Herbal Medicines Use: Remedies or Risks

Olufunsho Awodele[1], Olugbenga Fajemirokun[2], Ibrahim Oreagba[1], Titilola A. Samuel[3], Temidayo D. Popoola[1], Abdul Gafar V. Coulidiaty[4], Promise M. Emeka[5]

[1]Department of Pharmacology, Therapeutics and Toxicology, College of Medicine, University of Lagos, Lagos, P.M.B.12003, Lagos-Nigeria
[2]Department of Clinical Pharmacy, Faculty of Pharmacy, Olabisi Onabanjo University Sagamu, Ogun State, Nigeria.
[3]Department of Biochemistry, College of Medicine, University of Lagos, Lagos, P.M.B.12003, Lagos-Nigeria.
[4]Clinical Trials Team of the Clinical Research Department, Centre Muraz, Health Research Institute, 2054 Avenue Mamadou Konaté, 01 B.P. 390 Bobo-Dioulasso, Burkina Faso.
[5]Department of Pharmaceutical Sciences, College of Clinical Pharmacy, King Faisal University Hofuf Kingdom of Saudi Arabia

Corresponding author: Olufunsho Awodele
Email: awodeleo@gmail.com; Phone: +234-8023624044

ABSTRACT

Background: There is an increasing use of herbal products and herbal medicines globally with the belief that herbal medicines are always 'safe' and carry no risk because they are from natural sources. However, there are concerns regarding medicinal plants and their ability to produce adverse effects. The World Health Organization (WHO) directive encourages developing countries to supplement their health programmes with traditional herbal preparations provided they are proven to be non-toxic

Objectives: Some plants and their constituents have been shown to be potentially toxic. In this paper, we review data looking at the benefits and risks of herbal medicines use.

Results: Literature search shows the huge role herbs play in health and wellness as some conventional medicines were originally derived from natural sources. For example, Digitalis, a cardiac glycoside was derived from the foxglove plant (*Digitalis purpurea* L.); the anticancer drug Vincristine was derived from periwinkle (*Cantharnthus rosues* Linn. G. Donn); the antidiarrhoeal and narcotic analgesic drugs Codeine, Morphine and paregoric were derived from the opium poppy (*Papaver somniferum* L.); the antimalarial drugs Quinine and Artemisinin were, respectively, derived from *Cinchona pubescens* Vahl and *Artemisia annua* L.Despite the profound therapeutic benefits possessed by medicinal plants, some of them have been found to be toxic to specific organs, mutagenic or teratogenic. Current study revealed that *Azadirachta indica*, *Morinda lucida*, and *Enantia chlorantha* possessed mutagenic potentials in modified Ames assays, while *Alstonia boonei* induced testicular and kidney damage.

Conclusion: Herbal medicines have significant benefits in health and wellness, but must be cautiously used due to their potentials for toxicity. Overall, the integration of herbal medicine into national healthcare scheme may enhance safe use of herbal remedies via appropriate research, regulation and rational use of herbal medicine.

Key words: Herbal medicine, Nigeria, National Health Care Scheme, Safety, World Health Organization

Phytothérapie: Remèdes ou risques

Olufunsho Awodele[1], Olugbenga Fajemirokun[2], Ibrahim Oreagba[1], Titilola A. Samuel[3], Temidayo D. Popoola[1], Abdul Gafar V. Coulidiaty[4], Promise M. Emeka[5]

[1]Département de Pharmacologie, Thérapeutique et Toxicologie, Collège de Médecine, Université de Lagos, Lagos, P.M.B. 12003, Lagos-Nigeria

[2]Département de Pharmacie Clinique, Faculté de Pharmacie, Université Olabisi Onabanjo Sagamu, Etat d'Ogun, Nigeria.

[3]Département de biochimie, Collège de médecine, Université de Lagos, Lagos, B.P. 12003, Lagos-Nigeria

[4]Equipe des tests cliniques du département de recherche clinique, Centre Muraz, Institut de Recherche en Santé, 2054 Avenue Mamadou Konaté, 01 B.P. 390 Bobo-Dioulasso, Burkina Faso.

[5] Département des sciences pharmaceutiques, Collège de pharmacie clinique, Université King Faisal Hofuf. Royaume d'Arabie Saoudite

Correspondance : Olufunsho Awodele
Email awodeleo@gmail.com; Téléphone : +234-8023624044

RÉSUMÉ

Contexte : Les produits à base de plantes et les plantes médicinales sont de plus en plus utilisés dans le monde entier, sous la croyance que les médicaments à base de plantes sont toujours « sûrs » et ne comportent aucun risque car ils proviennent de sources naturelles. Cependant, il existe des préoccupations concernant les plantes médicinales et leur capacité à produire des effets indésirables. La directive de l'Organisation Mondiale de la Santé (OMS) encourage les pays en développement à compléter leur programme de santé par une préparation traditionnelle à base de plantes à condition de prouver qu'ils ne sont pas toxiques.

Objectifs : Certaines plantes et leurs constituants se sont révélés potentiellement toxiques. Dans cet article, nous passons en revue les données examinant les avantages et les risques de l'usage des médicaments à base de plantes.

Résultats : La recherche documentaire montre l'importance du rôle des herbes en santé et en bien-être, étant donné que certains médicaments conventionnels étaient à l'origine de sources naturelles. Par exemple, Digitalis, un glycoside cardiaque a été dérivé de la plante de digitale pourpre (Digitalis purpurea L.) ; le médicament anticancéreux Vincristine a été dérivé de la pervenche (Cantharnthus rosues Linn G. Donn); les analgésiques antidiarrhéiques et narcotiques Codéine, Morphine et parégorique ont été dérivés du pavot à opium (Papaver somniferum L.); les médicaments antipaludiques Quinine et Artémisinine provenaient respectivement de Cinchona pubescens Vahl et Artemisia annua L. Malgré les bienfaits thérapeutiques profonds des plantes médicinales, certaines d'entre elles se sont révélées toxiques pour certains organes, mutagènes ou tératogènes. L'étude actuelle a révélé que Azadirachta indica, Morinda lucida et Enantia chlorantha possédaient des potentiels mutagènes dans les tests d'Ames modifiés, tandis qu'Alstonia boonei induisait des lésions testiculaires et rénales.

Conclusion : La phytothérapie présente d'importants avantages pour la santé et le bien-être, mais doit être utilisée avec précaution à cause de leur toxicité potentielle. Dans l'ensemble, l'intégration de la phytothérapie dans le système national de soins de santé peut améliorer l'utilisation des remèdes à base de plantes médicinales par des recherches appropriées, la réglementation et l'utilisation rationnelle de la phytothérapie.

Mots-clés : Phytothérapie, Nigéria, Régime national de soins de santé, Sécurité, Organisation mondiale de la Santé

INTRODUCTION

Herbal Medicine is one of the major categories of complementary and alternative medicines (CAM). The term CAM commonly refers to practices that are not integral parts of modern or orthodox medicine and are consequently not included in the conventional medical education curriculum.[1] The National Institute of Health (NIH) categorized CAM into five main groups: alternative medical systems (e.g. traditional oriented medicine, acupuncture, Ayurveda, naturopathy, homeopathy, native American healing, and Tibetan medicine), mind–body interventions (meditation, hypnosis, dance, art and music therapy, spiritual healing, and prayer), biological-based therapies (herbal medicine and dietary supplements, special diets, and orthomolecular medicine), manipulative and body-based methods (chiropractic, massage, the Feldenkrais method, other ''body work'' systems and aspects of osteopathic medicine such as craniosacral work), and energy therapies (reiki, therapeutic touch and other methods affecting the ''bioelectric field'' of the body).[2]

Herbal medicines have important roles in traditional medicines as traditional medicines practitioners often incorporate the use of herbal medicines in their practice. Herbal medicines are parts of plants commonly employed as raw materials for self-administered pharmaceutical remedies and as supplementary products in the general population.[3] The plant materials used include fruits, seeds, berries, roots, rhizomes, leaves, bark and flowers.[4] The World Health Organization (WHO) approximates that about 80% of the world's population depends on traditional medicinal system for some aspect of primary health care.[5] Thus encourages developing countries to complement their health program with traditional herbal preparation provided they are proven to be non-toxic.[6] Vast majorities of people use these herbal medicines as first line remedies and as their primary form of health care.[1,5]Herbal prescriptions are employed in both developed and developing countries for the treatment of various diseases.[7]

Some conventional medicines were originally derived from natural sources. For example, Digitalis, a cardiac glycoside was derived from the foxglove plant (*Digitalis purpurea* L.),[8] the anticancer drug Vincristine was derived from periwinkle (*Cantharnthus rosues* Linn. G. Donn),[9] the anti-diarrhoeal and narcotic analgesic drugs Codeine, Morphine and paregoric were derived from the opium poppy (*Papaver somniferum* L.),[10] the non-steroidal anti-inflammatory and analgesic drug (Aspirin) is a derivative of salicylic acid which was originally derived from the white willow bark and the meadowsweet plant (*Filipendula ulmaria* (L.) Maxim.),[11] the antimalarial drugs Quinine and Artemisinin were, respectively, derived from *Cinchona pubescens* Vahl and *Artemisia annua* L.[12,13]

