level of exposure. In addition, certain people such as children, pregnant women, or aging populations may be more sensitive to the effects of pesticides than others.

5.3 Polycyclic Hydrocarbons (PAHs)
They are highly lipid soluble and thus readily absorbed from the gastrointestinal tract of mammals. They are rapidly distributed in a wide variety of tissues with a marked tendency for localization in body fat. Due to the high lipophilicity of this class of compounds, their bioavailability after ingestion and inhalation is significant. Scientific investigations have shown that detectable levels of PAHs occur in almost all internal organs, particularly in organs that are rich in adipose tissue. These organs can serve as storage depots from which the hydrocarbons can be gradually released (Campo et al., 2015).

The impact of PAHs on human health depend mainly on the length and route of exposure, the amount or concentration of PAHs one is exposed to, as well as the relative toxicity of the PAHs (ACGIH, 2005). A variety of other factors can also affect health impacts including subjective factors such as pre-existing health status and age. Mixtures of PAHs are known to cause skin irritation and inflammation. Anthracene, benzo(a)pyrene and naphthalene are direct skin irritants. They are reported to be skin sensitizers, i.e. cause an allergic reaction in skin in animals and humans (IPCS, 2010). Health effects from long-term or chronic
exposure to PAHs may include decreased immune function, cataracts, kidney and liver damage (e.g., jaundice), breathing problems, asthma-like symptoms, and lung function abnormalities. Evidence indicates that mixtures of PAHs are carcinogenic to humans.

6 Conclusion and Recommendation
The results of this study especially on the heavy metal contents of herbal medicine pose an impending danger for consumers. Significant serious consequences may appear due to accumulation of heavy metal contents through the years of frequent use of these herbal medicines. Several degenerative and life-threatening conditions were linked to accumulation of toxic metals in the body. When our body is compounded with microbial infection to an already toxin-filled system, the capacity of our immune system to defend itself could be compromised. Although some of the papers reviewed showed heavy metal levels within the acceptable limits, it is possible that some amounts can be taken up by the system and accumulate for years of use, thus cause serious consequences. Even if these metals found in herbal medicines are less likely than free to bind with molecules in our bodies and thus slower to be absorbed, the issue of safety and vigilance on their serious adverse effects should be of a concern. Furthermore, the continued practice of safety and precautionary measures from the harvest area (such as minimizing pesticides use) to the household such as thorough cleaning and washing of herbal plants prior to use should be practiced.

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References
Affum AO, Shiloh DO, Adomako D. 2013. Monitoring of arsenic levels in some ready-to-use anti-malaria herbal products from drug sales outlets in the Medina area of Accra, Ghana. Food and Chemical Toxicology, 56: 131-135


Inuwa Y, Mohammed MI. 2018. Pollution indices and transfer factors of metals in selected medicinal herbs from Kano Metropolis. Discovery Science, 14: 100-108


Iwuozor KO. 2019. Heavy metal concentration of aphrodisiac herbs locally sold in the south-eastern region of Nigeria. Pharmaceutical Science and Technology, 3(1): 22-26


Karayil S, Bhavani V. 2014. Heavy Metal Analysis from traditionally used Herb Ceropegia juncea (Roxb.). IOSR Journal of Pharmacy. 4(12): 7-11


Kim DN, Pham NK, Rainer L. 2010. Quantitative determination of trace elements in some oriental herb products. International Journal of Biological, Biomolecular, Agricultural, Food and Biotechnological Engineering, 4: 5


Mostafa D, Gholam RA, Farya A, Mahdi A. 2011. The study of toxic metals contamination (Pb, Cd, As, Al) on medicinal plants cultivated near Arak Industrial Manufactures. Iranian Journal of Toxicology, 5: 482
Ngari FW, Nicholas KG, Ruth NW, Eliud NM. 2013. Investigation of selected pathogenic microorganisms and toxic elements in herbal materials used in management of oral health in Nairobi County, Kenya. Journal of Applied Environmental and Biological Sciences, 3(12): 1-7


Onwordi CT, Agbo N, Ogunwande IA. 2015. Levels of potentially toxic metals in selected herbal medicines in Lagos, Nigeria. Journal of Natural Sciences Research, 5: 2


Reynaud S, Deschaux P. 2006. The effects of polycyclic aromatic hydrocarbons on the immune system of fish: a review. Aquatic Toxicology, 77: 229-238

Rufai SO, Olaniyi MB, Lawal IO. 2019. Evaluation of heavy metals in some selected medicinal plants growing within the University of Ibadan Campus. Journal of Medicinal Plants for Economic Development, 3(1): 63


Suchacz B, Wesolowski M. 2012. The analysis of heavy metals content in herbal infusions. Central European Journal of Medicine, 7(4): 45-464


