Chapter 5

Toxicity and Safety Implications of Herbal Medicines Used in Africa

Merlin L.K. Mensah, Gustav Komlaga, Arnold D. Forkuo, Caleb Firempong, Alexander K. Anning and Rita A. Dickson

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.72437

Abstract

The use of herbal medicines has seen a great upsurge globally. In developing countries, many patronize them largely due to cultural acceptability, availability and cost. In developed countries, they are used because they are natural and therefore assumed to be safer than allopathic medicines. In recent times, however, there has been a growing concern about their safety. This has created a situation of ambivalence in discussions regarding their use. Some medicinal plants are intrinsically toxic by virtue of their constituents and can cause adverse reactions if inappropriately used. Other factors such as herb-drug interactions, lack of adherence to good manufacturing practice (GMP), poor regulatory measures and adulteration may also lead to adverse events in their use. Many *in vivo* tests on aqueous extracts largely support the safety of herbal medicines, whereas most *in vitro* tests on isolated single cells mostly with extracts other than aqueous ones show contrary results and thus continue the debate on herbal medicine safety. It is expected that toxicity studies concerning herbal medicine should reflect their traditional use to allow for rational discussions regarding their safety for their beneficial use. While various attempts continue to establish the safety of various herbal medicines in man, their cautious and responsible use is required.

Keywords: traditional medicine, herbal medicine, medicinal plants, toxicity, safety

1. Introduction

This chapter is primarily to appraise the pertinent determinants of the safety of medicinal plants or herbal medicines used in African traditional medicine and the implications of their toxicity. In view of the current global upsurge in their usage, it has become necessary to

review issues related to herbal medicines toxicity within appropriate contexts to allow for their beneficial use. In this regard, the safety implications of medicinal plants used in traditional medicine and or in diets are discussed and some literature on animal toxicity, acute and chronic toxicities, and cytotoxicity of some African medicinal plants are reviewed.

Plants have been used since time immemorial for diverse purposes in the life of mankind particularly as food, and medicines for nutrition and the treatment of diseases, respectively, in both humans and animals. They are used in all cultures of the world and have been relied upon for several millennia to support, promote and restore human health. They form a vital component of traditional medicine (TM) and their use for the maintenance of health and well-being is a common practice in all African societies. They are used as remedies for the prevention and treatment or management of a plethora of disease conditions including relatively new ones such as HIV/AIDS [1].

Traditional medicine used to be the only health-care system available to the whole of the African population prior to the introduction of allopathic or conventional medicine [2]. The practice received international recognition after the 1978 Alma Ata Conference Declaration, which aimed to achieve primary health care for all by the year 2000 through the use of traditional medicine [3]. TM, especially herbal medicine, still forms the backbone of rural health care in Africa, supporting an estimated 80–90% of the population.

2. Justification for the use of herbal medicines

There exist diverse reasons for the continuing use of herbal medicines for health care in Africa; these include cultural acceptability, easy accessibility and affordability, and in some instances, non-availability and prohibitive cost of allopathic medicines [4]. Some people also employ herbal medicines under other circumstances, for example, in health conditions that had failed to respond to orthodox treatment or which allopathic medicines are deemed not to treat adequately and less safely [5]. Other health conditions believed to have spiritual origins [2] and those thought to need holistic therapies are also managed with herbal medicines.

3. Evolution of herbal medicine in traditional medicine

The practice of herbal medicine is embedded in traditional medicine which origins may be implied in varied anecdotes. It is claimed that its beginnings in humans were instinctive, as seems to be the case in animals. As humans were afflicted by various illnesses over time, they learned to pursue remedies from various formulations from plant and animal parts, and mineral substances. Over time, the therapeutic properties of medicinal plants for the treatment of certain diseases have been validated through scientific experiments; thus, medicinal plants usage gradually abandoned the anecdotal framework and became founded on empirical and explicatory facts [6].

Other diverse claims have been made in relation to the origin of herbal medicines used in traditional medicine in Africa. Some claimed the medicines originated from the deities

or superior beings as a gift to man through the medium of dwarfs or spirit beings who 'abducted' some individuals and took them away from human habitation into the spirit world either in the forest or in the water bodies. Such persons returned to human habitation trained and equipped to fight the diseases that threaten the well-being of not only individual sufferers but also the entire family or community. Some other knowledge of medicines is claimed to have come by revelation through dreams, visions and extrasensory perception. The above postulates on the origin of herbal medicines formed the basis of a sophisticated traditional medical system in Africa, a time-tested system where information on medicinal plants use was methodically collected over several years, and which provides remedies for most diseases today in Africa. The African Traditional Medicine practitioners' own experience, added to the accumulated knowledge passed on, usually orally, through generations, allow them to offer effective remedies for treating ailments that afflict the community [5].

Lately, the knowledge and use of traditional medicine have also been acquired through apprenticeship by individuals understudying a recognized practitioner over defined periods of time. More recently, with increased access to information, some practitioners, especially those outside the indigenous cultures, acquire the knowledge about medicinal plants and their uses from Internet sources including online scientific journals and books including e-books. Another avenue of knowledge acquisition has been through formal education and training in exclusively scientific settings as at colleges or universities where degrees or diplomas are awarded on graduation.

4. Attitudes toward traditional medicine

Ever since the dawn of the scientific era, prejudice against traditional medicine has been noted [7]. This has resulted in a situation described as 'passionate ambivalence' toward TM, fuelled by the influence of Western religion and education, urbanization and globalization phenomena in Africa [2]. The result has been continued as negative pronouncements from some segments of western-educated African elites concerning the use of TM especially concerning the quality, efficacy and safety of African medicinal products, creating doubts about the benefits of the medicines. This is in spite of the fact that TM still plays an important role in health-care delivery in Africa and had rarely witnessed major reported cases of adverse effects even after hundreds of years of practice [2].