The rising use of traditional medicine has informed the WHO's decision to encourage its incorporation into the national health care systems of countries and to inspire the formulation of national policy and regulations as important indicators of the extent of incorporation of such medicine within a national health care system.[14,15] Although traditional medicines in several countries including Nigeria have not been integrated into conventional medical practice, studies have confirmed the efficacy of some Nigerian medicinal plants that are used in indigenous medicine. Such plants include *Rauwolfia vomitoria* (Afzel) for managing hypertension, stroke, insomnia and convulsion,[16]*Ocimum gratissimum* L. for managing diarrheal diseases,[17] the seeds of *Citrus parasidi* Macfad for managing urinary tract infections that are resistant to the conventional antibiotics,[18] pure honey for healing infected wounds faster than eusol,[19] dried seeds of *Carica papaya* L. for the management of intestinal parasitosis,[19]*Garcinia kola* Heckel for the management of osteoarthritis,[20] and *Aloe vera* Mill. gel for the management of scabies.[21]

Despite the profound therapeutic benefits possessed by some of the medicinal plants, some constituents of these medicinal plants have been shown to be potentially toxic, mutagenic, carcinogenic and teratogenic.[22]*Azadirachta indica, Morinda lucida, and Enantia chlorantha* have been shown to possess mutagenic potentials in modified Ames assays,[23] while *Alstonia boonei* has been shown to induce testicular and kidney damage.[24] This review will generally discuss the remedies and risks associated with herbal medicines use.

Challenges with Herbal Medicines

The major concern with herbal medicines use is the safety and efficacy of herbal preparations. Pharmacological and toxicological studies are often used to determine the efficacy and safety profile of these products. However, scientific investigations on herbal medicines are complex with several confounding variables. Other prominent problems associated with herbal medicines include: lack of

clinical trials on these products within western pharmaceutical clinical standards, dosage specifications, problems of proper packaging, appropriateness of their level of hygiene, cost of production and their level of acceptability especially among the elites in the healthcare team who continues to prescribe only orthodox/conventional medicines in hospitals and clinics. Legislative controls of medicinal plants have not developed around a structured control model. There are diverse ways in which countries define medicinal plants or herbs or products obtained from them, and countries have adopted various approaches to issuance of licenses, dispensing, manufacturing and trading to guarantee their safety, quality and efficacy.[25] Despite the wide use of herbal medicines over many centuries, only a small number of plant species have been studied for plausible medical applications. Safety and efficacy data exist for smaller number of plants, their extracts and active ingredients and preparations containing them.[26]

Herbal medicines consumption is a well-known cause of kidney, liver, cardiac and blood dysfunction or diseases.[27] Kidney diseases demonstrated among CAM users include: Acute renal failure, acute interstitial nephritis, metabolic acidosis, rhabdomyolysis and tubular dysfunction.[28-32] Cardiac disorders described among CAM users include: bradycardia, heart block, tachyarrhythmia and hypotension.[33] Hepatic diseases which have been described among herbal medicines users include: acute hepatitis. Clinical manifestations usually occur few months after ingesting the herbal medications and include nausea, vomiting, abdominal discomfort, and jaundice. Raised levels of transaminases are found on initial laboratory investigation. Clinical course is usually mild and most patients improve after stopping the medicines. More severe cases may advance to hepatic failure and require serious supportive care. Liver transplant has been performed in patients with herb-induced fulminant hepatic failure.[34-39] Neurological complications associated with herbal medicine use include: weakness, seizure and intracranial bleeding. Plausible explanation for this association include reduced seizure threshold, interaction with anti-convulsive medications, direct neurotoxicity, strychnine poisoning, and cardiovascular collapse. *Ginkgo biloba* strongly inhibits platelet activating factor and elongates bleeding time after its use. Subdural hematoma and intra-cerebral bleeding have been associated with *Ginkgo biloba*.[40-43] Pulmonary complications which could result from use of herbs include: anaphylactic reactions, asthma exacerbation, severe interstitial pneumonitis, non-cardiogenic pulmonary edema, acute eosinophilic pneumonia and small airway disease.[44] Allergic diseases have been proven to be induced by CAM use via potentially sensitizing capacity of various herbal remedies which may lead to allergic contact dermatitis and more rarely, IgE mediated clinical symptoms.[27]

However, herbal medicines and dietary supplements have been used as biological-based therapies for decades. People in developing countries and even western countries still depend on herbal medicines for their health care. There are general assumptions that herbal medicines are generally safe because they are from natural origin. There are also conceptions that diseases may not develop resistance to herbal medicines as synthetic therapeutics, hence the value attached to the use of herbal medicines. It is now obvious that the future of pharmaceutical companies is on developing lead therapeutic molecules from natural sources.

Integration of Herbal Medicines into National Health Care Scheme

As mentioned earlier, statistics have shown that between 65% and 80% of the world's population use herbal medicines as their primary form of health care.[1,5] For example, in Nigeria, Ghana, Mali, and Zambia, herbal medicine constitute the first line treatment for 60% of children with high fever due to malaria.[44,45] The WHO is therefore encouraging developing countries to supplement their health programmes with traditional herbal preparations provided that the medicaments are proven to be non-toxic.[6] WHO has further proposed the organization and training of practitioners of traditional (herbal) medicine for primary health care services to enable the utilization of traditional systems of medicine in individual countries, with appropriate regulations based on their national health systems.[47] Despite the setting up of collaborating and training centers in these countries as one of the approaches embarked on by the WHO, the association between modern medicine and traditional medicine in some places has been far from expectations. In Nigeria, the practice of traditional medicine has been unofficial and usually health care is controlled by orthodox medicine.

To facilitate integration and the co-recognition of their practices in the National Health Care Scheme, traditional medicine practitioners are now recognizing the need for research and collaboration with the universities on the safety and efficacy of their herbal preparations. For integration to be successful however,

three factors must be addressed:
(1) Western medical doctors and healthcare practitioners must be receptive to the ideas of traditional African medicine. For biomedical and traditional practitioners to unite in Africa, they only need to be open to the idea of collaborating with one another as peers.
(2) Traditional medical practitioners must be open to sharing their methods and knowledge by allowing western doctors or healthcare practitioners to investigate and examine them using their own systems of fact finding.
(3) The patients must be ready to use different types of medical treatments in maintaining their health. It is noteworthy that the potential benefits of incorporating TM into the health care scheme may outweigh the afore listed mitigating factors, since it also has socioeconomic potentials for national development apart from the health benefits derived from it.

At the special health forum held at the economic community of West African state secretariat in Abuja, Nigeria in 1999, the then President of the Federal Republic of Nigeria, Chief Olusegun Obasanjo directed that the traditional medicine development program should be incorporated into the national healthcare plan of the government. Since then however, there has not been any significant advancement in the necessary recognition and output. Yet, traditional medicine is used by the majority of the population in Nigeria. This calls for an immediate review of the current strategies and an urgent need to inform the public, especially rural communities, about the availability and benefit of traditional health therapies and cost-effective means of delivering them. There is also a need to encourage government as well as donor agencies to support scientific validation of the safety and efficacy of herbal medicine while promoting their rational uses, also to caution that the loss of the medicinal plant resource base and biodiversity will have negative long term consequences for the poor and for humanity as a whole.[14]
The results obtained from our study[48] on "towards integrating traditional medicine (TM) into National Health Care Scheme (NHCS): Assessment of TM practitioners 'disposition in Lagos, Nigeria" showed that a high percentage 40% (n = 68) of the respondents had no formal education however, most of the respondents 59% (n = 101) were willing to further their education as affirmed by their responses. It is envisaged however, that improvements in their educational status would enhance their proficiency in the practice of the profession. The willingness of the traditional medicine practitioners to advance their education as shown in our study may be good and promising decisions that will lead to the co-recognition of traditional medicine practitioners in Nigeria.

It is disconcerting that most of the traditional medicine practitioners 59% (n = 101) were not willing to report any observed adverse reactions to any hospital for appropriate management. However, the respondents 64% (n = 108) were willing that their traditional herbs should be subjected to investigation by the scientists for their safety and efficacy. Furthermore, it is noteworthy from this study that the traditional medicine practitioners are willing to collaborate with orthodox medicine practitioners if they have the opportunity.

A study on the attitude of doctors to traditional herbal medicines conducted in Africa (Pluske) showed that 75% of the population of Ghana depended on traditional herbal medicines for their healthcare.[48-49] This may be due to factors such as the high cost of pharmaceutical medicines, hospitals and medical facilities which are not accessible to many, and overcrowding of patients in clinics and hospitals. Studies conducted among the Nigerian population have shown widespread use of traditional herbal medicines amongst hypertensive patients[51,52] and pregnant women.[53] The increasing use of these preparations could be as a result of the beliefs of patients in their efficacy, as well as the accessibility and affordability of the herbal medicaments.

