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A CRITICAL REVIEW ON LD50 OF SOME MEDICINAL PLANT

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ABSTRACT

Traditionally, humans have used herbal medicines for remedying various diseases since time immemorial. One major and overriding criterion in the selection of herbal medicines utilized in health care provision is safety. The LD50 for a particular substance is the amount that can be expected to cause death in half of animals (mice/rat). The objective of the paper was to comprehensively review the literature on the toxicity (LD50) of commonly used medicinal plant. We reviewed relevant articles and books published over the years on botany/ ethnopharmacology for their toxic effect; Vitex madiensis Oliv, Aquilaria malaccensis, Aristolochia longa, Psidium guajava, Annona squamosa, Lagerstroemia speciosa, Combretum micranthu, Ficus deltoidea, Peganum harmala, Rhizophora racemosa, Mangifera indica, Warburgia ugandensis, Alysicarpus glumaceus, Abrus precatorius, Aloe barbadensis and Tephrosia vogelii. We searched several scholarly publication. LD50 method of determining toxicity was mainly by OECD's and Lorke's, crude plant extracts were the most commonly used, Water and methanol were common solvent used, Biochemical, haematological and histopathology studies were the assay carried out to ascertain lethality (LD50) of the plant extract. The LD50 value varied with the type of cells, extracts and solvent used, making direct comparison of the plant species difficult. Most of the plant had tolerated LD50, two of plant species were toxic, namely; Abrus precatorius and Peganum harmala (2345 mg/kg and 1.8, 2.4 and 2.5mg/kg) respectively in animal models, the remaining fourteen plant species were non toxic. W. ugandensis decoctions were reported to cause adverse effect in humans by herbalist.

KEYWORDS: Acute toxicity; Chronic toxicity; Hematological parameters; Biochemical parameters; Safety.

INTRODUCTION

In recent years, the use of medicinal plants has risen rapidly and is very popular. The World Health Organization has estimated that 80% of African and Asian residents use traditional medicines to maintain health and treatment of disease. Research on the use of traditional medicines, including herbal medicines, has been rapidly increased, both in developed and developing countries.[1-3] Literature on antianaemia, antidiarrheal and antimalarial activities of plant-based products is on the increase as a result of volume of work carried out by Scientists.[4-6] One major and overriding criterion in the selection of herbal medicines utilized in health care provision is safety.[1] Side effects should be reduced to the barest level if any herbal extract must be used as a drug. Plant's extract should not only be efficacious but also safe for consumption. The earliest report of the toxicity of herbs originated from Galen, a Greek Pharmacist and Physician who showed that herbs do not contain only medicinal constituents, but may also be constituted with harmful substances. Thus, the common belief that those concoctions from medicinal plants are natural and generally regarded as safe does not always hold true. Therefore, evaluating the toxicities of herbal bioactivities is necessary particularly when the bioactives are amenable to the development of drugs for treating human ailments. Toxicity testing can reveal some of the risks that may be associated with use of herbs, therefore avoiding potential harmful effects when used as medicine.[7]

Acute toxicity test is test in which single dose of the drug is used in each animal on one occasion only for the determination of gross behavior and LD50 (the dose which has proved to be lethal causing death to 50% of the tested group of animals). It is usually the first step in the assessment and evaluation of the toxic characteristics of a substance. It is an initial assessment of toxic

manifestations, providing information on health hazards likely to arise from short-term exposure to drugs.[8] The LD50 for a particular substance is the amount that can be expected to cause death in half (i.e. 50%) of a group of some particular animal species, usually rats or mice, when administered by a particular route.[9] It is usually expressed as the amount of chemical administered (e.g. Milligrams) per 100 g (for small animals) or per kilogram (for bigger subjects) of the body weight of the test animal.[10] LD50 obtained at the end of a study is reported in relation to the route of administration of the test substance e.g. LD50 (oral), LD50 (dermal) etc. The most frequently performed lethal study is the oral LD50. Generally, the smaller the LD50 value, the more toxic the substance is and vice versa. The objective of this paper was to critically review the literature on the toxicity of commonly used medicinal plant species in treating various disease and to establish any correlation between traditional use and toxicity.