Besides, some persons with little or no knowledge of herbal medicines tend to focus on reported toxicities and criticize the practice often out of context. Moreover, mass media reports of adverse events tend to be sensationalized and give a negative impression about the outcomes from the use of herbal medicines, instead of identifying the causes of these events, which may relate to a variety of issues [8]. Several scientific studies conducted on the biochemical properties of medicinal plants used in traditional medicines to treat various illnesses have confirmed their efficacy and safety especially in animals. As seen in several publications, the efficacy [9] and sometimes the safety of some medicinal plants and herbal medicines have been validated through research [10–12].

5. Toxicity of chemicals

Toxicity refers to the relative ability of a substance to cause adverse effects in living organisms [13]. It may also be defined as the extent to which an exposed tissue is damaged by a chemical substance and covers the effect on a whole organism and sub-structural component of an organism such as the cell (cytotoxicity) or organ (organotoxicity). Toxicity may further be defined to cover the study of the adverse effects of chemicals on living organisms as well as their symptoms, mechanisms and treatments. Toxicity studies may be classified as acute, subacute/subchronic and chronic effects depending upon the quantity and duration of administration of the agents [14].

5.1. Acute toxicity

Acute toxicological studies investigate the toxic effects produced by a single large-dose exposure to a toxicant lasting no longer than 24 h. This may result in severe biological effects (harm or death) to the organism. The results of acute toxicity are not only important in the consideration of accidental poisoning with a chemical but also are used for the planning of chronic toxicological studies [15]. The development of tolerance is usually revealed by an acute exposure. The starting point for toxicological classification of chemicals uses the LD_{50} value, which is the dose administered in acute toxicity testing that causes death in 50% of experimental animals [16].

5.2. *Chronic* toxicity

Chronic exposure refers to the administration of a toxin over an extended period of time, usually measured in months or years; this can cause irreversible toxicity. Periods between acute and chronic exposure could be referred to as subacute or subchronic. The results of chronic and acute toxicological studies help in the evaluation of any possible hazardous effect of a new drug or a drug which is in use with little or no documentation of its systemic toxicity.

6. Toxicity of medicinal plants

Generally, medicinal plants contain bioactive compounds which demonstrate both intra- and inter-species variation in type and content. Plants by virtue of their chemical constituents are potentially toxic; thus, some plants used in traditional medicine are intrinsically toxic. Some plants well known in traditional medicine to be toxic or poisonous include *Atropa belladonna*, *Datura* spp., *Digitalis* spp. [17].

Many plants used in traditional medicine or used as food have demonstrated some toxicity (mutagenic and carcinogenic) effects [18]. The issue of the possible toxic, genotoxic and/or mutagenic effects of plants used in traditional medicine has been highlighted in the review by Fennell et al. [19]. However, some of the toxic plants are useful to man as medicines and also as poisons for hunting and for use as pesticides, for example, Datura (tropane alkaloids), Digitalis (cardiac glycosides) and Pyrethrum (pyrethrin insecticides). Well-known medicinal plants have demonstrated toxicity in laboratory studies and field observations. For example, *Lantana camara* used in the management of malaria and other diseases has been reported to be hepatotoxic in several animal species which could be of concern regarding its chronic use in man [20].

Similarly, *Momordica charantia*, a known anti-diabetic and antimalarial plant but also used in Ghana as an abortifacient [21, 22], has reportedly caused deadly hypoglycemia in children [23].

7. Medicinal plant use in therapy

The basis for the medicinal use of the plants is the presence of mixtures of different biologically active plant constituents or phytochemicals (secondary metabolites) such as alkaloids, glycosides, terpenoids, and so on that may act individually, additively or in synergy to demonstrate an effect which may be useful or harmful to health. Some of these plants have been designated as poisonous plants because of their effects in impacting biological functions in other organisms which are harmful [24]. They are therefore damaging to either the survival or the normal function of the individual. The dose received may be due to either acute (short) or chronic (long-term) exposure. However, in TM, plants with toxic constituents are known and are avoided or used cautiously in herbal product formulations. Even if these are employed in medicinal products, they are employed below toxic levels and hence, if at all, hardly result in any fatality when administered by professional practitioners or experienced persons.

8. Safety of medicinal plants and herbal medicines used in traditional medicine

Generally, plants used in traditional medicines have been considered safe as a result of the long history of use in the treatment of diseases based on knowledge accumulated over several centuries. In many cultural settings, toxic fatalities have been rare due to systematic selection of medicinal plants for use. While thousands of people die each year from even supposedly 'safe' over-the-counter remedies, deaths or hospitalizations due to herbs are so rare that they are hard to find; not even the United States National Poison Control Centers have a category in their database for adverse reactions to herbs [17].

When used appropriately as dietary supplements, food supplements or medicines, traditional medicines are generally regarded as safe. However, there are instances where adverse events ascribed to herbal medicines used have been reported in both humans and animals. For example, Barbosa et al. [25] reported clinical and pathological neurological disorders in horses following a large intake of fresh *Bambusa vulgaris* leaves. Paradoxically, the aqueous decoction is a popular antimalarial medicine in Ghana [11, 21] and this has been used without any report of adverse reaction. Besides, the aqueous extract of the leaves did not cause cytotoxicity in normal human cells [11, 21]. In these situations, the dose of the constituents administered is of great importance; as stated by Paracelsus that, 'All substances are poisons; there is none, which is not a poison. The right dose differentiates a poison and a remedy' [26]. This is to say that the toxicity of any substance, including medicinal plants and even food, is largely dependent on the amount or dose used. A non-toxic substance can be toxic at a high dose, and a very toxic substance can be considered safe if the dose is low [27]. Over-dosage in the course of treatment is bound to pose safety problems. The dose-toxicity relationship was illustrated by the toxicity of *Bupleuri chinense* in which the toxic dose was about 21 times than the common clinical dose of 9 g/60 kg [28].