Furthermore, our study[54] on "Doctors' attitudes towards the use of herbal medicines in Lagos, Nigeria" showed that most of the respondents 79.3% (n = 238) had never personally prescribed herbal remedies, perhaps due to lack of information regarding standard dosages and a comprehensive safety profile of these preparations. To improve the knowledge of orthodox medical doctors on herbal medicines, Owen et al.[55] suggested the inclusion of CAM in the university undergraduate medical curriculum, which is believed to be more fruitful than at post-qualifying level.[56] Overall, the integration of traditional (herbal) medicine into national health care scheme may enhance safety use of herbal remedies and appropriate practice of TM.

Specific Research Findings on Herbal Medicine Benefits and Risks

Mutagenic screening of some commonly used medicinal plants in Nigeria

Despite the profound therapeutic advantages

possessed by some of the medicinal plants, some constituents of medicinal plants have been shown to be potentially toxic, mutagenic, carcinogenic and teratogenic.[22] We investigated[23] the mutagenic potentials of commonly used medicinal plants in Nigeria; *Morinda lucida* (Rubiaceae), *Azadirachta indica* (Meliaceae), *Terapluera tetraptera* (Fabaceae), *Plumbago zeylanica* (Plumbaginaceae), *Xylopia aethiopica* (Annonaceae), *Newbouldia laevis* (Bignoniaceae), *Alstonia boonei* (Apocynaceae), *Enantia chlorantha* (Annonaceae), and *Rauwolfia vomitoria* (Apocynaceae),using modified Ames test (*Escherichia coli* 0157:H7) and *Allium cepa* assay. The results obtained with *Allium cepa* assay showed that all the medicinal plants demonstrated a concentration dependent root growth inhibition. As the concentration increased the root growth significantly ($P < 0.05$) decreased. There was also a concentration dependent decrease in mitotic index. All the concentrations (0.1, 1.0, 5 and 10 mg/ml) of the medicinal plants produced some level of chromosomal aberrations in the *Allium cepa* such as bridges and fragments, c-mitosis, anaphase with laggard and vagrant chromosomes (Figure 1). These aberrations were due to the effect of these medicinal plants on the spindle formation and thus resulting in cell division disturbances. The results also showed that higher concentrations of *N. laevis* inhibited mitotic cell division. Furthermore, *T. tetraptera* and *M. lucida* at higher concentrations showed mitostatic effect and this may be due to the effect of these medicinal plants on the mitotic cell division process. These results corroborate the study of Akinboro and Bakare[57] that showed five medicinal plants including *A. indica* and *M. lucida* to have mitodepressive, root growth inhibitory and turbagenic activities using *Allium cepa* assay. However, the results of modified Ames test showed that *A. indica*, *M. lucida*, and *E. chlorantha* altered at least three (3) biochemical characteristics of the normal organism, thus demonstrating mutagenicity. All the other medicinal plants except *P. zeylanica* which showed no alteration in any of the biochemical characteristics of the organism, altered less than three biochemical characteristics of the organism which may thus show them to have no or mild mutagenic potentials. However, these findings might not really be a limitation for the use of medicinal plants for primary health care purposes, as there are mechanistic ways by which the body system repair damage DNAs. Thus, *in vivo* study is hereby recommended to ascertain these findings from *in vitro* assay.

Toxicological Evaluation of Aqueous Leaf Extract of *Moringa oleifera* Lam. (Moringaceae)

Moringa oleifera preparations have been cited in the scientific literature as having antibiotic, antitrypanosomal, hypotensive, antispasmodic, anti-inflammatory, hypocholesterolemic, antiulcer, and hypoglycemic activities, as well as having considerable efficacy in water purification by flocculation, sedimentation and even reduction of Schistosome cercariae titer[58-62] Despite the extensive use of this herbal preparation for the management of various disorders, there is limited or no scientific data available regarding safety and efficacy of this herbal remedy. We carried out [63] a 60 day sub-chronic toxicological evaluation of the aqueous leaf extract of *M. oleifera*.

The result of acute oral toxicity (LD_{50}) study of aqueous leaf extract of *Moringa oleifera* showed no mortality at the maximum dose of 6400 mg/kg/body weight. There were no statistically significant differences ($p = 0.05$) in the % weight gain by the animals throughout the period of extract administration in all the doses compared with the control group. This observation indicated that the extract did not alter the metabolic processes of the treated animals which may subsequently affect the hormones and body weight.[64] It was observed that the food intake of all the treated animals was reduced compared with the control animals without subsequent reduction in body weight of animals. The earlier studies of D'souza and Kulkarni,[65] Anwar and Bhanger,[66] Anwar et al.[67] have all shown that *M. oleifera* may serve as food supplements. It has also been reported to contain a profile of important minerals and a good source of protein, vitamins, carotene, amino acids and various phenolics.[68-69]

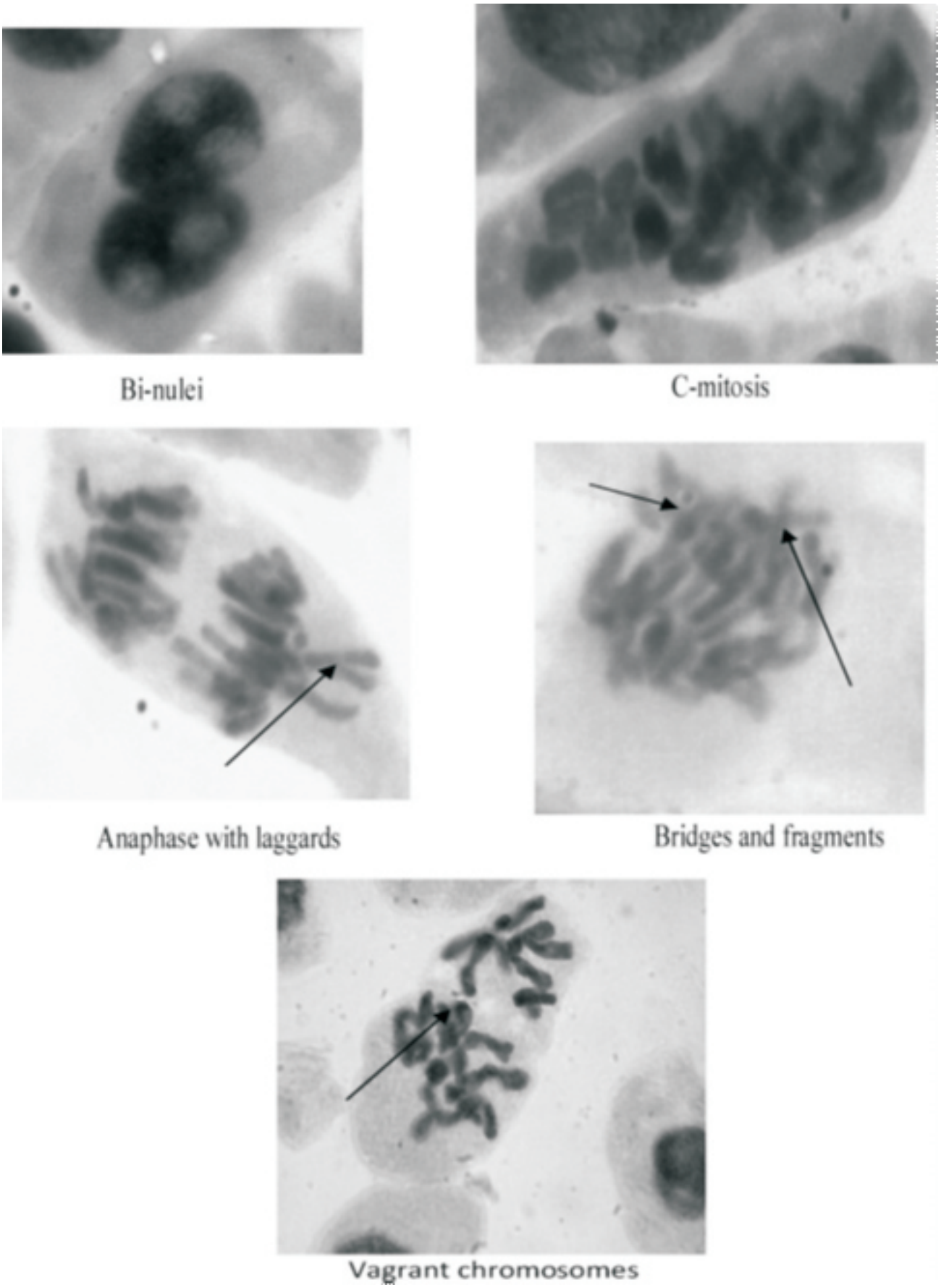

Figure 1: Aberrations at various stages of mitotic division in cells of *Allium cepa* treated with the mixture of different medicinal plants. Mag, x1000; Stain: Orcein. Adapted from Akintonwa *et al*.[23]

Furthermore, the results showed that there were no significant differences (p = 0.05) in all the haematological parameters of the test animals compared with the control animals. The urea and creatinine results also showed no significant differences (p = 0.05) in all groups of experimental animals compared with the control animals. The blood chemistry results corroborate the histological report of the kidney which showed no damage to the renal cells. However, there were slight increase in the levels of the urea and creatinine of the treated animals. Thus, there is need to exercise caution in the long-term consumption of this medicinal plant as it may exhibit long term nephrotoxicity. It was also discovered in this study that the liver biomarkers were not significantly altered by the extract. Though, the histopathology results (Figure 2) showed unremarkable sinusoidal congestion in the hepatic cells of the treated animals. The sperm quality examination revealed no toxic effect on the sperm count, motility and morphology as shown in this study.

