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Heavy metal contamination of herbal medicinal products and cosmetics: A course for concern

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ABSTRACT

Increasing numbers of people in the developed and developing countries use herbal medicinal products (HMPs). This is based on the wide misconception that HMPs are 'natural' means that they are 'safe'. More brands of HMPs are being introduced into the developing countries including Nigeria in the form of 'supplements'. Globally, there are warnings regarding the possible toxicity, adverse reaction and contamination or adulteration of HMPs. There is an urgent need for the regulation and control of the efficacy and safety, as well as quality control in the production of these products. The aim of this article is to review published data on the adverse effects, contamination and adulteration of HMPs and local cosmetics. There are increasing incidences of heavy metal contamination and adulteration of HMPs with pharmaceutical drugs and human poisoning from consumption of these products. Also of concern is heavy metal contamination of local cosmetics. Legislations to control safety and efficacy in HMP production are lacking in many countries while products testing and quality control, are rarely adhered to. Non-adherence to standards for purity and potency increases the possibility for drug-herb, herb-herb interactions as well as consumers reactions to contaminants. HMPs, as with other products intended for human use, should be incorporated within a regulatory framework. These products should be governed by standards of safety, quality, and efficacy that are equivalent to those required for other pharmaceutical products.

Keywords: Herbal Medicinal Products, Adverse drug reaction, Lead, Heavy metals, contamination, Cosmetics

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INTRODUCTION

Traditional medicine is still an important component of the health system in many countries especially countries in Africa and Asia. It accounts for over 10% of the overall expenditure. In Nigeria, the ratio of traditional to modern health practitioners is estimated to be 28 to 1 [1]. The World Health Organization (WHO) estimates that 65 - 80% of the world's population use traditional medicine as their primary form of health care [2-4]. This is prevalent in the developing countries and has been attributed to better cultural acceptability, better compatibility with human body and lesser side effects [5]. Presently many medicinal plants are still being investigated for their medicinal applications [6-10] This because many of these plants have curative properties due to the presence of various phytoconstituents called as alkaloids, glycosides, corticosteroids, essential oils etc [7]. Similarly, Jayanthi and Lalitha [9] observed that plants are rich source of free radical scavenging molecules such as vitamins, terpenoids, phenolic acids, lignins, stilbenes, tannins, flavonoids, quinones, coumarins, alkaloids, amines, betalains and other metabolites which are rich in antioxidant activity [9] The use of herbal and traditional medicines raises concerns in relation to their safety and there is a wide misconception that 'natural' means 'safe' [11]. Sajeeth et al [12] observed that herbal medicines are frequently considered to be less toxic and more free from side effects than synthetic ones

[12]. Herbal medicine in which plants (dried or in extract form) are used as therapeutic substances, is one of a number of practices encompassed by the term 'complementary and alternative .medicine' (CAM) and referred to as 'herbal medical products' (HMPs) [2,13,14]. The historic role of medicinal herbs in the treatment and prevention of disease, and their role as catalysts in the development of pharmacology do not , however, assure their safety for uncontrolled use by an uninformed public [15]. Consumer products, cosmetics and traditional medicine have been identified as sources of lead exposure in developing countries.

Ironically, most patients do not reveal their herbal use to their physicians and pharmacists. Adverse reactions to herbal medicine are probably under recognized and under reported. In recent years, an increasing percentage of people have been using complimentary and alternative medicine (CAM) against numerous warning regarding the toxicity of these therapies [4,16-19]. This indicates that people are becoming increasingly disillusioned with conventional medical care and are seeking to gain some measure of control over their illness. This has resulted in increasing popularity of alternative health care practices [20].

The popularity of traditional remedies has greatly increased in Westernized countries over recent years. The use of at least one of sixteen alternative therapies increased from 33.8% in 1990 to 42.1% in 1997 in the United States [21]. The therapies increasing the most include herbal medicine, massage, megavitamins, self-help group, folk remedies, energy healing and homeopathy [21]. More than 20,000 herbal and related products are in use in the United States [22]. Although many of these remedies are used safely, there have recently been an increasing number of case reports being published of heavy metal poisoning after use of traditional remedies, in particular in Indian Ayurvedic remedies [19, 23].

The increasing popularity of herbal medicinal products renders the assessment of their safety an urgent necessity. All HMPs contain a range of pharmacologically active ingredients and users of HMPs often combine HMPs with prescribed drugs. Thus, herb-drug interactions are a real possibility [14]. In most countries, especially in Africa, HMPs are not submitted to stringent regulations and control. This unreliable quality can be a problem especially with the increasing reports of lead poisoning after taking HMPs. Literature abound on cases of contamination of HMPs (especially with heavy metals) and in recent times of adulteration of HMPs, especially with prescription drugs [4,14].

Herbal poisoning exposure is increasing. There is therefore a need for health practitioners to remember to include herbal use history in their routine drug histories and remain informed of the beneficial and harmful effects of these treatments [22]. The last decade has witnessed an increase in consumption of herbal medicinal products in Nigeria, imported mostly from Asia, and Europe. Products from Europe are mostly supplements and users rarely regard them as medicine. The growing popularity of these products in Nigeria necessitates a critical evaluation of the risks associated with their use. The increasing cases of heavy metal contamination of these products require an urgent review of means of protecting the consumers [24].