LD50 studies on some medicinal plants Vitex madiensis Oliv Vitex genus to which belongs Vitex madiensis Oliv. is widely distributed in forest regions areas of East, Central, and West Africa. This plant was formerly classified in the Lamiaceae family.[11,12] Generally, the roots are used in the form of maceration to treat anemia, asthma, diabetes, and diarrhea, while the bark extracts are used in derma and dental diseases.[13] Several bacterial species and Plasmodium falciparum showed sensitivity to dichloromethane, ethyl acetate and methanolic extracts of the leaves and stem bark of Vitex madiensis as an antioxidant, antimicrobial and anti-plasmodial activities respectively.[14,15] His-aqueous extract has an analgesic effect on mice.[16,17] reported that extract of Vitex madiensis. The oral LD50 was determined with the mortality rate by the Dragstedt and Lang method. In sub-acute toxicity, a daily single oral dose of Vitex madiensis aqueous extract 0.1g/kg and 1 g/kg (about the LD50). The LD50 calculated was 1.4 g/kg with change in mobility behavior, weight loss, alopecia, asthenia, convulsion, and bloating of the abdomen. The aqueous extract of Vitex madiensis induced significant changes in body weights. However, hematological, and biochemical parameters showed a significant decrease in ALT, AST, and creatinine levels suggesting disturbances of haemopoiesis, liver, and kidney functions.[16] under Standard procedures using OECD Guideline helped to consider the Vitex madiensis extract and thus, reported the extract as non-toxic with an LD50 greater than 5000 mg / kg in mice.

Aquilaria malaccensis

A. malaccensis is a native species of Aquilaria in Malaysia, Indonesia, and Thailand. It is classified under the family Thymelaeaceae and one of the agarwood-producing trees. It is locally known as karas, engkaras, gaharu, or depu.[18,19] addressed the local ethnomedicinal use of A. malaccensis in treating general dropsy or oedema using. Hepatoprotective effect,[20] anticancer activity.[21] antidiabetic.[22] and antimicrobial activity.[23,24] It's essential oil can act as mosquito larvicidal and repellent.[25,26] reported based on.[27,28] The assessment of acute toxicity based on the.[29]

Organization for Economic Cooperation and Development (OECD) Guideline 420 revealed findings at a dose of 2000 mg/kg body weight, Aquilaria malaccensis did not influence mortality, clinical appearance, body weight gain, or necropsy. In the sub-acute toxicity, all doses did not significantly modify the body weight and food and water intake. In male rats treated with 2000 mg/kg, there was a significant reduction in the relative weight of liver, there was also an increase in alkaline phosphatase and alanine transaminase was also observed in different groups among the female rats. A significant decrease in the creatinine level was also seen among male rats administered with different doses of Aquilaria malaccensis. In both sexes, histopathological analysis had shown abnormalities in the liver and kidney of rats treated at the dose of 2000 mg/kg.[30] Rizky et al., unraveled the Thomson-Weil method for the measurement of LD50 values. The LD50 for male mice of various plant extract (Aquilaria malaccensis) was 2454mg/kg body weight, while others; 1546 mg/kg body weight and 2065mg/kg body weight respectively. The LD50 value for female mice was a pseudo LD50.