The results of lipid peroxidation and antioxidants level of treated rats as shown in this study revealed non-significant increase (p = 0.05) in the level of MDA and decrease in the levels of SOD and catalase at higher doses of 500 mg/kg and 1500 mg/kg. This indicates that *M. oleifera* has the potential to induce free radical generation and this may be the rational for slight increase in the values of urea and creatinine of the treated animals.

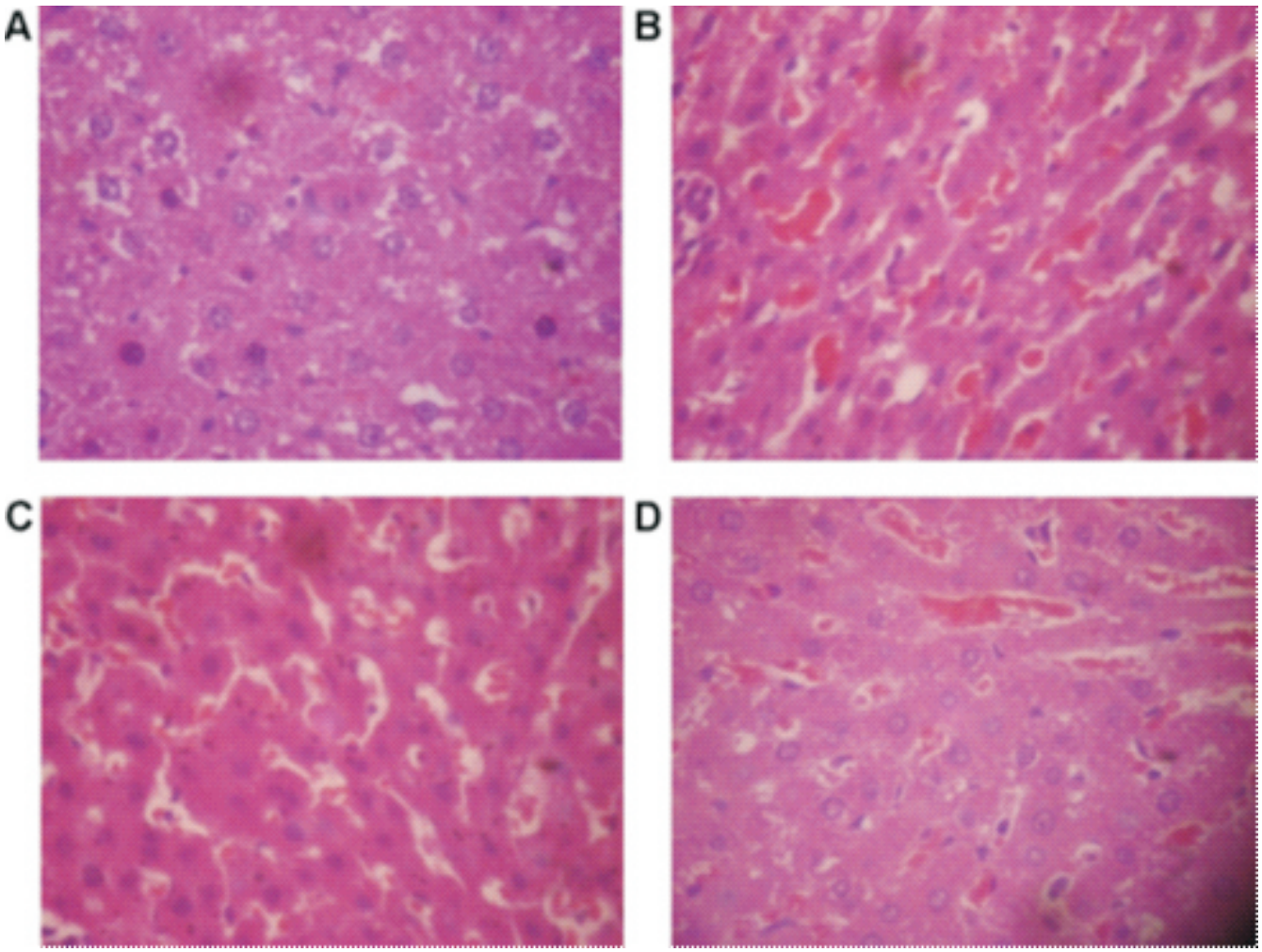

Figure 2: Photomicrographs of the liver sections obtained from rats untreated and rats treated with various doses of aqueous leaf extract of *M. oleifera*; Magnification x40.;(A) Rats untreated (control). (B) Rats treated with 250 mg/kg. (C) Rats treated with 500 mg/kg. (D) Rats treated with 1500 mg/kg.
Adapted from Awodele *et al*.[63]

Heavy Metal Contamination of Traditional Medicinal Plants

Soil pollution as a result of increasing industrialization is a reality that is taking its toll on mankind today. Bearing in mind the population of people that use herbal remedies especially in developing countries and the discharge of industrial waste on surrounding herbal vegetation, it is imperative to always determine the heavy metals contamination in commonly used medicinal plants before consumption. The addition of herbs that may be contaminated with heavy metals[69-71] to medications may result in chronic accumulation of these metals in human organs. Bio-accumulation of heavy metals may result in both middle-term and long-term health risks such as abdominal pain, illness to human fetus (causing abortion and/or preterm labor) and mental retardation to children. Adults may also experience high blood pressure, fatigue, kidney and brain disturbances.[73] Chronic heavy metal ingestion may also lead to, skin eruptions, intestinal ulcer and different types of cancers.[74] In our study "traditional medicinal plants in Nigeria—remedies or risks"[75] we quantified the levels of heavy metals in selected medicinal plants used as traditional remedies such as, *Ageratum conyzoides* used as an anti-inflammatory and in wound healing;[76] *Aspilia africana* is used as a contraceptive and antifertility agent;[77] *Alchornea cordifolia* is indicated in fever, rheumatism and toothaches;[78] *Amaranthus brasiliensis* is used as an emetic and laxative[79] and *Chromolaena odorata* employed in sore throats, colds and in aromatic baths.[80]

The concentrations of the heavy metals Pb, Cd, Cr, Ni and Zn were significantly higher (p=0.05) in the leaves and roots of the plants collected from polluted soil than found in the plants harvested from an unpolluted environment. Analysis of the soil samples (Table 1) also show that the concentrations of heavy metals were significantly (p=0.05) higher in polluted soil as against that found in unpolluted soil samples and thus may predispose to increased levels of these heavy metals in plants cultivated on the polluted soil. These results are suggesting the increased risk/toxicity associated with intake of herbal remedies more especially plants grown on polluted/contaminated soils. In view of this, there is need for cautious use of the medicinal plants cultivated in polluted soil due to high tendency for bio-accumulation and subsequent systemic toxicity.

Table 1: Heavy metal contents of soil samples in polluted and unpolluted areas

Soil source	Pb (mg/kg)	Cd (mg/kg)	Cr (mg/kg)	Ni (mg/kg)	Zn (mg/kg)
Unpolluted	0.095±0.001	ND	0.130±0.001	0.070±0.001	2.455±0.001
Polluted	0.105±0.001*	ND	0.155±0.001*	0.105±0.001*	3.235±0.001*

Values represent the mean ± standard deviation (n=3) heavy metal amount mg/kg soil sample.
*Represents significance at p = 0.05.

·Toxicological evaluation of the lyophilized fruit juice extract of Annona muricata Linn. (Annonaceae) in rodents

Soursops (*Annona muricata* L.) (AM) is used in traditional medicine for the treatment of various ailments, especially for parasitic infections and cancer."[81] It has also been used in some African herbal medicine systems for its sedative and antispasmodic properties. In tropical Africa, including Nigeria, the plant is generally used as an antimalarial, antimutagenic (cellular protector), emetic (induce vomiting), antispasmodic, astringent, anticancerous[82,83] antidiabetic'[84] and antibacterial85 agent. The plant is also reported to have good antioxidant property.[86] We carried out toxicological evaluation of the lyophilized fruit juice extract of AM.[87]

Findings from this study showed that the lyophilized fruit extract of AM was relatively safe, as oral and intraperitoneal acute administration of the fruit juice of AM did not produce mortality in mice up to 2000 mg/kg. On chronic exposure, AM treatment did not have any significant impact on the body weight and organ weight, which signified that chronic consumption of AM is relatively safe in healthy individuals. No significant alterations of the hematological and biochemical parameters of treated rats could also be attributed to

AM administration. However, AM treatment caused significant reduction in PCV and PLT 400 mg/kg and 2000 mg/kg, respectively, but these effects were reversed after 14 days of cessation of administration. Furthermore, no significant alteration in the plasma urea and creatinine AST and ALT levels due to AM treatment. Histological assessment of the vital organs revealed that the liver was the only organ adversely affected on long-term usage of this fruit (Figure 3). The liver of animals treated with the low dose showed congested blood vessels with sinusoids. Mild chronic inflammation of the liver cells was observed at 400 mg/kg treatment, whereas the high dose produced congestion in the liver of the animals, which was not reversed after 14 days of cessation of administration. The effects of the fruit juice on the reproductive system were assessed using motility, count and morphology (% abnormality) of the male sex cells. From this study, subchronic treatment with AM increased sperm count and motility. Moreover, it reduced the number of malformed sperm cells.