The aim of this article is to review published data on contamination and adulteration of HMPs and discuss the potential health implications. Case reports of human poisoning from consumption of HMPs contaminated by heavy metals are also presented. A comprehensive review of heavy metal contamination and herb-drug interactions of HMPs is impossible in this setting. Hence, more attention will be paid to literature that relates to HMPs or cosmetics that are readily available or are more likely to be consumed in most developing countries including Nigeria.

1. Increasing Popularity of HMPS

The last few decades have witnessed a global resurgence of interest in herbal or alternative medicine. In Western societies, some patients have become disillusioned about scientific medicine. They are dissatisfied with the unempathetic, complex and expensive forms of treatment that often fails to cure chronic diseases, such as asthma and arthritis. It is important to note that the World Health Organization (WHO) encourages, recommends and promotes traditional/herbal remedies in national health care programmes considering that herbal remedies are readily available at relatively low cost. Literature also indicates that consumers consider herbal remedies to be safe and people have faith in them [8]

Plants and herbs have provided natural remedies for human ailments from time immortal. Following the advent of modern medicine, herbal medicine suffered a setback. However, advances in phytochemistry and identification of plant compounds, which are effective in curing certain diseases have renewed the interest in herbal medicine [3].

Spices are in common use and apart from enhancing the taste and flavor of food, they have been widely believed to exert digestive stimulant action. A few medicinal properties of spices such as tonic, carminative, stomachic, diuretic, and antispasmodic have long been recognized. These attributes, largely empirical, nevertheless efficacious, have earned them pharmacological applications in the indigenous systems of medicine as digestive stimulants and to relieve digestive disorder [25]. Spices and medicinal plants are known to contain trace metals which play vital roles as structural and functional components of metalloprotiens and enzymes in living cells [26]. Plant substances contain hundreds, sometimes thousands of bioactive compounds. Bioflavonoid, flavones, lactones, glycosides, polysaccharides, essential oils, and tarpenes are but a few of the type of biologically active substances found in herbs [22].

Patients who are using HMPs are often self-directed in their care. Patients most often take herbal supplements for conditions that are chronic, have a fluctuating courses, and have no definitive treatment. The perception that botanical products used as folk remedies are inherently safe is based on traditional use rather than on systematic studies designed to detect adverse effects [27]. Nevertheless, evidence of the toxicity of such products has accumulated. People taking herbal medicine give the following reasons for taking them:

♦ they are "natural" and hence, safe,
♦ they can self-medicate,
♦ they are cheaper than conventional medications, and
♦ today's formal medicinal care is "too technical; impersonal, and expensive" [22].

There is the common belief that long use of a medicine based on tradition, assures both efficacy and safety. There are examples of traditional and herbal medicines being adulterated or contaminated with allopathic medicines, chemicals such as corticosteroids, non-steroidal anti-inflammatory agents and heavy metals [11].Some major concerns regarding the marketing and use of medicinal herbs are those of standardization and stability. Unlike pharmaceuticals, botanical products are complex mixtures in which the active ingredients may not be known or may constitute only a small percent of the total product [15].

The myth that natural products are completely safe is constantly promoted in advertising of these products and creates a need for responsible public education [28]. Therefore, the common belief that everything natural is safe is not correct. A detailed review of the abnormal test results associated with the use of herbal medicine, as well as interactions between Western medicine and herbal products can be found in Dasgupta (2003). Many commonly used herbal medicines are toxic. These toxic effects range from allergic reactions to cardiovascular, hepatic, renal, neurologic, and dermatologic toxic effects [29]. A discussion of the interactions of natural products with drugs can be found in Scott and Elmer, [28].

2. Quality Control in HMPs

The integration of herbal medicine into modern practices including cancer treatments must take into account the interrelated issues of quality, safety, and efficacy. Quality is paramount issue because it can affect the efficacy and/or safety of the herbal products being used. The manner in which medicinal herbs are produced complicates quality control. They are gathered in the wild, or grown in relatively small plots. Thus, the active ingredient may vary significantly with the part of the plant used, the season in which it is harvested, and/or the growing conditions (e.g. weather, soil etc) [15].

Pharmaceutical drugs and a significant level of heavy metals have been reported in some herbal patents. Without a standard for purity and potency, the possibility for interactions increases greatly for drug-herb, herb-herb, or reactions to contaminants. Besides posing risks of toxicity for patients, it is also difficult to verify reports on herb-drug adverse reactions due to numerous unknown variables [30]. About half the drugs in the modern pharmacopoeia are inspired by plants, but until recently, there has been an important distinction between herbal medicines and synthetic drugs. Whole plant extracts used by herbalists have not been prescription materials and often contain hundreds of different compounds whereas conventional pharmaceutical drugs typically have only one active ingredient. The process of developing pharmaceutical products from plants is very costly and sufficiently large market is needed [31]. Presently so many herbal medicinal products are used for various reasons without proper investigation [32]. Manufacturers of these HMPs may not make claims for treatment or cure of a disease but may state a product's physiologic effects. Consumers have little information to make decision about the safety, adverse

effects, contraindications, interactions or effectiveness and must rely on manufacturers to provide ingredients that are accurately labeled [33].

The WHO has produced a series of manuals giving details of simple tests to confirm the identity of pharmaceutical and recently herbal medicines. These tests are aimed at confirming the identity of formulations, many of which have low intrinsic toxicity, prior to clinical use, and a range of reagents are needed in order to perform the tests. Traditional medicines have always been widely used in developing countries and are becoming more widely used in developed countries. Toxicity related to use of such medicine is becoming more widely recognized. However, the analysis of herbal remedies, ethnic remedies etc is usually difficult as the ingredients are often unknown except when undeclared pharmaceuticals such as steroids or inorganic poisons such as toxic metals are found to be present on testing using the conventional procedures [34].