Apart from an overdose, adverse events may also arise from the misidentification of medicinal plants, errors in the use of herbal medicines both by health-care providers and by consumers, and misuse and use over long periods even at tolerable dose [8, 29].

Interactions between herbs (herbal medicines) and drugs (allopathic medicines) may increase or decrease the pharmacological or toxicological effects of either component. Thus, synergistic therapeutic effects may complicate the administration of medications for chronic diseases, for example, herbs traditionally used to treat diabetes could theoretically lead to hypoglycemia if taken concomitantly with conventional antihyperglycaemic drugs [30].

In the formal herbal industry, the toxicity problems of medicinal plants could be attributable to insufficient quality assurance and non-compliance with the standards of good manufacturing practice [8, 31], and also inadequate access to the information required for the effective use of herbal medicines and inappropriate approaches to their use. Furthermore, the problem could be complicated by adulteration of herbal remedies by the addition of synthetic drugs and other potentially toxic compounds such as other botanicals, pathogenic microorganisms, toxins, pesticides and fumigants agrochemical residues or heavy metals [8, 29, 32]. The majority of adverse events related to the use of herbal products are attributable to weak quality control systems leading either to poor product quality [8]. According to WHO [8], poor regulatory measures and largely uncontrolled distribution channels could partly account for such events. These give rise to poor quality products arising from such situations as adulteration of herbal products with other undeclared medicines and potent pharmaceutical substances, such as corticosteroids and non-steroidal anti-inflammatory agents [8].

Usually, it is difficult to identify genuine adverse reactions to herbal medicines and herbal products until the cause of such events has been established. When appropriately employed, herbal medicines are relatively safe. Long historical including experience passed on from generation to generation has demonstrated their safety and efficacy [33].

It is worth noting that toxicity results of many medicinal plants are very often misinterpreted and wrong conclusions drawn with regard to traditional practices. Many toxicity studies were conducted on medicinal plants extracted in organic solvents such as methanol, dichloromethane, and so on other than aqueous extracts as used in traditional medicine practice. This was the case as reported in the degree of hepatotoxicity damage caused by the alcohol extracted *B. chinense* which proved more serious than that caused by the water extract [28].

9. Challenges of contemporary herbal medicine practice in Africa

Traditional medicines are increasingly being used outside the confines of traditional cultures and far beyond geographical areas without proper knowledge of their use and the underlying principles [8]. They are therefore practiced in ways that deviate from the traditional norm of practice within the specific traditional setting. Such deviations include the method of extraction—where highly efficient and sophisticated technological tools are frequently used for extracting medicinal plants and then reformulating the extract into a final product. Such an approach is entirely different from the hitherto traditional approaches of macerating

the plant materials either dried or fresh often in boiling water to produce decoctions, which are then administered. This traditional approach therefore tends to make the herbal medicine safe since potentially toxic compounds are not extracted due to the inherent inefficiency in the aqueous extraction method (preparation of the decoction). Also, doses employed in contemporary practice often tend to be different from the traditional doses, which were systematically established over several years of practice and proven to be safe. Besides, herbal medicines are used for non-traditional indications in recent years. A typical example is the use of herbal medicines for relieving constipation but abused as an abortifacient by the youth due to its induced contractive effect on smooth muscles such as the endometrial muscles. The concomitant use of traditional medicines with other types of medicines is quite outside the traditional context and has become a matter of particular safety concern [8].

Another challenge posed to the practice is the lack of appropriate foundational knowledge in traditional medicine practice and the herbal medicines used to treat diseases. This is a common occurrence among many contemporary practitioners, especially those in urban and cosmopolitan areas. The work of such practitioners is based on information gathered from indirect sources such as the Internet or from reading books and therefore lacking in specific knowledge. These 'neo-herbalists' most often lack the expertise and basic principles necessary for the use of herbal medicines. Their practice may therefore not be entirely safe and can put patrons at risk of adverse reactions.

Besides, documented knowledge about medicinal plants and their uses within cultural settings rarely contains information on potential toxicity of the plants. This is because many ethnopharmacologists tend to focus more on the therapeutic property of the plants and hence do not inventory their toxicological information. This failure to document and contextualize potential toxicity of plants in the perspective of local healing traditions and healing practitioners' methods and approaches to treatment does not promote the safe use of medicinal plants outside the boundaries of the cultures where the medicinal plants are used.

10. Cytotoxicity of African medicinal plants

Cytotoxicity refers to the ability of a substance to interfere with cell attachment, alter its growth, proliferation and or cause death [34]. Accurate determination of cytotoxicity is necessary to identify compounds or effective parts that might pose health risks to humans. Surprisingly, most cytotoxic assays are geared toward screening only bioactive compounds that can kill rapidly dividing cancer cells. Cytotoxic substances may destroy living cells via either necrosis/lysis (i.e. accidental cell death) or apoptosis (i.e. programmed cell death) [35]. In cancer drug discovery, for example, potential cytotoxic agents induce apoptosis instead of necrosis with very low or no toxicity toward normal cells. Only few case studies have investigated normal cells to determine the cytotoxicity of especially African medicinal plants.