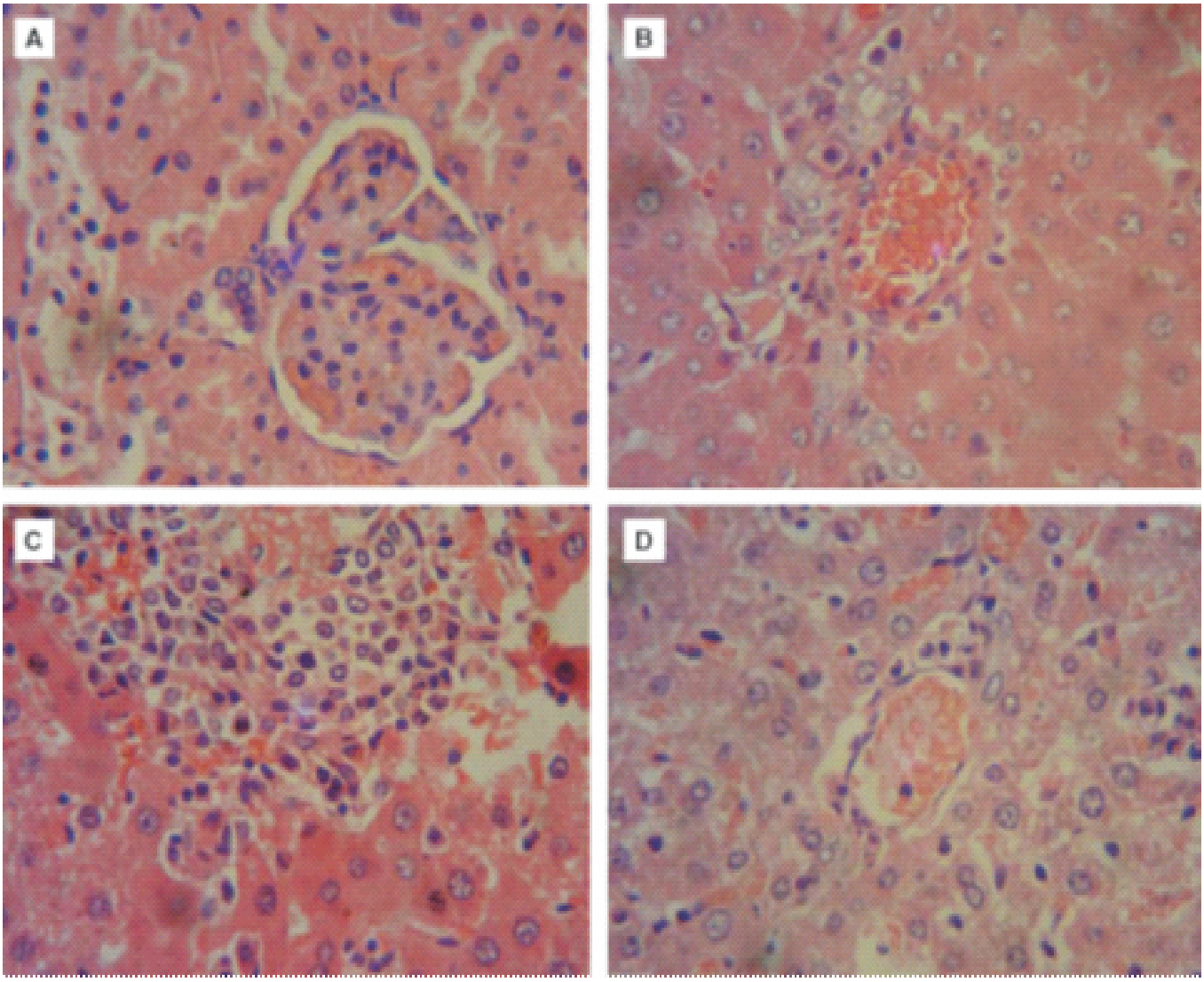

Figure 3 (A– D) Histological presentation of the Liver. Effect of (A) vehicle-treated control 10 mL/kg, (B) AM 80 mg/kg showing congested blood vessels and sinusoids, (C) AM 400 mg/kg showing mild chronic inflammation, (D) AM 2000 mg/kg showing congestion. Adapted from Awodele *et al*.[87]

Table 2:Effects of AM on sperm motility, count and morphology (% abnormality) in a reversibility study

Treatment	Dose Mg/kg	Motility, %	Count, x10^6	Morphology / abnormalityvehicule
Vehicle	10±1.58	26.00±1.58	33.12±1.94	13.5±0.86
AM	80	41.50±1.32	49.06±1.94[a]	8.50±2.36
AM	400	50.75±1.79	59.06±3.93[b]	3.25±0.85
AM	2000	33.50±1.56	36.25±1.32	10.50±1.32

Values represent the mean ± standard deviation (n=5), [a]p = 0.01, [b]p = 0.001.

Significant increase vs vehicle-treated control group using one-way ANOVA followed by Dunett's post hoc multiple comparison test.

Safety evaluation of Bon-santé cleanser® polyherbal in male Wistar rats

Bon-santé cleanser® (BSC) is a marketed polyherbal formula manufactured by Dabiron Natural Life Care in Nigeria. BSC comprises of different constituents as follows: *Anogeissus leiocarpus*DC. (Combretaceae), *Terminalia ivorensis*A. Chev. (Combretaceae), *Massularia acuminate* (G.Don,) Bullock ex Hoyle (Rubiaceae) and *Macuna pruriens* (L.,) DC (Fabaceae) formulated into capsule. (BSC) is formulated from these medicinal plants with the purpose to boost body hormones and energizes the body. Considering the wide usage of BSC, we studied on its safety in male Wistar rats.[88]

Our results showed that when BSC was given orally, the herbal preparation was relatively safe as there was no mortality during the acute toxicity tests. The acute oral and intraperitoneal LD_{50} in mice were >4000 mg/kg and 600 mg/kg respectively. On continuous exposure however, there were small but statistically insignificant changes in serum liver and renal enzymes as well as serum electrolytes. Whether this will later translate into outright hepatic and renal damage with the chronic administration is very hard to tell. One important outcome of this study was the increase in PCV and decrease in LDL. No histological changes following a subchronic oral administration were seen in the kidneys unlike mild to moderate alterations that were observed in the liver and heart when the highest dose (1000 mg/kg) was administered (Figure 4).