There seems to be no effective control in quality, if any, of herbal medicinal preparations. Approximately 10% of 500 Chinese patent medicinal products imported into the USA were observed to contain undeclared drugs or potentially toxic levels of heavy metals, including mercury [35]. A similar study in Malaysia indicated that 36 out of 100 Malaysian herbal medicinal preparations tested for mercury did not comply with the Malaysian quality requirements [36]. Lack of regulation of quality control and product standardization makes it difficult to establish safe doses of herbal products. Active compounds may vary 200-fold between manufacturers and batches [37]. Additives and contaminants including caffeine, indomethacin, and heavy metals, such as lead, mercury and arsenic have been found in herbal remedies. The addition of pharmaceutical drugs to herbal products is a particular problem with Chinese patent medicines. Of 2609 samples of traditional medicines collected from eight hospitals in Taiwan, 23.7% contained pharmaceutical adulterants, mostly commonly caffeine, paracetamol, indomethacin, hydrochlorothiazide, and prednisolone [38]. Labeling of herbal products may not accurately reflect their contents, and adverse events or interactions attributed to specific herbs may actually be due to misidentified plants, pharmaceutical drugs or heavy metals [39]. One major problem with traditional remedies is lack of standardization. Consistency in composition and biologic activity are essential requirements for safe and effective use of therapeutic agents. However, botanical preparations rarely meet this standard, because of problems in identifying plants, genetic variability, variable growing conditions, differences in harvesting procedures, and processing of extracts and above all, the lack of information about active pharmacologic principles [27]. In most developing countries, there are hardly any legislation controlling the safety and efficacy in the manufacture/preparation of herbal remedies nor the submission or documentation of products testing, quality control or approval before these products enter the market. The therapeutic/toxic components of plants vary depending on part of the plant used, stage of ripeness, geographic area where the plant is grown, and storage conditions. This implies that significant variation in herbal medicine should be expected. This is worsened in developing countries by lack of standardization resulting from the crude methods of preparing herbal remedies. In fact, the traditional African medicine (TAM) has not made significant progress [40].

3. Sources Of Heavy Metals/Contaminants in HMPs

Herbs and spices can presumably acquire metals during growth in contaminated soils- including contamination of plant material with soil. High levels of toxic metals can occur in medicinal preparations when they are used as active ingredients as in the case of Pb and Hg in some Chinese, Mexican and Indian herbal medicine or when the plants are grown in polluted areas, such as near roadways or metal mining and smelting operations.

Use of fertilizers contaminated with Cd or Pd, pesticides contaminated with heavy metals (organic mercury or lead based pesticides) and contaminated irrigation water during the growing of herbs and spices may be a source of heavy metal contamination of the final products [4, 41-42]. Literature abounds on the contamination of HMPs with heavy metals such as lead, mercury, arsenic, cadmium and on cases of human poisoning resulting from such consumptions. However, some Indian herbal (Ayurveda) remedies, folk medicines, and homeopathic remedies are purposely adulterated with metals in the mistaken belief that they confer a health benefit to the user [43]. Heavy metals are often found in herbal as they are thought to help cure without being absorbable [22]. Heavy metal contamination is not uncommon in Asian herbal products. 24 of 251 Asian patent medicines collected from herbal stores in California, USA contained lead (at least 1ppm); 36 products contained arsenic, and 35 contained mercury [39, 44].

Mining activities and or high levels of background levels of heavy metals in surface soil and ground water may also account for high levels of heavy metals observed in herbal remedies prepared in such areas. A study of 30 herbal

remedies used by traditional healers in South Africa indicated high levels of uranium in 5 samples with concentrations above 40,000ppb uranium. Eight of the samples had levels below the limit of detection whereas the mean uranium concentration of the remainder of the samples was 15,000ppb [45]. The natural source of the uranium is soil. Additives may also be used but not listed on labels; these may be the source of the therapeutic effects. Examples include steroids, nonsteroidal anti-inflammatory agents, prescription antibiotics, sedatives and narcotics. Intentional use of pharmaceutical adulterants has been reported [22].

The local methods of preparation, distribution/sale and use of herbal medicinal products in the developing countries have not changed much. The root, bark, or leave, or combination of these from one or more plants are usually cut into pieces or ground before extraction using water, oil or alcohol. The processing of crude plant materials carried out by manufacturers or CAM practitioners or the patient is a major determinant of the pharmacological activity of the finished product [2]. The boiling of some CAM may change the alkaloid composition thereby increasing/reducing the plants' toxicity. Thus, there is the need to follow strictly the directions for the manufacture of CAM or the preparation of such drugs by individuals at home following the instructions on the label. The activity of a crude plant material may differ from that of the purified constituents, as some constituents may modify the toxicity of others [2].

Herbs can also be contaminated in the course of the milling or other processing procedures [43], or in the extraction processes [13].In the indigenous/traditional systems of medicine, the drugs are primarily dispensed as water decoction or ethanolic extracts. Fresh plant parts, juice or crude powder are a rarity rather than the rule [5]. The use of contaminated water or ethanol in such extraction processes can result in the contamination of the finished products.