Toxicity studies on most medicinal plants using animal models have provided results that strengthen their use among humans; however, many such plants could be associated with some cytotoxicity (**Table 1**). As a consequence, researchers have supported the use of human cell lines for *in vitro* cytotoxicity assays in predicting human acute toxicity as alternatives

Species	Normal cell type	Popular medicinal use	Plant part	References
Low cytotoxicity (>50 μg/ml)				
Afrostyrax lepidophyllus	MRC-5 cells	Anthelmintic, vomiting, urinary infections	Stem bark	[41]
Drypetes gossweileri	MRC-5 cells	Anthelmintic, purgative, tonic, bronchitis, cough, pains, relieve urethral discharge, diarrhea	Stem bark	[41]
Napoleona vogelii	MRC-5 cells	Dermatosis, sexual asthenia, stomach aches, diarrhea	Stem bark	[41]
Tectona grandis	HUVECs	Bronchitis, hyperacidity, dysentery, verminosis, diabetes, leprosy, inflammation, skin diseases, pruritus, stomatitis, ulcers, hemorrhages, constipation, piles, leucoderma, headache, biliousness, anuria, urethral discharges, body swellings, menstrual disorders	Leaf	[11]
Moderate cytotoxicity (30–50 μg/ml)				
Cryptolepis sanguinolenta	V79 cells	Fever, hepatitis, malaria, hypertension, urinary and upper respiratory tract infections, colic, stomach complaints, amoebic dysentery, diarrhea, wounds, measles, hernia, snakebites, rheumatism, insomnia, antiplasmodial activity, anticancer, antifungal, antibacterial, hypotensive, antipyretic, anti-inflammation, antihyperglycemia	Root	[42]
Isolona hexaloba (Rb)	MRC-5 cells	Pains, sexual weakness, headache, intestinal cramps, malaria, rheumatism	Root back	[41]
Mammea africana (Sb)	MRC-5 cells	Wounds, filariasis, mycosis, skin diseases	Stem back	[41]
Phyllanthus fraternus	HUVECs	Malaria, chronic pyrexia, chills, intermittent fever, painful joints, diarrhea, ulcer, dysmenorrhea and edema	Whole plant	[11]
Psidium guajava	MRC-5 cells	Antispasmodic, astringent, febrifuge, vulnerary, astringent, dysentery, diarrhea, constipation, diabetes, hepatitis, gonorrhea, diarrhea.	Leaf	[41]
High cytotoxicity (10–30 μg/ml)				
Terminalia ivorensis	HUVECs	Wounds, hemorrhoids, infections, gonorrhea, kidney disease, aphrodisiac	Leaf	[11]
Tetrapleura tetraptera	MRC-5 cells	Enema, malaria, fungal infections, arthritis, filariasis, gastritis, epilepsy	Fruit	[41]
Harungana madagascariensis	MRC-5 cells	Anemia, venereal diseases, nephrosis, gastrointestinal disorders, malaria.	Stem bark	[41]
Very high cytotoxicity (<5 μg/ml)				
Enantia chlorantha	MRC-5 cells	Intestinal worms, spasms malaria, sexual asthenia.	stem bark	[41]
Piptadeniastrum africanum	MRC-5 cells	Sexual asthenia, Constipation, intestinal cramps, pain.	stem bark	[41]

Species	Normal cell type	Popular medicinal use	Plant part	References
Quassia africana	MRC-5 cells	Malaria, blenorragia, hypertension, scabies, gastrointestinal affections, hernia, febrifuge, anti-rheumatic, anthelmintic, antalgic, tonic, stomach pains, gastric hemorrhoids, diarrhea, antiwounds	root bark	[41]

Table 1. Cytotoxic activities of aqueous extracts of African medicinal plants.

to acute lethality studies in rodents [36]. The selectivity exhibited by cytotoxic plants also underscores the need to distinguish highly active but toxic extracts from those that are selectively active against certain pathogens, diseased conditions and even cancerous cells. This provides good leads for continuous research on promising extracts, the sources of interesting biologically active and therapeutically useful compounds with excellent activity and low toxicity [37]. Toxicity testing at the cellular level is therefore very useful and recommended for all bioactive medicinal plants. Clearly, information on cytotoxicity of plants commonly used in traditional medicine in Africa is essential for assessing the quality, efficacy and safety of their preparations. Such knowledge is also critical in developing new therapeutic products to ensure the safety of end users of herbal medicine.

In spite of the assumed safety of African medicinal plants, studies have shown that many plants used as food or traditional medicines are also potentially cytotoxic, mutagenic and carcinogenic [38–40]. A comprehensive survey by [37], for instance, recorded 400 plants of African origin with cytotoxic effects. These plant species, according to the study, are used to treat diseases of considerable economic burden to the African continent, of which malaria, leishmaniasis and sleeping sickness received much attention. The study, however, identified approximately 14 or 56% of the listed plant species as having significant cytotoxic activities (IC_{50} < 30 μg/ml) against some normal cells such as human normal lung fibroblast (MRC-5), human kidney epithelial and human monocytes. While the list compiled by McGaw et al. [37] comprised many species with high efficacy against cancerous cells or pathogens, it indicated that at least 14% of these African medicinal plants may be harmful to humans.

Although the above observation calls for great care in plant use and close monitoring of their potential side effects, there are also clear reasons why cytotoxicity results could not always be wholly extrapolated into safety prediction in TM: except when organotypic cultures are used [37].