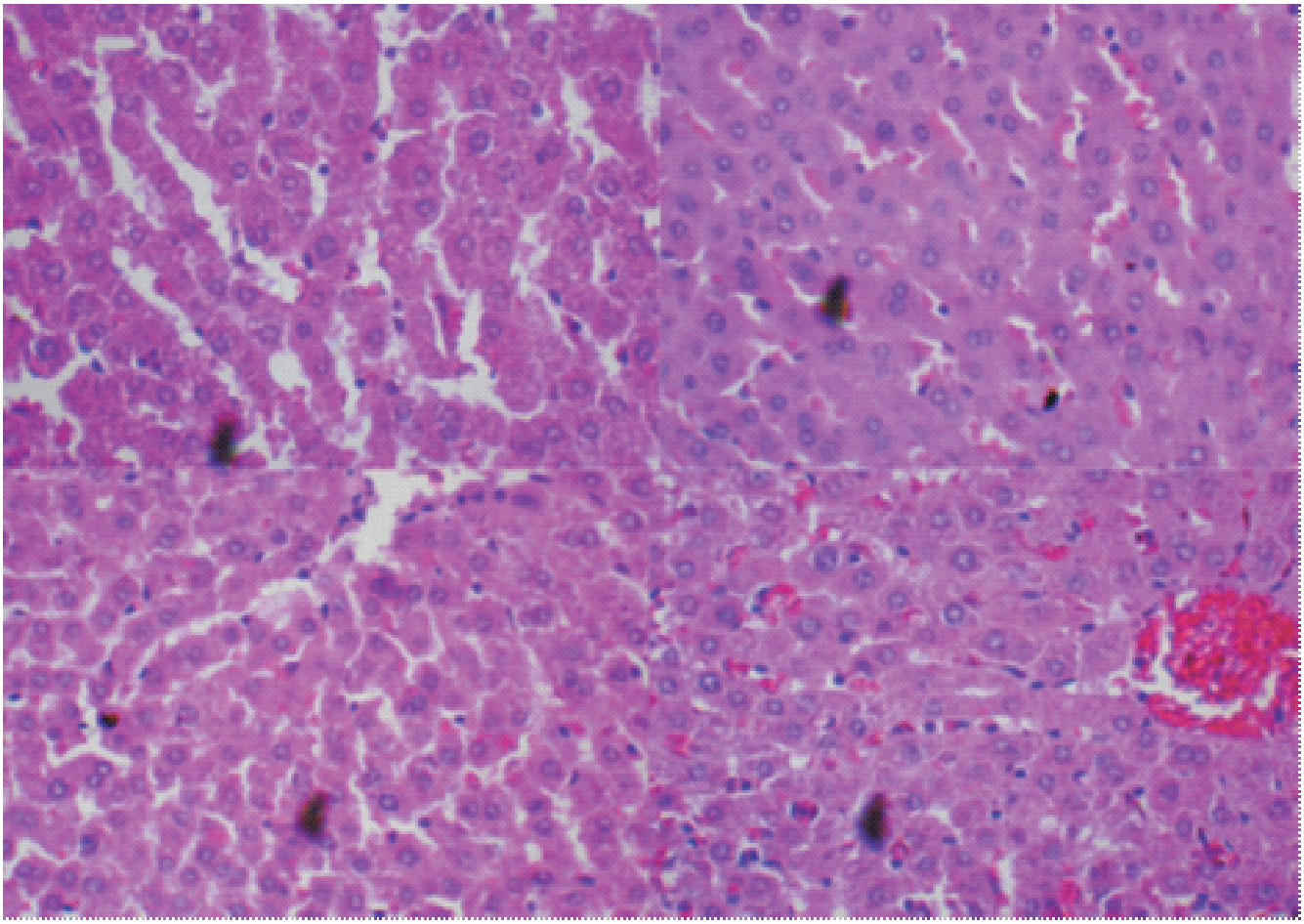

Figure 4: Histological presentation of the Liver following treatment with Bon-santé cleanser®. Control (Distilled Water, 10ml/kg) shows normal liver and BSC (1000mg/kg) shows congestion of the hepatic sinusoids and the central vein liver (see arrow); X400; Adapted from Kale and Awodele[88]

Pharmacovigilance of herbal medicines

Standards for herbal drugs are being developed worldwide but as yet there is no common consensus as to how these should be adopted.[89] This resulted to the establishment of the 'WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems. These guidelines provide practical technical guidance for monitoring the safety of herbal medicines within the pharmacovigilance systems. The safety monitoring of herbal medicines is compared and contrasted with that of other medicines currently undertaken in the context of the WHO International Drug Monitoring Program.[7] The guidelines were developed with the view that, within the current pharmacovigilance systems, monitoring of the safety of medicines should be improved and expanded in ways that will allow the successful monitoring of herbal medicines. Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects of drugs or any other possible drug related problems.[90]

We investigated the perceptions of traditional herbal sellers, natural health practitioners and pharmacists on the safety of herbal medicines and their opinion/observation on adverse effects of herbal medicines as related to feedbacks from the consumers/patients.[75]

Herbals are traditionally considered as harmless since they belong to natural sources,[91] most of the respondents in this study (339/378; 89.7%) were of the same opinion. They believe herbal medicines are safe because they are gotten from natural sources (Table 3) but other reports suggest that the fact that herbs are of natural origin does not automatically guaranty their safety.[92-94] The data on the adverse effects inventory suggest that the respondents opined that adverse effects rarely occur and have not had complains with the use of herbal medicines. This was contrary to earlier reports that showed that a number of herbs are likely to cause adverse effects.[95]

According to the WHO,[7] the following examples illustrate the ranges of problems encountered with the use of herbal medicines and products:

- Some herbal products were found to contain 0.1–0.3 mg of betamethasone per capsule after some patients developed corticosteroid-like side effects.
- Owing to misidentification of the medicinal plant species, plant materials containing aristolochic acid were used for manufacturing herbal products, which caused severe kidney failure in patients in several countries (i.e. intrinsically toxic constituents).
- Reports have been received by drug safety monitoring agencies of prolonged prothrombin times, increased coagulation time, subcutaneous haematomas and intracranial haemorrhage associated with the use of *Ginkgo biloba*

A small portion of the respondents (91/378; 24.1%) said patients/customers complain of some mild to moderate adverse effect. These adverse effects range from skin reactions to gastrointestinal pain. Major adverse effects reported were those related to the gastrointestinal tract, like nausea and vomiting (16%), diarrhoea (23%) and stomach pain (9%). The data obtained from this present study further revealed that respondents take varied actions in the event of an adverse reaction. 36.3% (33/91) will stop the use of the herbal products, while 27.5% (25/91) try to manage the adverse effect, some even send the users home. Only 20.9% (19/91) of the respondents treat and document the side effects reported by users but never forwarded these reports to the necessary regulatory body or pharmacovigilance centre. This indicates a lack of proper pharmacovigilance of herbal medicines among the studied population of practitioners. It also seems that the Pharmacists though have the knowledge of pharmacovigilance, however do not engage their pharmacovigilance obligations when it concerns herbal medicines. The outcome of this study suggests an urgent need to evaluate current pharmacovigilance systems and ensure the incorporation of herbal medicines especially with knowledge that herbal medicine adverse effects may sometimes be life-threatening or lethal to patients.[93,94] One major way to ascertain this incorporation is through the integration of both the traditional and orthodox medicine practices.

Table 3: Herbal preparations and their components

Name of herbal preparation	Components
'Agbo iba' (extemporaneous)	Dongoyaro' (*Azadirachta indica*) leaves, Bark of pineapple (*Ananas comosus*) fruit, paw paw (*Carica papaya*) leaves and seeds,lemon grass (*Cymbopogon citrates*) leaves, guava (*Psidium guajava*) leaves, scented - leaves (*Pelargonium zonale*), lime juice
'Agbo jedi - jedi'(extemporaneous)	Bitter leaf (*Vernonia amygdalina*)Scented-leaves (*Pelargonium zonale*), Sorghum (*Sorghum bicolour*) leaves, garlic (*Allium sativum*), grapefruit (*Citrus paradisi*) juice extracts, naphthalene tablets
Alomo bitter ®	African breadfruit (*Treculia africana*), stem bark of African mahogany (*Khaya ivorensis*)
Yoyo bitter®	*Aloe vera, Acinos arvensis,Citrus aurantifolia, Chenopodium murale, Cinamonum aromticum*
Dudu -Osun soap®	Palm kernel (*Elaeis guineensis*) oil

Swedish bitter®	Aloe (*cape aloe*), Myrrh (*commiphora molmol*), Saffron (*Crocus sativus*), Senna (*Cassia angustifolia*), Camphor (*Cinamomum camphora*), Rhubarb (*Rheum palmatum*), Zedoary (*Curcuma zedoria*), Bamboo (Bamboo manna), *Theriac venezian* , Carline Thistle (*Artemisia vulgaris*), and Angelica (*Angelic archangelica*).
Oroki herbal mixture®	Stem bark of African mahogany (*Khaya ivorensis*) tree, pattern wood (*Alstonia congensis*), mango (*Mangif era indica*) leaves, Sorghum (*Sorghum bicolour*)
Jobelyn® capsule	Sorghum (*Sorghum bicolour*) leaves
7 keys Herbal mixture®	*Allium sativum, Xylopia aromatica, Tetrapleura tetraptra, Ficus carica, Nauclea latifolia, Sterculia urena, Combretum miscranthum*
Herbal tooth paste	Aloe vera (*Aloe barbadensis*)
Honey	Natural honey

We obtained most of the materials used for this review from our personal research work.

CONCLUSION

The high demand for herbal medicines from traditional medical practitioners in Nigeria and elsewhere in the world is a clear indication of the attitude and beliefs of people about these medicines. This increase in popularity or interest in alternative/herbal medicine for the prevention and treatment of various illnesses has also brought some concerns and fears over the quality and safety of the 'natural' formulations available in the market. The positive benefits of traditional or herbal medicine cannot be brought to bear on the health situations of the people without adequate regulation, even with the most experienced experts and well-intended policy statements. This is particularly important given the fact that herbal medicines, which have the potential to affect human bodily functions, can impact positively or negatively on the health of people. Having the clear understanding that the safety of herbal medicine use is dependent on policy and regulation, the government, international organizations and stakeholders should step up efforts to harmonize all structures that will ensure effective implementation of policy and regulations to guarantee safe use of herbal medicines. In view of all the above, it is imperative for regulatory authorities to adopt and incorporate the concept of pharmacovigilance in the national laws and regulations of herbal medicines. This is particularly pertinent considering the fact that no medicine, herbal or orthodox, is completely devoid of adverse effects.

ACKNOWLEDGEMENT

All the students and laboratory technologists involved in the experimental procedures of the data published in this review paper are acknowledged.