Aristolochia longa L. Aristolochia longa L. is a common medicinal plant widely distributed in Algeria that belongs to the family Aristolochiaceae. The plant commonly called “Beroustoum in Algeria, Aristolochia longa is used as sources of abortifacient, emmenagogue, sedative, analgesic, anti-inflammatory, anti-feedant, muscle relaxant, antihistaminic, and antiallergic drugs.[31] Aristolochia species have been used in herbal medicines since ancient times for treatment of snakebite, festering wounds, and tumors.[32,33] reported the LD50 of Aristolochia longa, the procedure was followed by OECD (Organization of Economic Cooperation and Development) guidelines 423). The acute oral toxicity result revealed that LD50 of the tubers and fruit aqueous extracts was respectively more than 12 g/kg and 5 g/kg, but LD50 of the aerial aqueous extract was at 5 g/kg. It also revealed that liver and kidney function of different groups receiving high doses was affected as ASAT, ALAT, Urea, creatinine was significantly increased. Histological examination showed alterations of the renal parenchyma and the liver which is greater in animals treated with high dose.[34] also reported the administration of the aqueous extract induced the appearance of several symptoms of toxicity like weakness, convulsion, diarrhea, hypoactivity. It showed that the highest dose killing all animals or LD100 is 12 g / kg, maximum tolerated dose is 5 g / kg and the LD50 is 7.6 g/kg. The study suggest non toxicity of the Aristolochia longa aqueous extract.[34] Also there was a likely toxic effect of the extract on liver and kidney function, histopathological examination showed organ toxicity, the team of researchers concluded that ALAE

has a low toxicity potential in non prolonged oral administrations. However, another findings has it that at high chronic oral doses, A. longa appears to have significant toxicity on the organs tested.[35]

Psidium guajava

Psidium guajava belongs to the family Myrtaceae, it is considered to have originated from tropical South America. Psidium guajava tree grows in tropical and sub-tropical areas of the world such as Asia, Africa and Hawaii.[36] The plant is also called Guava in English. In Nigeria, the common names include, guaba in Yoruba, giba in Hausa, gova in Igbo and ugwaba in Efik.[37,38] Various parts of Psidium guajava plant have been used in traditional medicine to manage conditions like malaria, gastroenteritis, vomiting, diarrhea, dysentery, wounds, ulcers, toothache, coughs, sore throat, and inflamed gums, diabetes, hypertension, obesity.[39,40,41] Showed the acute toxicity of the LD50 of the extract of P. guajava to be less than 5000 mg/kg. Chronic toxicological study revealed that at 200 mg/kg, there were no significant ($P > 0.05$) differences in hematological and biochemical parameters, and there were no alterations in the histology of the organs, however with increased dose the concentrations of the liver biomarkers were increased, with distorted liver. Additionally,[42] Yamssi et al., also revealed that the methanol extracts of P. macrophylla and P. guajava showed no evidence of single dose toxicity (5000 mg/kg). The acute toxicity study showed no signs of toxicity, hematological or histological parameters. So the LD50 values of the tested extracts were more than 5000 mg/kg body weight.

Annona squamosa

Annona squamosa commonly known as custard Apple or Sweet Sop is a semi-evergreen shrub or small tree reaching 6-8m (20-26ft) tall. The plant is a native of tropical America and the West Indies, but its original home is uncertain.[43] It has antibacterial, antimalarial activity.[43] Administration of the methanolic extract of Annona squamosa significantly prevent isoniazid-rifampicin-induced elevation in liver marker enzymes, together with increased total protein and reduced glutathione (GSH) levels.[44]

According to,[45] the LD50 (Lorkes method) was found to be greater than 5000mg/kg body weight without any significant decrease ($p>0.05$) in body weight. Biochemical analysis of Aspartate amino transferase (AST), Alanine amino transferase (ALT), Albumin and globulin of animals administered with extract showed no significant difference ($p>0.05$), however concentration of Alkaline Phosphatase (ALP) indicated obvious changes in the treated groups ($p<0.05$). Also, histopathology of the kidney revealed some inflammation at 1000, 1600, and 5000 mg/kg body weight.[46] also acceded with Saleh's report: the team administered varying doses of ethanolic extract of Annona squamosa. The results showed that the ethanolic extract of A. squamosa leaves with doses of 2,000 and 5,000 mg/kg bw did not show any toxicity signs. At a dose of 5,000 mg/kg bw caused hydropic degeneration, necrosis hepatocyte, glomerular atrophy, and tubular dilatation. No mortality was observed. It was estimated that LD50 of ethanolic extract of A. squamosa leaves was higher than 5,000 mg/kg and the extract were practically non-toxic.