11. Drawbacks of using cytotoxicity to predict safety of herbal medicines in TM

There are some shortcomings to extrapolating cytotoxicity studies to the safety of herbal medicine used in traditional medicine. Among this is the fact that tissue responses due to *in vivo* toxicity cannot be addressed by toxic responses in cells [37]. According to McGraw et al. [37], a critical factor in toxicology is metabolism *in vivo*, as some substances lacking toxicity initially may produce toxic metabolites after being exposed to liver enzymes, while other

substances that are toxic in vitro may become detoxified. Other factors such as the capacity of the substance to penetrate the tissue, and clearance and excretion of the product cannot be accounted for using the cellular model. The time of exposure and the rate of change for these extracts are not the same in both *in vitro* and *in vivo* studies. Notwithstanding these limitations of cytotoxicity assay, it still needs to be an integral part of evaluating the safety of medicinal plants because they provide direct information at the cellular level which may be important in assessing the true toxicity of such plants.

Other limitations in cytotoxicity studies with regard to safety prediction for herbal medicines is the use of organic solvent such as methanol, dichloromethane, petroleum ether, ethyl acetate, and so on extracts as against water decoctions/extracts. In situations like this, it is not reasonable to compare the cytotoxicity results of the organic solvent extract with what pertains in TM. Such studies are common because the focus of most cytotoxicity studies has not been the safety assessment of the plants as used in TM but to determine the fractions which contain the potentially safe and efficacious compounds. In some cases, while efficacy study was conducted for both organic solvent and aqueous extracts, cytotoxicity was determined for only the organic solvents. This makes it difficult to relate the toxicity of the plant to safety in traditional use. In most cases, the organic extracts tend to be more efficacious than the aqueous extracts. This could imply that the organic extracts are more cytotoxic than the aqueous extracts since, generally, they (organic extracts) tend to extract more active compounds, which are both efficacious and cytotoxic.

12. Some herbal medicine products clinically evaluated for safety

There have been few reports of the clinical safety of herbal product used in TM. A coded herbal medicine made of *Saraca indica,* Foeniculum vulgare, Juniperus communis, *Mentha piperita* and Zingiber officinale used to treat dysmenorrhea was found to be safe from such toxic effects as hepatotoxicity, nephrotoxicity and other side effects such as menorrhagia, gastro-intestinal disturbance and palpitation in a random-controlled clinical trial [43]. Also an unnamed herbal product made of Capparis spinosa root, Cichorium intybus seed, whole plant of Solanum nigrum, *Terminalia arjuna* bark, Cassia occidentalis seed, aerial part of *Achillea millefolium* and whole plant of Tamarix gallica and used for the management of liver disorders evaluated clinically was well tolerated and did not produce any adverse event in participants [44]. Tetteh et al. [12] reported that a Ghanaian polyherbal medicine, Adutwumwaa malamix, used in the treatment of malaria did not show any hepatotoxic or hematotoxic effects nor any adverse complaint in the populations studied for its clinical effectiveness and safety. Turkson et al. also reported the safety of another Ghanaian herbal medicine for the treatment of malaria and indicated that kidney and liver function tests and full blood count were within normal range at the end of the study, an indication that the product is clinically safe [45]. The tea bag formulation of the root powder of C. sanguinolenta has effectively treated acute uncomplicated malaria on relatively short treatment regimens and did not show any toxicity in man [46]. This was against the fact that the aqueous extract of the root is genotoxic in the Chinese hamster lung fibroblast (V79) cell line [42, 47] and the ethanolic extract of the stem increased platelet counts in albino rats [48].

http://dx.doi.org/10.5772/intechopen.72437

13. Toxicity studies on some African medicinal plants

13.1. *Cryptolepis sanguinolenta* (Lindl.) Schltr

C. sanguinolenta (Apocynaceae) is a West African climbing shrub. The aqueous extract of the root has been used for centuries in African traditional medicine for the treatment of diseases including malaria, bacterial infections, hepatitis and rheumatism. It is also used as a spasmolytic and tonic [49]. In Ghana, several cryptolepis-based products are prescribed in herbal medicine clinics, sold in pharmacies, licensed chemical and herbal medicine shops for the treatment of malaria [21].

13.1.1. Animal and cell toxicity

Acute and sub-acute oral toxicity evaluation of the aqueous extract of the root suggested general safety at oral dosages below 500 mg/kg in Sprague Dawley rats. The extract did not exhibit either physiological or behavioral abnormality [50]. However, the ethanolic extract of the stem demonstrated localized systemic acute and sub-chronic toxicity by selectively stimulating the bone marrow leading to an increase in platelet counts in albino rats [48]. On the other hand, the aqueous extract of the root demonstrated genotoxicity against the Chinese hamster lung fibroblast (V79) cell line inducing mutagenicity at high concentrations and causing DNA damage [42, 47]. The ethanolic extract of the stem thus poses hematological challenges to white blood cells and platelets and showed localized systemic toxicity by selectively stimulating the bone marrow.

13.2. *Artemisia afra* (Jacq. Ex. Willd), 'African wormwood'

A. afra has been used for coughs, colic, fever, loss of appetite, earache, headache, malaria and intestinal worms [51]. Several studies have been conducted to substantiate the traditional use of this herb; it is also being investigated in diseases like diabetes, cancer and respiratory diseases among others [51].

In acute toxicity studies of aqueous extract of *A. afra* in mice administered doses (i.p., 1.5–5.5 g/kg) caused a regular dose-dependent increase in the death rate and also of general adverse behavior, but with single doses (2–24 g/kg) administered orally, the previous observed increases in the incidence of death rate and adverse general behavior that did not show were dose-independent. The route of administration, acute intraperitoneal and oral doses, showed LD_{50} of 2.45 and 8.96 g/kg, respectively [51].