In Nigeria, most locally produced, cheap and readily available alcoholic products are prepared either from the dilution of industrial grade alcohol or from the crude distillation of locally fermented palm wine, commonly referred to as *ogogoro* or *illicit gin*. There may be serious contamination in these processes as they are rarely carried out under hygienic conditions. The water used in these processes is readily obtained untreated either from boreholes or from natural surface water bodies which may have become contaminated from the metal contents of such geological strata, industrial effluents or solid wastes disposed into surface water bodies. Sometimes the active ingredients of herbal therapies are substituted in part or completely with other compounds that may or may not contain the same active ingredient or the same curative properties. Additives may also be used but not listed on the label. Adulterants can also be added by unethical herbalists compounding preparations for individual patient.

4. Heavy Metal Contamination of Local Cosmetics and HMPs

The public health implication of the use of kohl, bint al dhahab and henna in the Middle East has been a source of worry to physicians and environmentalists. Eye cosmetics such as kohl and surma have been identified as a source of Pb exposure to the ocular system in a number of adults and children [46-48]. Kohl is a black eye make-up used since ancient Egypt [49]. The main component of kohl is galena. Other major components in some types of kohl are amorphous carbon, zincite (ZnO), sassolite (H_3BO_3), or calcite/argonite, $CaCO_3$ [50]. In addition, some kohl samples from Oman contain minium (Pb_3SO_3) and magnetite (Fe_3O_4) [51]. Kohl samples from Cairo were observed to contain in addition to the above goethite (FeO(OH)), elemental silicon, or talc ($Mg_3Si_4O_{10}(OH)_2$) and cuprite (Cu_2O) [52].

Samples from Israel were observed to contain between 17.3% - 79.5% lead [53]. High level of lead 2.9-100% (mean 48.5%) was also reported in kohl samples collected within the Middle East, Asia, and Africa [54].Similarly, Al-Asban [55] reported levels up to 53% in some kohl preparations, and some were found to contain camphor and menthol. The modification of these products by the addition of various herbs or other substances in order to strengthen them has been observed to increase the Pb content of these products [56].The lead levels reported in some traditional cosmetic products are given in Table 1. The use of kohl and surma has been associated with high blood lead levels (BLL) (Table 2). Smart and Madan [57] described the use of surma within the Asian communities and the need to raise awareness among health professionals on the potential hazard this practice presents.

Table 1. Lead levels reported in some cosmetics around the world

Country	Name/class	Lead level	Reference
Morocco*	kohl	0.6- 50%	Parry and Eaton, [46]
Israel	kohl	17.3 – 79.5%	Nir et al, [53]
Saudi Arabia	kohl	up to 53%	Al-Ashben et al, [55]
Bahrain	kohl, surma	0.07 – 156mg/g	Madany and Akhter, [96]
India/Middle East	kohl	2.9 – 100%	Al-Hazza and Krahn, [54]
Saudi Arabia	henna	1.2 – 16.48 µg/g	Al-Saleh and Coate, [97]
Oman, UAE	bint al Dhahab	up to 91% (PbO)	Worthing et al, [98]
Nigeria	eye liner/eye pencil	66.0 – 213.6µg/g	Nnorom et al, [63]
Nigeria	kwali (galena based)	58.8 – 62.4%	Funtua and Oyewale, [61]
Nigeria	kwali (graphite based)	23 – 32 µg/g	Funtua and Oyewale, [61]
--	surma	0 – 88%	Moghraby et al, [99]

** Mauritania, US, Britain*

Table 2. Blood lead levels reported in some victims of lead poisoning from HMPs and cosmetics

Material used	Blood lead level	Reference
Ayurvedic	108.2µg/dL	Tait et al, [100]
Kohl	490 µg/dL	Bruyneel et al, [49]
Surma	34.2µg/dL*	Ali et al, [101]
Kohl	12.9µg/dL‡	Sprinkle, [47]
Alkohl	20.6µg/dL†	Markowitz et al, [90]
Cordyceps	130µg/dL	Wu et al, [89]
Indian herbal medicine	69.3µg/dL	Roche et al, [102]
Swanuri marili etc	21 - 37µg/dL	Woolf and Woolf, [43]
Hai ge fen	76µg/dL	Warkowitz et al, [90]
Cordyceps	46 - 130µg/dL	Wu et al, [89]

**BLL of unexposed non-user is 20.3µg/dL*
‡BLL of unexposed non-users is 4.3µg/dL
†BLL of unexposed non-users is 5.4µg/dL
Acceptable BLL = 10µg/dL (0.048µMol/L)

Lead sulphide is reported as the main component of kohl. Although one of the least soluble lead compounds, the use of kohl as an eye powder have been directly associated with elevated BLL in children and other users [58]. Conversion of the sulphide to the more soluble and hence more readily absorbed chloride form is shown to occur in gastric fluid and significantly, a marked dependence of the rate of dissolution on particle size is found [58]. Besides lifestyle, living conditions and culture have tended to govern exposure to toxic metals including Pb [59]. Lead has been applied for its supposed magical or chthonic properties. Otanjere (Nigerian name in Igbo language) that contains up to 81% of lead is commonly scavenged from the Benue valley trough of which the abandoned Enyingba – Abakiliki lead and zinc mine is part, and applied in the treatment of ophthalmogic infections, as an eye cleanser and in cosmetics [59-60]. Similar studies of traditional eye make-ups used in Nigeria have reported very high levels of toxic metal in locally sourced cosmetics [13, 61-63]. Funtua and Oyewale [61] reported high levels of up to 62% lead in galena based kwali eye make-ups. The galena is mined in Nigeria from lead – zinc ores found in sedimentary rocks of the Benue trough at Abakiliki and Zurak (Nigeria) and in smaller quantities associated with other minerals such as cassiterite (tin ore).A recent study of processed cosmetic used in Nigeria reported lead levels of 66.4 - 213.6µg/g in eye liners and 66.0 - 187µg/g in eye pencils and Cd levels generally below 2µg/g in the two sample categories [63].