Lagerstroemia speciosa

Lagerstroemia speciosa (LS) leaves are known as banaba, and the tree is popular in the Philippines. People have been using a decoction of L. Speciosa leaves as blood-glucose-lowering aid for several years.[47] It has antioxidant activity in HepG2 cell lines.[48] It has anti-inflammatory activity.[49,50] reported Lagerstroemia speciosa (LS) leaves, single oral dose of LS (2000 mg/kg). It was done as per Organization for Economic Co-operation and Development (OECD) guidelines 423 for acute toxicity studies.[51] and OECD guideline 407.[52,53] The LS (2000 mg/kg) did not illustrate any indications of toxicity or mortality through the whole observation time in acute toxicity experimentation. Therefore, LS's approximate median lethal dose is assessed to be greater than 2000 mg/kg. The body weight, organ weight, food, water intake, biochemical, haematological parameters, and histopathology were studied. The findings of this study showed no mortality or morbidity was found in acute and sub-acute toxicity studies in rats.

Combretum micranthum

Combretum micranthum (CM) (Combretaceae) is widely used in traditional medicine throughout West Africa for the treatment of diabetes, hypertension, inflammation, malaria and liver ailments. In a recent research it was demonstrated that CM has nephroprotective potentials in diabetes mellitus, hypertension and renal disorders. Combretum micranthum exhibited good antioxidant and nephroprotective potentials in in-vivo, ex-vivo and in-vitro HEK-293 (Human embryonic kidney) cell line experiments.[54] and nephroprotective activity in cisplatin induced nephrotoxicity in rats.[55] According to.[56] The C. micranthum extract upon subjection to Fourier transform infrared spectrophotometric examination, no cyanide toxic compound was detected. This suggested that the C. micranthum extract may not contain toxic substances, no mortality or adverse effects were noted at the dose of 5000 mg/kg, and no adverse effect related to body weight, general behaviour, relative organ weights, hematological and biochemical parameters. Histopathological examination of vital organs showed normal architecture suggesting no morphological alterations. The median lethal dose of the extract was estimated to be more than 5000 mg/kg.[57] Combretum micranthum showed no toxicity when administered orally to mice ($LD50 \geq 2000$ mg/kg). C. micranthum is non-toxic.[58] adopted.[59] method. Administration of the aqueous extracts did not produce any mortality in the rats for dosages of up to 5000 mg/kg at a daily dose of 500 mg/kg, the serum liver enzyme activities was significantly high, whereas those treated with a daily

dose of 1500 mg/kg had serum liver enzymes activities even higher than those treated with 500 mg/kg dose rats. Thus, both 500 and 1500 mg/kg doses for seven days induce liver toxicity.

Ficus deltoidea

F. deltoidea is a perennial cultivated plant whose height rarely exceeds 2 m. In some countries, these plants are known by various names such as Mas Cotek in Malaysia, Barito Barat in Indonesia, Agoluran in the Philippines, and Kangkalibang in Africa.[60] The fruit is chewed to relieve headaches and toothache, wounds, rheumatism.[61,62] Conventionally, these plants are also consumed to help strengthen a woman's womb after giving birth.[60,63] and function as a libido booster for men and women.[64,65] showed that the ethanol extract of F.deltoidea Jack leaves at 2000 mg/kg BW dose resulted in no symptoms of toxicity and mortality, indicating that the 50% lethal dose (LD50) was above 2000 mg/kg BW. Meanwhile, there were no behavioral changes, significant differences in weight changes, hematological parameters, and serum biochemistry of mice in subchronic toxicity tests. The LD50 of the ethanol extract of F. deltoidea leaves for mice >2000 mg/kg is considered as practically non-toxic. The acute toxicity study showed that the LD50 of the extract was greater than 5000 mg/kg.[66] also reported that the subchronic toxicity study, there were no significant adverse effects on, body weight, organ weights, mortality, clinical chemistry, hematology, gross pathology, or histopathology.