13.2.1. Animal toxicity

In the chronic studies, rats administered *A. afra* aqueous extract (0.1 or 1 g/kg/day) survived the 3 months of daily dosing with LD_{50} greater than 1 g/kg. No significant changes were observed in the general behavior, hematological and biochemical parameters except for a transient decrease in aspartate aminotransaminase (AST) activity. No significant changes were observed in the organ weights and histopathological results showed no morphological alterations. High doses of the extract were also shown to be hepatoprotective. The aqueous extract of *A. afra* has been shown to be nontoxic in acute use and low chronic toxicity potential in rodent models [51].

13.3. *C. occidentalis* L

C. occidentalis is an annual shrub found in many African and Asian countries. Its leaves and roots are used in some traditional herbal medicines, but its pods or beans are avoided or used sparingly [52]. In Ghana, however, the roasted seeds are used as a beverage in the treatment of hypertension [53]. Many popular herbal tonics and medicines for liver disorders contain the leaves or roots of the plant. *C. occidentalis* has also been used in the treatment of scabies, snake and scorpion bites, diabetes, edema, fever, inflammation, rheumatism and ringworm. It is widely used for the treatment of bacterial and fungal infections and to boost the immune system.

13.3.1. Animal toxicity

The fresh or dried/roasted seeds have demonstrated toxicity in several animal studies [54]. Toxicity in animals is usually seen on the kidney, liver, skeletal muscle and the heart. Grazing animals such as cattle, sheep, horses and goats have shown toxicity upon the ingestion of large amount of the seed pods, the most poisonous even though all parts of the plants have shown some level of toxicity [55, 56].

Although the toxicity of the plant has been demonstrated in different animal species, the toxicity of the pod and bean is dose-dependent: low doses result in mild liver damage and myodegeneration while higher doses cause fatal hepatic degeneration followed by myodegeneration [56]. As the amount of *Cassia* in the animal's diet increases, muscle degeneration becomes a predominant characteristic of the poisoning and cause of the clinical signs. Roasting the seeds from the pod has, however, been shown to reduce the toxicity. Studies in rats [57] and chicken [58] fed a ration with *C. occidentalis* seeds at different concentrations showed histopathological and biochemical changes in muscles, liver and central nervous system. Barbosa-Ferreira et al. [57] in a study involved Wistar rats in four groups of 10 animals each, three of them fed rations containing 1, 2 and 4%, respectively, of *C. occidentalis* seeds, and the control fed normal commercial ration for a period of 2 weeks; rats in the experimental groups showed lethargy, weakness, among other adverse reactions. Histopathological study showed fiber degenerations in the skeletal and cardiac muscles. In the liver parenchyma, vacuolar degeneration was observed and, in the kidney, mild necrosis in the proximal convoluted tubules. All the adverse effects occurred in a dose-dependent manner [57].

Haraguchi et al. [58] studied the chronic effect of varying concentrations of *C. occidentalis* seeds in broiler chicks. All birds were killed on day 49 of age. Low doses of seeds showed no significant variation in biochemical parameters compared to the control group. Degenerative changes in striated skeletal muscles particularly pectoral as well as the liver and myocardium were observed in chicks treated with 0.3 and 0.5% of *Cassia* beans.

13.3.2. Human toxicity

Studies have shown that the ingestion of *C. occidentalis* can cause severe purging possibly due to the anthracene glycoside content [59]. Whereas this may produce great discomfort and pain in adults, in a child, this can be fatal; thus, while few pods might not have any ill effect

in an adult or an older child when eaten, it could cause death in a young child [60]. Other *Cassia* species products such as senna extract (*C. acutifolia*) consumed as health drink resulted in severe hepatotoxicity in an adult [61]. *C. senna* leaves and pods have been used in orthodox medicine and still form part of traditional pharmacopeia [53].

The clinical spectrum of *C. occidentalis* poisoning in children resembles the toxicity observed in animals. Most cases in children occur when they eat the beans. As with animals, the clinical toxic features depend upon the amount of beans eaten. While the consumption of two to three pods by a young child may not have any deleterious impact, a large quantity can lead to serious morbidity and even death [62, 63].

Since some children eat very few beans and remain asymptomatic, people tend to consider the beans as non-toxic. With a larger 'dose', such as the beans in six to seven pods, they develop a non-fatal illness with vomiting, diarrhea, malaise, giddiness, drowsiness, change in voice and general weakness among other effects. However, recovery occurs after about 3–4 days of illness. The fatal hepatomyoencephalopathy syndrome may occur with relatively larger amount of beans—such as the cupped hand of a child [63].

13.4. *Calotropis procera* (Aiton)

The plant is widely distributed in Asia, tropical and subtropical Africa [64]. In ancient Egypt, it was recommended for the treatment of nodular leprosy [64]. In Indian traditional medicine, the decoction is used for the treatment of asthma, dysentery, rheumatism, fever, painful muscular spasm and as a purgative and expectorant [65], and as a proteolytic enzyme for the coagulation of cow milk in Ghana [66]. The extract from the plant has been reported to possess antibacterial, nematocidal and larvicidal [67] and anticancer [68] properties. The flower of the plant has been shown to possess potent antimicrobial and anti-inflammatory activities [69].

13.4.1. Animal toxicity

C. procera has been shown to adversely affect early and late pregnancy in rats [70]. Acute toxicity studies in mice, however, showed no significant change in the hematological parameters. Behavioral changes, symptoms of toxicity and mortality were absent during the 24-h duration of the experiment. In the 3-month chronic toxicity study with 100 mg/kg, body weight per day, a 50% mortality of the animals was recorded. No significant changes in the hematological parameters were observed. This study suggested a safe use of the plant in single high dose but a serious health hazard may ensue with prolong use.