REFERENCES

1. Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, and Kessler RC (1998). Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey.*JAMA280 (18): 1569-1575*
2. Hughes EF, Jacobs BP, Berman BM (2005) Complementary and Alternative Medicine: Current medical diagnosis and treatment. Edited by Tierney LM, McPhee SJ and Papadakis MA, pp. 1696-1719
3. Chizzola R, Michitsch H and Franz C (2003). Monitoring of metallic micronutrients and heavy metals in herbs, spices and medicinal plants from *Austria.Eur. Food Res. Technol.216(5): 407-411*
4. Ehrlich SD (2013) Herbal medicine(University of Maryland Medical Center). Available from: https://www.umm.edu/health/medical/altmed/treatment/herbal-medicine. [Accessed: 30-Nov-2017]
5. Farnsworth N, Akerele O, Bingel A, Soejarta D and Eno Z (1985). Medicinal plants in therapy.*Bulletin of the World Health Organization* 63: 965-81
6. WHO (1985). The WHO traditional medicine programme: policy and implementation.Int. *Tradit. Med. Newsl., 1: 1-5*
7. WHO (2004). WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems [Online]. Available: http://apps.who.int/medicinedocs/en/d/Js7148e/. [Accessed: 30-Nov-2017].
8. Hollman A (1985). Plants and cardiac glycosides.*Heart* 54 (3): 258-261
9. Arcamone F, Cassinelli G and Casazza AM (1980). New antitumor drugs from plants.*Journal of Ethnopharmacology* 2(2): 149-160
10. Elhardallo SB (2011). Cytotoxicity and Biological Activity of Selected Sudanese Medicinal Plants. *Research Journal of Medicinal Plants* 5: 201-229
11. Raskin I (1992). Role of Salicylic Acid in Plants.*Annual Review of Plant Biology*43 (1): 439-463
12. Rain Tree Nutrition (2001). Tropical plant database: Database for Quinine (Cinchona officinalis).
13. Covello PS. Making artemisinin. *Phytochemistry* 69 (17): 2881-2885
14. WHO (2005). National Policy on Traditional Medicine and Regulation of Herbal Medicines - Report of a *WHO Global Survey* [Online]. Available: http://apps.who.int/medicinedocs/en/d/Js7916e/. [Accessed: 30-Nov-2017].
15. WHO (2014). WHO Traditional, complementary and integrative medicine. Geneva
16. Amole AOO, Yemitan O and Oshikoya K (2009). Anticonvulsant activity of Rauvolfia Vomitoria (Afzel).*African Journal of Pharmacy and Pharmacology* 3(2): 319-322
17. Ilori M, Sheteolu AO, Omonigbehin EA and Adeneye AA (1996). Antidiarrhoeal activities of Ocimum gratissimum (Lamiaceae).J. *Diarrhoeal Diseases Research* 14(4): 283-285
18. Oyelami OA, Agbakwuru EA, Adeyemi LA and Adedeji GB (2005). The effectiveness of grapefruit (Citrus paradisi) seeds in treating urinary tract infections. *Journal of alternative and complementary medicine* (New York, NY) 11(2): 369-371
19. Okeniyi JOA, Ogunlesi TA, Oyelami OA and Adeyemi LA (2007)Effectiveness of dried Carica papaya seeds against human intestinal parasitosis: a pilot study. *Journal of Medicinal Food*10(1): pp. 194-196
20. Adegbehingbe OO, Adesanya SA, Idowu TO, Okimi, Oyelami OA and Iwalewa EO (2008). Clinical effects of Garcinia kola in knee osteoarthritis.Journal of *Orthopaedic Surgery*3: 34
21. Oyelami OA, Onayemi A, Oyedeji OA and Adeyemi LA (2009). Preliminary study of effectiveness of Aloe vera in scabies treatment. *Phytotherapy Research* 23(10): 1482-1484
22. Gadano AB, Gurni AA and Carballo MA (2006). Argentine folk medicine: genotoxic effects of Chenopodiaceae family. *Journal of Ethnopharmacology* 103(2): 246-251
23. Akintonwa A, Awodele O, Afolayan G and Coker HAB (2009). Mutagenic screening of some commonly used medicinal plants in Nigeria. *Journal of Ethnopharmacology* 125(3): 461-470
24. Awodele O, Osunkalu VO, Akinde OR, Teixeira da Silva JA, Okunowo WO, Odogwu EC, Akintonwa A (2010). Modulatory roles of antioxidants against the aqueous stem bark extract of Alstonia boonei (Apocynaceae)-induced nephrotoxicity and testicular damage. *International Journal of Biomedical and Pharmaceutical Sciences*4(2):76-80.25.
25. Jayasuriya DC (1990). A review of legislation concerning medicinal plants. Unpublished Report
26. Heide L (1991). Traditionelle Arzneipflanzen in der Gesundheitsversorgung der dritten Welt-Möglichkeiten und Grenzen Zeitschrift für *Phytotherapie* 12: 1-8

27. Niggemann B and Grüber C (2003). Side-effects of complementary and alternative medicine.*Allergy* 58(8): 707-716
28. Abt AB, Oh JY, Huntington RA and Burkhart KK (1995). Chinese herbal medicine induced acute renal failure.*Archives of Internal Medicine* 155(2): 211-212
29. Lee CT, Wu MS, Lu K and Hsu KT (1999). Renal tubular acidosis, hypokalemic paralysis, rhabdomyolysis and acute renal failure - A rare presentation of Chinese herbal nephropathy. *Ren. Fail.* 21(2): 227-230
30. Šubat-Dez?ulovi? M, Slavi? I, Roz?mani? V, Perši? M, Medjimurec B and Š?ukanec-Špoljar M (2002). Drug-induced acute tubulointerstitial nephritis: a case with elevated urinary cadmium. *Pediatric Nephrology* 17(5): 382-385
31. Luyckx VA, Ballantine R, Claeys M, Cuyckens F, Van den Heuvel H, Cimanga RK, Vlietinck AJ, De Broe ME, Katz IJ (2002). Herbal remedy-associated acute renal failure secondary to Cape aloes. *American journal of kidney diseases*39 (3): e13-1
32. Au TC (2006). Acute renal failure associated with prolonged intake of slimming pills containing anthraquinones. *Hong Kong Medical Journal* 12(5):394-7.
33. Lin CC and Chen JC (2002). Medicinal herb Erycibe henri Prain ('Ting Kung Teng') resulting in acute cholinergic syndrome. *Journal of Toxicology: Clinical Toxicology* 40(2): 185-187
34. Nadir A, Agrawal S, King PD and Marshall JB (1996). Acute hepatitis associated with the use of a Chinese herbal product, ma-huang.The American Journal of *Gastroenterology* 91(7): 1436-1438
35. Tyler VE and Foster S (1999).The honest herbal: a sensible guide to the use of herbs and related remedies. New York; London: Haworth Herbal Press
36. Borum ML (2001). Fulminant exacerbation of autoimmune hepatitis after the use of ma huang. *The American Journal of Gastroenterology* 96(5): 1654
37. Escher M, Desmeules J, Giostra E and Mentha G (2001). Hepatitis associated with Kava, a herbal remedy for anxiety. BMJ 322(7279): 139
38. Webb AN, Hardikar W, Cranswick NE and Somers GR (2005). Probable herbal medication induced fulminant hepatic failure.J. *Paediatr. Child Health* 41(9-10): 530-531
39. Hsu LM, Huang YS, Tsay SH, Chang FY and Lee SD (2006). Acute hepatitis induced by Chinese hepatoprotective herb, xiao-chai-hu-tang.*Journal of the Chinese Medical Association* 69(2): 86-88
40. Rowin J and Lewis SL (1996). Spontaneous bilateral subdural hematomas associated with chronic Ginkgo biloba ingestion. *Neurology* 46(6): 1775-1776
41. Granger AS (2001). Ginkgo biloba precipitating epileptic seizures. Age and Ageing 30(6): 523-525
42. Benjamin J, Muir T, Briggs K and Pentland B(2001). A case of cerebral haemorrhage-can Ginkgo biloba be implicated? *Postgraduate Medical Journal* 77(904): 112-113
43. Chan TYK (2002). Herbal medicine causing likely strychnine poisoning. *Human and Experimental Toxicology* 21(8): 467-468
44. Vahid B (2007). Severe complications of herbal medicines. *Critical care and shock* 10: 4-10
45. Bannerman RH, Burton J, Chen WC (1983). Traditional medicine and health care coverage: a reader for health administrators and practitioners.
46. Kassaye KD, Amberbir A, Getachew B and Mussema Y (2006). A historical overview of traditional medicine practices and policy in Ethiopia. *Ethiopian Journal of Health Development* 20(2): 127-134
47. Agbaje EO and Babatunde EO (2005). A KAP study of the attitude and practice of traditional medicine in a contemporary Nigerian community. *Central African Journal of Medicine* 51(5-6): 58-62
48. Awodele O, Agbaje EO, Ogunkeye FA, Kolapo AG and Awodele DF (2011). Towards integrating traditional medicine (TM) into National Health Care Scheme (NHCS): Assessment of TM practitioners' disposition in Lagos, Nigeria. *Journal of Herbal Medicine* 1(3): 90-94
49. Abel C and Busia K (2005). An exploratory ethnobotanical study of the practice of herbal medicine by the Akan peoples of Ghana.Alternative Medicine Review - *A Journal of Clinical Therapeutics* 10(2): 112-122
50. Tabi MM, Powell M and Hodnicki D (2006). Use of traditional healers and modern medicine in Ghana. *International Nursing Review* 53(1): 52-58
51. Amira OC and Okubadejo NU (2007). Frequency of complementary and alternative medicine utilization in hypertensive patients attending an