High levels of lead (5-37000), and mercury (28-104000ppm) have been reported in Ayurvedic herbs manufactured in South Asia [19]. Garvey et al, [17] studied randomly selected samples of Asian medicines and observed that these remedies contained levels of arsenic, lead and mercury that ranged from toxic (49%) to those exceeding public health guidelines for prevention of illness (74%) when consumed according to the directions given in or on the packages. The quality requirement for traditional medicines in Malaysia is that they should not exceed 10ppm of lead. a study of some registered traditional medicines in Malaysia indicated that 5 out of 15 registered products exhibited a lead level of 10.23-23.05ppm, whereas a level of 12.24-20.72ppm lead was obtained in products not registered [36].The Pb and Hg levels reported in HMPs is given in Table 3.

Table 3. Lead and mercury levels reported in some herbal medicinal preparations

Product name/class	Pb	Hg	Reference
Ginseng products		5.53 – 15.3ng/g	Levine et al, [103]
Ginger products		10.8 – 27.4ng/g	Levine et al, [103]
St Johns wort		2.27 – 3.86ng/g	Levine et al, [103]
Senna products		1.81 – 16.7ng/g	Levine et al, [103]
Swanuri marili	100 - 2040mg/kg		Woolf and Woolf, [43]
Kharchos suneli	23,100mg/kg		Woolf and Woolf, [43]
Kozhambu	310mg/kg		Woolf and Woolf, [43]
--	6 – 60%w/w		Drew and Myers, [2]
Ayurvedic	0.003 – 8.9%*	0.002 – 0.08%‡	Tait et al, [100]
Cordyceps	20,000ppm		Wu et al, [89]
Ayurvedic	0.9 – 72,990µg/g†		Prepic-Majic et al, [92]
Bint Al zahab	82.50%		Rahman et al, [91]
--	2 - 1480µg/g	ND – 0.087µg/g	Caldas and Machado,
--	0.01 – 0.75µg/g		De Pasquale et al, [104]
--	0.05 – 0.30µg/g		Abou-Arab et al, [42]
--	0.008 – 0.12µg/g		Khan et al, [41]
Similax myosotiflora	10.23 – 23.05µg/g		Ang et al, [66]
Similax luzonensis	10.02 – 21.21 µg/g		Ang et al, [36]
Ayurvedic	5 - 37000 µg/g	28 - 104000 µg/g	Saper et al., [19]
--	ND – 138.19 µg/g		Nnorom et al, [13]

** (1-45mg/tablet); ‡ (10 - 400µg/tablet); † (0.35 – 29,900µg Pb/tablet)*

5. Heath Implications of Lead Exposure

In recent times there has been an increasing number of case reports of heavy metal poisoning after use of traditional remedies and cosmetics [23, 64-65].Increasing toxicity of herbal remedies is speculated to be related to lack of child-resistant packaging, new issues of contamination, proliferation of multiple ingredient products, excessive concentration of active ingredients, and discovery of new drug-herb interactions (Susan, 2005). In most developing countries, especially in Africa, imported and locally produced HMPs and cosmetics are not usually submitted to stringent regulation and control. These drugs are produced and marketed using a chain of networks of individuals and pharmaceutical drug stores. Literature abound on the heavy metal contamination of HMPs. Heavy metals particularly Pb has been identified as a regular constituent of Indian and Asian remedies and this has repeatedly caused serious harm to patients taking such remedies [17, 24, 66]. Clinically, lead poisoning is presented with abdominal crampoid pain, encephalopathy (manifested as anxiety and irritability), a Burtinian gingival border and microcytic sideropenic anemia [49]. The effect of exposure to toxic metals may among other factors depend upon exposure time and concentration.

Resources on activity, dosage, toxicities, contraindications, and drug interactions of herbal remedies are constrained by limited research and information. Herbal remedies may induce adverse cardiac effects including sympathomimetic activity, hypertension, and arrhythmias. Some herbal products with adverse cardiac effect are given in Table 4. Third-world physicians and health care workers appear to be unaware of possible lead uptake from unsuspected traditionally used items such as cosmetics and herbal remedies [46].

Table 4. Drugs with adverse cardiovascular effects

Herb	Adverse effect
Belladonia	tachycardia
Danshen	platelet dysfunction
Dong quai	increased bleeding tendency
Garlic	increased bleeding tendency
Ginger	platelet dysfunction, hypertension
Ma huang	stroke, myocardia infarction, arrhythmia, hypertension
Oleander	arrhythmia
Kava	platelet dysfunction

Adapted from Valli and Giardina, [33]

Physicians in developed nations with patients from Asia, the Middle East and North Africa have now included the possibility of past or present lead intake from unorthodox sources such as cosmetics, herbal remedies and spices in the diagnosis of symptoms relating to lead toxicity. The use of leaded cosmetics has been observed to be strongly

correlated with elevated BLL [37,49, 58]. The fact that these HMPs and cosmetics are used on children and pediatric age group should elicit concern.