13.5. *Senna alata* (L.) Roxb

S. alata grows in several regions of Africa and in other parts of the world [71]. The leaves and stem bark of *S. alata* are widely used to treat hepatitis, skin diseases, jaundice, gastroenteritis, intestinal helminthiasis, eczema, tryphoenteritis and ringworm. The leaves of the plant have been shown to possess antibacterial activity on both Gram positive and negative bacteria, for example, *Bacillus megaterium, Streptococcus haemolyticus, Staphylococcus aureus, Salmonella typhi, Pseudomonas aeruginosa and Klebsiella pneumoniae* [71].

13.5.1. Animal toxicity

In acute toxicity studies, mice treated with the dose of 20 g/kg body weight showed some behavioral changes 120 min after oral administration. These changes included slow response to external stimuli, reduction of mobility and aggression, slight excitability sketching and sluggishness all of which disappeared after 24 h. On the contrary, no adverse changes were noted in mice treated with less than 12 g/kg body weight. Weight gain recorded was increased in both sexes 8 days after oral administration of *S. alata*.

In the sub-acute toxicity, the hydro-ethanolic extract of *S. alata* at doses of 500 and 1000 mg/kg given *per os* every 48 h for 26 days did not result in death of the animals. Also, there was no sign of toxicity *during* the experimental period. However, there was a progressive increase in body weight at the stated doses of 500 and 1000 mg/kg of the rats for 26 days of administration of the extract of *S. alata* which may indicate the improvement of the nutritional state of the animal. The relative weights of the control and treated animal groups showed variation from one organ to another: the hearts and livers from the control group had relative weights quite similar to those of the treated groups. Same observations were noted in the relative weights of the liver, lung and kidney [72].

The histopathological study of the liver of groups of rats showed a normal architecture but they showed slight abnormalities such as steatosis and ballooning of hepatocytes when treated orally with the extract of *S. alata* for 26 days at doses of 1000 mg/kg body weight. However, no necrosis, infiltration, edema and conjunction, which are the signs of hepatotoxicity, were found. The effect of *S. alata* seems to have a protective effect on hepatocytes and improves liver architecture, giving justification for the wide usage of the hydro-ethanolic extract of *S. alata* [72].

13.6. *Zanthoxylum xanthoxyloides* (lam.) Waterm

Z. xanthoxyloides (Lam.) is widely distributed in several African countries. It is known for varied uses in traditional medicine: the root-bark extract is used in treating elephantiasis, toothache, sexual impotence, gonorrhea, malaria, dysmenorrhea and abdominal pain [73]. Workers in West Africa have reported the anti-sickling and antimicrobial activity of the extracts of the plant [74]. In Nigeria, *Z. xanthoxyloides* is used as a chewing stick; water extracts from the plant showed activities against bacteria significant to periodontal disease [75]. It is a very popular anthelmintic among the various tribes in Uganda [76]. It has also been found that the alcoholic extracts of the root bark possess considerable antibacterial activity [77]. Its methanolic extract of the root bark has anthelmintic activity [76], anti-sickling [74] and is anti-inflammatory [78].

13.6.1. Animal toxicity

In a study of the acute toxicity of the methanol extract of *Z. xanthoxyloides*, mice were given 10.0 and 2.0 g/kg of extract. Animals that received 10.0 g/kg all died within 6 h of administration of the extract. However, those on 2.0 g/kg survived beyond the 24 h of observation.

No animals showed immediate behavioral changes on administration of the extract. Yet, mice on both doses showed piloerection and were restless for 24 h following extract administration. They, however, did not vomit nor was there ptosis. Those animals placed on higher doses went into convulsions and died in hyperextension. Post-mortem examination revealed no gross abnormality of the brain, the organs of the chest and abdominal cavities. On the other hand, histopathological examination showed congestion and focal necrosis in the liver and renal tubules [76].

13.7. *Vernonia amygdalina* del

V. amygdalina is a shrub which is widely found in West Africa. The leaves are very popular vegetables used for soup. The roots and the leaves are used in ethnomedicine to treat fever, hiccups, kidney problems and stomach discomfort among other uses [79]. Both aqueous and alcoholic extracts of the stem, bark, roots and leaves are used extensively as purgative, antimalarial and in the treatment of eczema [80]. The use of the plant has been validated in humans to possess potent antimalarial and antihelminthic properties [81], antitumorigenic properties [82] and antiparasitic activity. It has been found to be used for self-medication by parasitized chimpanzees [83]. It has also been shown that the leaf extract has both hypoglycemic and hypolipidemic properties in experimental animals [84].

13.7.1. Animal toxicity

Acute toxicity studies produced an LD_{50} of 500 mg/kg body weight in Wistar albino rats. Biochemical parameters such as total, conjugated and unconjugated bilirubin levels showed no significant increase. The levels of both alanine aminotransferase and alkaline phosphatase in the presence of *V. amygdalina* leaf extract increased slightly in a dose-dependent manner when compared with the control but none of the observed increases was statistically significant ($P > 0.05$) when compared to the control or when compared within doses. The processed extracts of the plant were able to reverse carbon tetrachloride-induced hepatotoxicity in rats [85].

13.8. Herbal mixtures containing *Alstonia congensis* Engler bark and *Xylopia aethiopica* fruits (Dunal) A. Rich

In Africa and other parts of the world, herbal medications are prepared mostly from a combination of two or more plant parts which contain many active constituents with multiple physiological activities and could be used in the treatment of various health conditions [72] and possibly to reduce toxicity. The herbal formulation prepared with *A. congensis* bark and *X. aethiopica* fruits in equal proportion is a popular local herbal product taken over a long time for the treatment of diabetes.