Peganum harmala

Peganum harmala, also called in Morocco harmal, is a species of medicinal plant of the family Zygophyllaceae, perennial, with yellowish-white flowers and small dark brown seeds.[67] It is a perennial herbaceous glabrous plant that grows in semi-arid range lands and sandy soils, especially along the Mediterranean region in North Africa and the Middle East.[68] In Morocco Peganum harmala intoxication, is responsible for 4.6% of all plant poisonings received at the Poison Control Center of Morocco (CAPM) in 2010. Peganum harmala The most important traditional uses of P. harmala are cardiovascular, gasterointestinal, nervous, endocrine, neoplasm and tumors, pain relieving, diabetes, respiratory diseases, disinfectant, anti-pyretic, skin and hair, ulcers, rheumatism, arthritis and inflammation.[69,70]

Administration of the aqueous extract at different doses taken intraperitoneal injection on male mice showed severe symptoms of toxicity. These symptoms are presented by Drowsiness, hypoactivity, anorexia, isolation, bradycardia, difficulty breathing, exicitaion and death, the results obtained show that, the highest dose that killed all animals or 100% lethal dose (LD 100) is 10 g / kg for peganum harmala L. while for the maximum tolerated dose it is 1g / kg. The LD50 was determined by three methods.[71-73] very close values were obtained, viz; 1.8 g/kg for the Karber and Behrens method, 2.4 g/kg for Trevane and 2.5 g/kg for that of Bliss respectively, it was therefore conclude that the three values are very close.[74] revealed that a substance can be considered toxic only if it has an LD50 of less than 3 g /kg, based on this result we can confirm that Peganum harmala Morocco is a toxic plant. From findings the LD50 is close to that of,[75] she found a value of 2.8585g / kg in the mice administered by the aqueous extract of peganum harmala, such result was also reported by,[76] who reported the acute and chronic toxicity of Peganum harmala seeds to be LD50 equal to 2.70g / kg.[77] rated 1.07g / kg as LD50. In another study.[78] the team of investigators administered varying doses of the aqueous extract of peganum harmala, the LD50 was 420 mg / kg. The value was much lower than that found by,[79] possibly due to plant extract variation, humidity, soil etc.

Rhizophora racemosa

Rhizophora racemosa is a species of mangrove plant of the family of Rhizophoraceae. It is found commonly in the Niger Delta region of Nigeria and along the West African coastline. Several species of mangrove produce bioactive compounds that may control microbial growth.[80]

None of the animals in the first group showed any clinical or behavioural changes throughout the observation period and as such were active. However, depression, weakness and loss of appetite in the first 5 hours were observed in subsequent groups of animals that were treated with the higher doses of the extract and eventually died after 48 hours. The LD50 of the extract was calculated to be 1583.33 mg/kg/ i.p body weight.[81] by Karber's method. It has been suggested that any substance with an intraperitoneal LD50 of above 1000 mg/kg should be regarded as safe.[82-83] It can therefore be inferred that, the plant is of low toxicity and safe.

Mangifera indica L. (Mango)

Is a perennial fruit plant that belongs to the family Anacardiaceae cultivated mostly in Asia, America and part of Africa. Currently, India is the largest producer of mango.[84] It is grown for its fruit, stem bark, leaves and peels. In developing countries, the leaves and stem bark have been used in preparing concoctions for bacterial infections, malaria and ulcerative inflammation.[85] Often, their milled samples are known to be curative agents for diabetes, hypertension, inflammation, diarrhea in animal models.[86-87] and neutralization of venoms during snake bite.[88,89] revealed that the lower doses of the two extracts did not show signs of toxicity or cause the death of any mice. However, at higher doses before the death of mice, they showed signs such as tremor, weakness, respiratory failure and convulsion. At 3000 mg/kg and 5000 mg/kg doses, Opioro extract produced 20% and 60% mortality while Julie produced 20% mortality at 5000 mg/kg. The lethal dose (LD50) of Opioro (3700 mg/kg) and Julie (4300 mg/kg) extracts fell within the safety range. The biochemical, antioxidant and hematological parameters showed various levels of