Apart from an extensive data available on Pb intoxication of the central nervous system and the homopoietic system, very little information is available regarding its effects on the ocular system. Data on the elemental analysis of the ocular lenses exposed to Pb demonstrates that long-term Pb exposure results in significant perturbation in the status of the essential trace metal ions such as Ca, Fe, Cu, and Zn. The effect of Pb on the levels of these divalent metal ions could be the result of competition for common binding sites [67]. Lead is a biogeochemical analogue to calcium. As such it is readily incorporated into trophic and metabolic pathways [68].The use of HMPs and leaded eye cosmetics should be considered as a factor in analyzing the sources of exposure to relatively high levels of Pb reported in human breast milk and hair samples in Nigeria [62, 69, 70]. These products are used regularly on children and on the pediatric age group. This practice can result in baseline human exposure that may place large populations of infants and children at risk of developmental lead toxicity [13]. The observation that this practice is common among low-income earners corroborates the observation that poverty is crucial in the elevation of whole blood lead levels [71, 72]. Elevated blood lead levels in children have been associated with behavioral problems, loss in intelligence and other neurological disorders [73-75]. Children are more vulnerable to Pb exposure for three reasons: young children are more at risk of ingesting environmental Pb through the normal mouthing behavior and craving for non-food items referred to as pica, [76-77]; absorption from the gastrointestinal tract is higher in children than in adults and the developing nervous system is thought to be far more vulnerable to the toxic effects of Pb than the mature brain [78-79]. Lead toxicity can affect several organ systems including the hematopoietic system, the peripheral and central nervous system, the kidney, the cardiovascular system and the reproductive system [80].

Emergency chelate treatment of lead poisoning from use of local cosmetics (kohl) has permitted improvement of clinical state of victims and decrease BLLs. Bruyneel et al, [49] reported a decrease of blood lead initially of 490µg/dL to 49µg/dL after 6 weeks of treatment. Studies of the effect of blood lead on children's mental development has shown intelligence quotient deficits of an estimated 0.25 points for every microgram per deciliter (µg/dL) increment in blood lead level [81-83]. It has been suggested that lead may have this effect by interfering with the role of calcium in brain cell development [84] and because the developing nervous system is thought to be far more vulnerable to toxic effect of lead than the nature brain [79]. Unfortunately, it is not known whether treatment to reduce blood lead levels prevents or reduces such impairment [85]. On a societal basis, the aggregate loss on cognitive acuity due to lead exposure can be enormous. Acknowledging there impacts, the US Centers for Disease Control (CDC), the principal advisory agency for child health in the United States established a goal of reducing children's blood lead levels to below 10µg/dL [82]. Studies have reported a lowering of blood lead levels in children with treatment with succimer. This however did not improve scores on tests of cognition, behavior, or neuro-psychological function in children with high blood lead levels [85]. Rogan et al, [85] reported a randomized trial of an oral lead-chelating agent, succimer, in children whose blood lead levels were 20 to 44µg/dL. The performance of these children on several cognitive assessments was below average - an observation consistent with previous reports of deficits in academic achievements, abstract thinking, attention span, conceptual reasoning, and visuospatial perception in children with moderately high BLL. This study suggests that even with succimer therapy, the neuro-cognitive effects of chronically elevated BLLs and total-body lead burden are irreversible. This confirms the need for collective and concerted efforts to prevent Pb poisoning in children [86].

Emphasis should be on the prevention of lead poisoning rather than on the treatment after lead poisoning [86]. The health implications of indulging in this practice can only be monitored by a survey of the blood lead levels of groups engaging in these practices because Pb determination in blood is presently the prevailing indicator of Pb exposure and risk [80].

6. Herb - Drug Interactions

Adverse drug reaction (ADR) reporting is essential for pharmaceuticals in providing post marketing surveillance. ADR of any medication whether alternative or conventional is well established and is usually undertaken by a medical practitioner, pharmacist or dentist. The adverse effects of herbal medicine includes toxicity due to overdose; contamination by other medicinal plants, mistaken plants; physiological changes on bodily systems; and adverse drug interactions. However the low number of reports of ADR in persons using CAM/HMPs has been observed even in developed countries where considerable efforts has been made at controlling both the intrinsic and extrinsic effects of CAM/HMPs. This implies that these products have either a low risk of adverse effects or that such effects

are significantly under-reported. Although limited evidence suggests that these products maybe associated with a lower risk than conventional medicines, under-reporting is likely, as:

1. relevant agencies do not actively encourage the reporting of adverse effects by practitioners and consumers of alternative medicine,
2. CAM use is not routinely included in patient's drug histories or in reports of adverse effects. In Africa this is worsened by the observation that most people do not keep medical records ,which makes medical practitioners not to request for such, and,
3. the public believes that "natural' products are safe. This perception biases against an association being made between CAM products and adverse effects [2]

Most herbal medicines have ADRs. Interaction between herbal drugs and prescribed medications exist and can have serious clinical consequences. These are more likely among individuals with chronic medical conditions, such as liver or kidney disease-conditions that are likely to be found in older populations. Patients should be advised to avoid using a wide variety of herbs concomitantly because herb-herb interactions are poorly understood [22]. Because medicinal herbs are usually self-prescribed by the customer, recommendations for the use of prescribed drugs like dose, manner and frequency of administration, which are reviewed and controlled by the prescribing physician are lacking. These factors increase the risk of toxicity of herbal medicines, as consumers use them as long as their conditions last, and even at increased doses [15].