13.8.1. Animal toxicity

In the acute and sub-acute study of the mixture in Swiss albino mice and Wistar albino rats, respectively, no changes in the behavior and in the sensory nervous system responses were

observed. Gastro-intestinal effects were not observed in either male or female mice used in the experiments. The median acute toxicity value (LD_{50}) of the extract was above 20.0 g/kg body weight [86]. There was no significant change observed in the protein levels of the rats treated with lower doses of the extract (50 and 100 mg/kg) compared with control, while an observed significant decrease in the protein levels of the rats treated with a high dose (500 mg/kg) may be a sign of impaired renal function. Also, there was a significant increase ($p < 0.05$) in the plasma creatinine levels of all the treated groups [86]. There was no significant increase in AST and alanine aminotransferase (ALT) in the animals treated with lower doses of the extract compared with control but a significant increase in ALT was observed in the group treated with a high dose of the extract (500 mg/kg). This implies that the extract at the doses used had no effects on the heart tissue but at a high dose could have some deleterious effects on the liver tissue. The extract did neither improve nor produced any deleterious effects on the hematological parameters [86].

13.9. *Aspalathus linearis* (Burm. F.) Dahlg

The popular herbal tea, rooibos, also known as the 'long-life tea' in South Africa [86], is produced from the plant *A. linearis*. It is endemic to the South Africa [87]. Rooibos tea is known to have several health benefits, including antispasmodic, antioxidant, antiaging and antieczema activities [87].

Rooibos is exported to the East and Europe [88] and is currently sold in several countries including The Netherlands, Japan, the United Kingdom, Germany and the United States of America. The tea is mainly patronized due to its health-promoting properties when compared to black tea (*Camellia sinensis*) [89]. Rooibos is used as a beverage by the Khoi-descended people of the Cape; pregnant women take it for the iron content, and to relieve nausea and heartburns associated with pregnancy. It also serves as a milk substitute for infants and as colic relief in babies. Rooibos is well known for its antioxidant activity which also relates to its hepatoprotective properties [87] and immune-modulating effect in stimulating antibody production [90].

13.9.1. Animal toxicity

The safety assessment of rooibos has been addressed by some studies [87, 89]. Although some compounds in rooibos have been shown to contain mutagenic properties [91], it is, however, very unlikely that the mutagenic effect of rooibos would be relevant to tea drinkers when considering the quantities consumed [87]. In a study in rats, chronic consumption of aqueous extracts of unfermented and fermented rooibos over a period of 10 weeks did not cause any adverse effects in the liver and kidney [87].

13.10. *Musanga cecropioides* R. Br. Ex Tedlie

This plant is widely found in the tropical rainforest, particularly in West Africa. In Nigeria, the boiled leaves are used by the Igbo tribe as a powerful oxytocic to induce or augment labor while others use the decoction as a remedy for hypertension [92]. Parts of the plant have been

used by traditional healers in the treatment of an array of diseases including lumbago, rheumatism, leprosy, chest infections and trypanosomiasis [92].

13.10.1. Animal toxicity

Acute toxicity study of *M. cecropioides* aqueous stem bark extract showed no mortality in rats, at a limit dose of 3000 mg/kg body weight given orally. This is an indication that the extract has low acute toxicity when orally administered. Administration of the aqueous extract for 28 days in a chronic study did not affect most of the biochemical parameters except for creatinine which was significantly elevated. Hematological parameters were not significantly affected during the 28-day treatment. Liver enzymes, AST and ALT, were not affected in the treatment showing that the extract is non-toxic on the hepatocytes. The study concluded that the absence of clinical signs of acute toxicities in human when the extract was orally administered as an antihypertensive may reflect the oral route of administration, low dose administration as well as short duration of exposure when used as an antihypertensive agent [93].

14. Conclusion

There is an increasing use of medicinal plants and herbal medicines which contribute significantly to the health of humanity worldwide, especially in developing countries. The limited scientific knowledge among the general population has led to the general assumption that herbal medicines being natural are therefore safe. However, evidence is being adduced from toxicological studies that show plant products to be potentially toxic thus affecting their safe use.

The source of potential toxicity could be traced to a number of factors: the type of constituents some of which may be intrinsically toxic such as tropane alkaloids and cardiac glycosides though they had been used in traditional medicine. Also, it is noted that the route of administration and dose, of any chemical, are important regarding safety due to chemical or pharmacological interactions; this is undergirded by the need for a regulatory regime for quality.

Serious adverse effects of therapies involving aqueous traditional medicines are rare. However, efforts to investigate toxicity, organ toxicity and cytotoxicity, have involved the use of organic solvent plant extracts and routes of administration which constitute a drawback to the conclusions drawn from such studies.

Information on the traditional formulation and use of the herbal medicines should be satisfactory to avoid possible toxicity from the medicinal plants. Manufacturers of herbal medicines should consider standardization of the products while patrons of herbal medicines need to inform their health-care providers about any herbal products they use to ensure effective and safe care. This is to avoid interaction between herbal and allopathic medicines which could yield adverse reactions.

Author details

Merlin L.K. Mensah[1], Gustav Komlaga[2]*, Arnold D. Forkuo[3], Caleb Firempong[4], Alexander K. Anning[5] and Rita A. Dickson[2]

*Address all correspondence to: gustkomla@yahoo.com

1 Department of Herbal Medicine, Faculty of Pharmacy and Pharmaceutical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

2 Department of Pharmacognosy, Faculty of Pharmacy and Pharmaceutical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

3 Department of Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

4 Departments of Biochemistry and Biotechnology, Faculty of Science, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

5 Department of Theoretical and Applied Biology, Faculty of Science, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

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