urban tertiary care centre in Nigeria. *BMC Complementary and Alternative Medicine* 7: 30
52. Osamor PE and Owumi BE (2010). Complementary and alternative medicine in the management of hypertension in an urban Nigerian community. *BMC Complementary and Alternative Medicine* 10: 36
53. Fakeye TO, Adisa R and Musa IE (2009). Attitude and use of herbal medicines among pregnant women in Nigeria. *BMC Complementary and Alternative Medicine* 9: 53
54. Awodele O, Agbaje EO, Abiola OO, Awodele DF and Dolapo DC (2012). Doctors' attitudes towards the use of herbal medicine in Lagos, Nigeria. *Journal of Herbal Medicine* 1(2): 16-22
55. Owen DK, Lewith G and Stephens CR (2001). Can doctors respond to patients' increasing interest in complementary and alternative medicine? *BMJ* 322(7279): 154-158
56. Zollman C and Vickers A (1999). Complementary medicine and the doctor. *BMJ* 319(7224): 1558-1561
57. Akinboro A and Bakare AA (2007). Cytotoxic and genotoxic effects of aqueous extracts of five medicinal plants on Allium cepa Linn. *Journal of Ethnopharmacology* 112(3): 470-475
58. Eilert U (1978). Antibiotic principles of seeds of Moringa oleifera. *West Indian Medical Journal* 38(235): 1013-1016
59. Eilert U, Wolters B and Nahrstedt A (1981). The antibiotic principle of seeds of Moringa oleifera and Moringa stenopetala. *Planta Medica* 42: 55-61
60. Ezeamuzie IC, Ambakederemo AW, Shode FO, Ekwebelem SC (1996). Antiinflammatory effects of Moringa oleifera root extract. International *Journal of Pharmacognosy* 34(3):207-12.
61. Ferreira R, Napoleão TH, Santos AF, Sá RA, Carneiro?da?Cunha MG, Morais MM, Silva?Lucca RA, Oliva ML, Coelho LC, Paiva PM (2011). Coagulant and antibacterial activities of the water?soluble seed lectin from Moringa oleifera. *Letters in applied microbiology* 53(2):186-92.
62. Sreelatha S, Jeyachitra A, Padma PR (2011). Antiproliferation and induction of apoptosis by Moringa oleifera leaf extract on human cancer cells. *Food and Chemical Toxicology* 49(6):1270-5..
63. Awodele O, Oreagba IA, Odoma S, da Silva JA, Osunkalu VO (2012). Toxicological evaluation of the aqueous leaf extract of Moringa oleifera Lam.(Moringaceae). *Journal of Ethnopharmacology* 139(2):330-6.
64. Cajuday LA and Pocsidio GL (2010). Effects of Moringa oleifera Lam.(Moringaceae) on the reproduction of male mice (Mus musculus). *Journal of Medicinal Plants Research* 4(12):1115-21
65. D'souza J and Kulkarni AR (1993). Comparative studies on nutritive values of tender foliage of seedlings and mature plants of Moringa oleifera Lam. *Journal of Economic and Taxonomic Botany* 17(2):479-85.
66. Anwar F and Bhanger MI (2003). Analytical characterization of Moringa oleifera seed oil grown in temperate regions of Pakistan. *Journal of Agricultural and Food Chemistry* 51(22): 6558-6563
67. Anwar F, Ashraf M and Bhanger MI (2005). Interprovenance variation in the composition of Moringa oleifera oilseeds from Pakistan. *Journal of the American Oil Chemists' Society* 82(1): 45-51
68. Siddhuraju P and Becker K (2003). Antioxidant properties of various solvent extracts of total phenolic constituents from three different agroclimatic origins of drumstick tree (Moringa oleifera Lam.) leaves. *Journal of Agricultural and Food Chemistry* 51(8): 2144-2155
69. Posmontier B (2011). The medicinal qualities of Moringa oleifera. *Holistic Nursing Practice* 25(2): 80-87
70. Ajasa AMO, Bello MO, Ibrahim AO, Ogunwande IA and Olawore NO (2004). Heavy trace metals and macronutrients status in herbal plants of Nigeria. *Food Chemistry* 85(1): 67-71
71. Ang HH and Lee KL (2006). Contamination of mercury in tongkat Ali hitam herbal preparations. *Food and chemical toxicology* 44(8): 1245-50.
72. Arzani A, Zeinali H and Razmjo K (2007). Iron and magnesium concentrations of mint accessions (Mentha spp.). *Plant Physiol. Biochem. PPB,* 45(5): 323-329
73. Mubeen H, Naeem I, Taskeen A and Saddiqe Z (2009). Investigations of heavy metals in commercial spices brands. New York Science Journal 2(5): 20-6.
74. Khan SA, Khan L, Hussain I, Marwat KB and Akhtar N (2008). Profile of heavy metals in selected medicinal plants. *Pakistan Journal of Weed Science Research* 14:101-110
75. Awodele O, Popoola TD, Amadi KC, Coker HAB and Akintonwa A (2013). Traditional medicinal plants

in Nigeria-Remedies or risks. *Journal of Ethnopharmacology* 150(2): 614-618

76. Moura AC, Silva EL, Fraga MC, Wanderley AG, Afiatpour P and Maia MB (2005). Anti-inflammatory and chronic toxicity study of the leaves of Ageratum conyzoides L. in rats. *Phytomedicine* 12(1-2):138-42.
77. Oluyemi KA, Okwuonu UC, Baxter DG and Oyesola T (2007). Toxic Effects of Methanolic Extract of Aspilia africana Leaf on the Estrous Cycle and Uterine Tissues of Wistar Rats. *International Journal of Morphology* 25(3): 609-614
78. Odugbemi T (2006).Outlines and pictures of medicinal plants from Nigeria [1st ed.]. Lagos: University of Lagos Press
79. Prasad MNV (2001). Bioremediation potential of amaranthaceae. In Phytoremediation, Wetlands, and Sediments. Leeson A, Foote EA, Banks MK and Magar VS (Eds.). ColumbuS: Proceedings of the Sixth International In Situ & On- Site Bioremediation Symposium, Battelle Press
80. Stables NLT (1997). Descriptive Flora of Puerto Rico and Adjacent Islands [Online]. Available: https://www.nhbs.com/descriptive-flora-of-puerto-rico-and-adjacent-islands-volume-5-book. [Accessed: 30-Nov-2017].
81. Adewole SO and Ojewole JAO (2008). Protective Effects of Annona muricata Linn. (Annonaceae) Leaf Aqueous Extract on Serum Lipid Profiles and Oxidative Stress in Hepatocytes of Streptozotocin-Treated Diabetic Rats.African *Journal of Traditional, Complementary and Alternative Medicines* 6(1): 30-41
82. Oberlies NH, Jones JL, Corbett TH, Fotopoulos SS and McLaughlin JL (1995). Tumor cell growth inhibition by several Annonaceous acetogenins in an in vitro disk diffusion assay. *Cancer Letters* 96(1): 55-62
83. Tormo JR, Royo I, Gallardo T, Zafra-Polo MC, Hernández P, Cortes D and Peláez F (2003). In vitro antitumor structure-activity relationships of threo/trans/threo mono-tetrahydrofuranic acetogenins: correlations with their inhibition of mitochondrial complex I. *Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics* 14(3): 147- 54
84. Vasquez MR (1990). Useful plants of Amazonian Peru, Second draft Filed with USDA's National Agricultural Library. FL, USA: CRC Press Inc.
85. Takahashi JA, Pereira CR, Pimenta LPS, Boaventura MAD and Silva LGFE (2006). Antibacterial activity of eight Brazilian annonaceae plants. *Natural Product Research* 20(1): 21-26
86. Baskar R, Rajeswari V and Kumar TS (2007). In vitro antioxidant studies in leaves of Annona species. *Indian Journal of Experimental Biology* 45(5): 480-485
87. Awodele O, Ishola IO, Ikumawoyi VO, Akindele AJ and Akintonwa A (2014). Toxicological evaluation of the lyophilized fruit juice extract of Annona muricata Linn.(Annonaceae) in rodents. *Journal of basic and clinical physiology and pharmacology* 25(4): 411-21
88. Kale OE and Awodele O (2016). Safety evaluation of Bon-santé cleanser® polyherbal in male Wistar rats. *BMC complementary and alternative medicine* 16(1): 188
89. Sahoo N, Manchikanti P and Dey S (2010). Herbal drugs: standards and regulation. *Fitoterapia* 81(6): 462-471
90. WHO (2002). The Importance of Pharmacovigilance - Safety Monitoring of Medicinal Products
91. Bigoniya P (2009). Pharmacovigilance of herbal medicines: current status and future strategies. *Pharmacological Reviews* 7: 77-88
92. De Smet PA (1995). Health risks of herbal remedies. *Drug Safety* 13(2): 81-93
93. Furnharm A (1996). Why do people choose and use complementary therapies?Ernst E (Eds.), Editorial Oxford: Butterworth-Heinemann.
94. De Smet PAGM (1997). Adverse effect of herbal remedies. *Adverse Drug Reaction Bulletin* 183(n95-8): 695
95. Talalay P and Talalay P (2001). The importance of using scientific principles in the development of medicinal agents from plants. *Academic Medicine* 76(3): 238-47