It is possible to predict when herb-drugs interact by knowing their pharmacokinetic properties, and their pharmacodynamic behaviors. Pharmacokinetic properties entail changes in absorption, metabolism, and elimination of the drug/herbs whereas pharmacodynamic behaviors refer to how the herb/drug interacts inside the body (synergistic or antagonistic). In general, herb/drug that alters the stomach pH (anti-acids) or intestinal motility (laxatives) will have an effect on absorption. Drug/herb metabolism occurs principally in the liver. The duration (life span) of an herb or drug in the body depends on whether the liver's metabolism is induced or inhibited. An herb lasts longer in the body if its metabolism is inhibited by another drug; likewise, it is excreted faster if ones liver metabolism is induced. Further, drug/herb elimination primarily occurs at the kidney and is affected by the individuals kidney function or by drugs toxic side effects. Lastly, the extent to which an herb-drug interacts depends on the individual's health conditions, age, body weight, metabolic rate, and dosage [30].

Adverse effects of herbal medications can be classified into intrinsic and extrinsic. In general, the patient's age, genetic constitution, nutritional state, concomitant diseases and concurrent medication may affect the risk and severity of adverse events, as can consumption of large amounts or a wide variety of herbal preparations or long-term use. Intrinsic effects are the effects of the herb itself and have been characterized by pharmaceuticals into Type A (predictable, dose-dependent) and Type B (unpredictable, idiosyncratic) reactions. Extrinsic effects are not related to the herb itself, but to a problem in preparation or commercial manufacture or extemporaneous compounding [2].

Ernst [64], reviewed cases of adverse events associated with unconventional therapies and observed that most of the adverse events were associated with herbal medications. Inadequately regulated herbal medicines may contain toxic plant materials, be contaminated with heavy metals, or be adulterated with synthetic drugs. The adverse events include bradycardia, brain damage, cardiogenic shock, diabetic coma, encephalopathy, heart rupture, intravascular haemolysis, liver failure, respiratory failure, toxic hepatitis and death [64].

Drews and Myers [2] classified the sources of extrinsic effects of herbs into seven,
1. misidentification,
2. lack of standardization
3. contamination,
4. substitution,
5. adulteration,
6. incorrect preparation/dosage,
7. inappropriate labeling/advertising.

Any particular herb that is not toxic or therapeutic in one form or strength may be helpful or harmful in a different preparation. The same common name may be applied to different plants recommended for different illnesses. Potential failure to adhere to code of good manufacturing practice, while not specific to herbal medicine, can occur,

particularly in developing countries where such a code is not in place. This makes it more difficult for medical practitioners and other health professionals to assess the adverse effects of herbal preparations compared to pharmaceuticals [2].

8. Case Reports of Human Lead Exposure

History of herbal drug use has been identified as a major risk factor for high BLL in males and females in Taiwan [87]. Similarly, factors including Chinese herbal drug consumption were identified by Liou et al, [88] as an important consideration in Taiwan when examining ways to prevent over exposure to lead in the general population. Cases abound in literature of human exposure to lead from use of herbal remedies and local cosmetics.

Wu et al [89] reported two cases of Pb poisoning caused by the Chinese herbal medicine Cordyceps (a combination of the fungus Cordyceps sinensis and the larva of Hepialus armoricanus) in Taipei, Taiwan. Two patients took Cordyceps herbal medicine for treatment of underlying diseases. Loss of appetite and anemic signs of Pb poisoning were manifested in one patient with BLL of 130µg/dL, while the other patient was asymptomatic with BLL of 46µg/dL. The lead content in the Cordyceps powder was found to be as high as 20, 000ppm.

Markowitz et al, [90] reported a case of a 45-year-old Korean man who developed abdominal colic, muscle pain, and fatigue with a high level of urinary delta-aminolevulenic acid. High BL of 3.7µMol/dL or 76µg/dL led to a correct diagnosis of lead poisoning. Investigation revealed the patient ingested a Chinese herbal preparation for 4 weeks prior to becoming ill. A public health investigation revealed that the source of Pb exposure was hai ge fen (Clamshell powder), one of the 36 ingredients of the Chinese herbal medicine. Rahman et al, [91] reported a case of six infants, 3 of them neonates, who were diagnosed as having acute lead poisoning: four of them had acute encephalopathy. All had been given an indigenous preparation, Bint Al Zahab (Daughter of Gold) for abdominal colic and early passage of meconium after birth. Chemical analysis of the powder revealed a Pb content of 82.5%. Similarly, other studies by Prpic-Majic et al, [92], and Ibrahim and Latif, [93] made similar observations.

Similarly, case reports abound also for human exposure to lead after use of local cosmetics. The toxicity and extent of use of alkohl in Saudi Arabia was investigated by Alkawajah, [48]. The study observed that about 28% of the users of alkohl experienced some type of adverse reaction. The mean blood lead level (BLL) of the users of Alkohl was 0.99µMol/L as compared to 0.26µMol/L in non-users. This supports the high levels of Lead reported in these samples. A similar leaded eye cosmetics product (imported from Pakistan) was identified as the source of lead intake in Pakistani/Indian children residing in the US who had a mean lead level of 12.9µg/dL (0.62µMd/L) for the children using the leaded cosmetics compared to 4.3µg/dL (0.21µMol/dL) for Pakistani/Indian children not using eye cosmetics [47].

There is concern that previously accumulated lead stores may constitute an internal source of exposure particularly during periods of increased bone mineral loss (e.g. pregnancy, lactation, and menopause). Further, the contribution of Pb mobilized from bone plasma may not be adequately reflected by whole-blood lead levels. This possibility is especially alarming because plasma is the main circulating compartment of lead that is available to cross cell membranes and deposit in soft tissues [94]. Lead impairs the renal, homopoietic and nervous system and reports of various surveys suggest that Pb is causally related to deficiency in cognitive functioning.