significance (P<0.05– P<0.0001). Evaluation of the organ histology indicated that liver and kidney were unaffected by the extracts. The acute and sub-acute toxicity study was performed using the method described by.[90,91] In another study, no toxic effects were observed after dermal exposure to mangiferin 2000 mg/kg but transient dyspnea, flank position and piloerection were observed after oral administration. I.p. administration induced similar toxicity signs, but at the highest dose (2000 mg/kg). Abnormal clinical signs or hematology alterations were not observed with 250-1000mg/kg. Histopathological alterations like vacuolar degeneration, necrosis and increment of apoptosis of the acinar cells were observed in the exocrine pancreas of rats at 1000 mg/kg, thus suggesting that exocrine pancreas was the target organ for mangiferin's toxicity.[92] Subsequently research by,[93] agreed with the finding of Nwachukwu et al., the LD50 of the Azadirachta indica and Mangifera indica methanol leaves extract were between 500 - 5000 mg / kg body weight, which showed that the extracts were slightly toxic.

Warburgia ugandensis

W. ugandensis belong to the family Canellaceae it is an evergreen tree native to East Africa, is one of the most commonly used multipurpose medicinal plant species in Uganda and is also widely used in other countries like Kenya, Tanzania and South Africa.[94,95] The extracts of Warburgia, particularly those from stem bark and leaves, exhibited a wide range of pharmacological effects, including antibacterial, antifungal, antimycobacterial, antioxidant, anti-inflammatory, antifeedant, antiplasmodial, antileishmanial, anthelmintic, cytotoxic and molluscicidal activities.[96] W. ugandensis extracts is highly toxic.[97,95] Mwitari and colleagues have showed W. ugandensis to be cytotoxic to intestinal epithelial cells IEC-6, with IC50 values < 50µg/ml.[95] Both the DMSO (CC50 1.5µg/ml) and the ethanol (CC50 7.6µg/ml) root were highly cytotoxic to U87CD4CXCR4 cells.[97] W. ugandensis contains cytotoxic sesquiterpenes called muzigadials.[98] It was previously documented that the careful and judicious use of W. ugandensis by experienced herbalists in Uganda W. ugandensis had CC50 > 250µg/ml in Vero E6 cells and was classified as not cytotoxic.[94] W. ugandensis aqueous stem bark extracts were also found to be non-toxic in BALB/c mice, with the LD50 > 5000 mg/kg body weight and no mortality recorded.[99] However, when decoctions of W. ugandensis are used in doses exceeding what is prescribed by the herbalist, toxic effects such as vomiting, dizziness, weakness and ulcers are experienced. Because of its popularity and toxicity, the use of W. ugandensis should be with caution. W. ugandensis extracts were contraindicated in pregnancy and in weak patients.[94,97] Like A. coriaria, there is conflicting information on the toxicity of W. ugandensis. Whereas one study indicated W. ugandensi to be cytotoxic, one study in mice and another cellular assay indicate that W. ugandensis is not toxic. Because of varying reports of toxicity by herbalists, there is need for further investigation in different cell-lines.

Alysicarpus glumaceus

Alysicarpus glumaceus (Vahl D.C), family- leguminosae is used traditionally for a number of ailments in African countries, Asia and middle east. The leaf is taken orally for thrush, sores and asthma. While root decoction is taken for coughs and its combination with leaf sap is taken for diarrhea and as an abortifacient. The aerial parts are used for the management of neuropsychiatric disorders mainly depression and currently been used by drivers in combination with tea to keep alert on long drive in northern Nigeria.[100]

The oral median dose of aqueous methanol extract of A. glumaceus and its fractions were estimated to be greater than 5000 mg/kg, hence suggesting that they are safe or practically non-toxic.[59] LD50 was greater than 5000 mg/kg, it had no significant effect on their body weights as well as on their physical behaviour. Slight lesions were observed in kidney and liver of animals given 1500 mg/kg of AME, neither were there significant and consistent alterations in the histopathological and haematological parameters. Although, this finding does not accede with Bawa and his team.[101] who reported the LD50 from methanol extract of A. glumaceus and its fractions was less than 5000 mg/kg.[100] The inconsistent reports of toxicity by different scientist need further investigation in different cells and tissues.