9. Concerns Over Regulations

The regulatory status of herbal products differs significantly from country to country. As at 2002, less than 70 countries regulate herbal medicines and a few countries have systems in place for the regulation of traditional health practitioners [11]. These disparities in regulation between countries have serious implications for international access to and distribution of such products. For instance, in one country an herbal product may be obtained only on prescription and from authorized pharmacy, whereas in another country, it may be obtained from a health food shop, or even, as has become common practice, by mail order or Internet [11]. There are considerable risks associated with herbal medicines, which at times may result in significant morbidity and mortality especially in children and older patients. The following issues need urgent attention:

♦ There should be dose monitoring of herbal remedies for known adverse effects and drug interactions especially for patients taking both herbs and conventional medications.

♦ Many traditional medicines are manufactured for global use and they have moved beyond the traditional and cultural framework for which they were originally intended. As such, rigorous regulation of the herbal industry at a

global level is recommended to address concerns such as contamination, bioavailability of active ingredients and so fort.

♦ There are concerns over the lack of quality control in the preparation/production of HMPs. Because of the lack of requirements for quality control, safety and efficacy data, consumers cannot determine whether the ingredients is bioavailable, whether the next dosage is appropriate, whether the next bottle they buy will have the same components, or what else is in the HMP package besides the claimed ingredient(s).

♦ Herbal medicines are ubiquitous: the dearth of reports of adverse events and interactions probably reflects a combination of under-reporting and the benign nature of most herbs used. Experimental data in the field of herb-drug interactions are limited, case reports scarce and case series rare [39].

♦ The instructions on most imported herbal remedies, if any, are often written in foreign languages. Therefore, information on dosage and composition becomes problematic. As a result recommendations are that patients be advised not to use such herbal products from foreign sources even if their costs are substantially lower

♦ Self-medication further aggravates the risk to patients. This practice in HMP consumption is common. There is need for regulation of this in order to check over dosage and drug abuse.

Marcus and Grollman [27] reviewed the problems inherent in the manufacture, analysis, and post-marketing surveillance of botanical medicines and proposed new legislative regulations to address these issues in the United States. They proposed six legislative proposals, which amongst others include:

o The address and telephone numbers of all companies, as well as the names of the responsible persons, involved in manufacturing dietary supplements should be registered with the Food and Drug Administration, FDA, the regulatory agency,

o The manufacturers of dietary supplements should provide evidence of good manufacturing practices and the FDA should be given the authority to inspect manufacturers' records.

o The labels of dietary supplements should contain a list of constituents that unambiguously identifies herbs by their botanical and common names. information about possible adverse effects, including the potential for herb-drug interactions should be included

These issues should be of interest to the developing countries in preparing draft legislations aimed at establishing a regulatory framework for these products.

DISCUSSION

There is an increasing use of traditional medicine and herbal medicine with other medicine with potential for adverse interactions. There is therefore a need for a consideration of pharmacovigilance practice in the light of the lack of clear definition of boundaries between food, medicine (including traditional medicines, herbal medicines, and 'natural products'), medical devices and cosmetics [11].

In developing countries, exposure sources of heavy metals are diverse and often vary from those in developed countries, and vary dramatically from country to country. Limited economic conditions and poverty have strong impact on environmental exposures, health care delivery, and the potential for environmental protection. In addition, many factors enhance or magnify the impact of lead exposure. For example, industrial sites are often located in residential areas, warm climate contribute to full-year exposure to outdoor environments, and poor nutritional status magnify the effects of lead poisoning. From a public health perspective, laboratory capacity for measuring blood level (or even environmental lead) concentration is limited. Consequently, almost no data exists in many countries on blood lead concentration. In addition, health care systems usually have limited ability to deal with toxic chemical exposures, such as lead poisoning, and chelating agents are often unavailable or markedly limited to treat severe poisoning [95].

As with other products intended for human use (medicines, dietary supplements and foods), herbal medicines should be incorporated within a regulatory framework. These products should be governed by standards of safety, quality and efficacy that are equivalent to those required for other pharmaceutical products. Difficulties in achieving this arise from the growth of an ambiguous zone between foods and medicines, into which an increasing number of herbal products fall [11]. Evidence of effectiveness of various herbs is incomplete, and risk-benefit assessment is not completely reliable. Hence, physicians should minimize the use of conventional medications and herbs for the same clinical condition because of the potential for herb-drug interactions that may compromise the beneficial effects of the prescribed medicine.

Heavy metals contained in herbal remedies and local cosmetics may cause illness of unknown origin and result in the consumption of health care resources that are attributable to other causes [17]. There is paucity of information on the treatment of lead poisoning from use of HMPs and cosmetics in Africa. This is more so because of the factors listed by Fulk, [95]. There should therefore be a concerted attempt at checking lead poisoning from HMPs and cosmetics in the developing countries rather than treatment when the facilities are not existent.

Even with compliance with the stipulate quality requirements for registration, strict regular surveillance is required as such products cannot be assumed to be safe from heavy metal contamination because of batch - to - batch inconsistencies [13, 22, 36]. There is an urgent need for periodic monitoring of herbal medicinal preparations in Nigeria and other developing countries, and to seek means of protecting the consumer from such risks.

One sure way of reducing the use of these products is by creating awareness among health professionals and the general public on the potential hazards of these practices [57]. Education of parents and childcare workers regarding the risks of administering lead-based substances to children and themselves needs to be incorporated into health and healthcare framework systems in developing nations [59].

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