Abrus precatorius Linn

Abrus precatorius is one of the plants with a wide traditional medicinal use across different cultures, globally. It is a legume with long, pinnately compound leaves of the family name Fabaceae. Its flowers are arranged in violet or pink clusters. The seed pod curls back when it opens and reveals the seeds.[102] The seeds are truncate shaped, 1.5- 2cm long, with attractive scarlet and black color. It has slender branches and a cylindrical wrinkled stem with a smooth-textured brown bark. Abrus precatorius is derived from the Greek word Abrus which means delicate and refers to the leaflets; precatorius refers to 'petitioning' and was chosen because of the use of the seed in Rosaries. Abrus precatorius leaves have been used in traditional medicine for the treatment of cough, malaria and infertility in women.[103,103] Saganuwan et al., reported an estimated median lethal dose (LD50) of 2559 mg/kg for aqueous extract of Abrus precatorius leaf which is similar to.[103] Findingsalso showed that Abrus precatorius leaf had an LD50 of 2345 mg/kg toxicity studies. However, the study went further to provide estimated LD50 values for 70% Methanol, Petroleum Ether and Acetone extracts as follows; 3942, 407 and 187mg/kg respectively. Thus, evidence showed that 70% methanolic and aqueous extracts are safer than acetone and petroleum ether green rind extract at 200 mg/kg significantly. The extracts. The study also revealed that methanol was the Creatinine levels increased. Conversely, Mean least toxic solvent

(3942mg/kg) used in the extraction. Corpuscular Hemoglobin Concentration (MCHC) levels Furthermore, histopathological results reveal significantly decreased at lower doses of the green rind pathological changes in the organs examined, revealing a extract. Histopathology of the kidney revealed the renal possible hepatotoxicity, cardiotoxicity and interstitium's inflammation. The findings demonstrated nephrotoxicity of the extracts at the oral limit dose. The that A. vera green rind and whole leaf extracts are non- graphical method of Miller and Tainter was used to toxic at relatively high doses when used for a short estimate their LD50.[103] duration.[111] Another acute toxicity study demonstrated a maximum tolerated dose of 100 mg/kg body weight and Aloe barbadensis LD50 of 250 mg/kg, when the whole Aloe vera plant Aloe barbadensis(L.) Burm. is of the Family powder was extracted with 50% ethanol and Asphodelaceae, is also known as Aloe vera. It is among administered intraperitoneally to adult albino mice at an the most commonly used medicinal plant to manage initial dose of 400 to 500 mg/kg. several ailments among local communities in Uganda.[105] A. vera is a stemless or very short-stemmed, Tephrosia vogelii Hook.f evergreen perennial succulent plant growing to 60–100 Tephrosia vogelii Hook.f. is The Fabaceae or cm tall, spreading by offsets and root sprouts.[106] The Leguminosae is a soft, woody herb with dense foliage. It local Ugandan communities use A. vera whole leaf stands 0.5–4 m tall, a medicinal plant used decoction for malaria, blood cleansing, stomach- ache, ethnomedically for the treatment of skin infection, scabs, allergy, yellow fever, worms, fever, urinary tract deworming and ectoparasites.[112-118] It has also been used infections, wasting, and scar removal.[107-109] They also traditionally in fishing activities and as traditional smear leaf extracts on wounds, burns, and skin pesticides in local agricultural activiities for many infections.[109] decades.[119-121] The pharmacological study of methanolic extracts of T. vogelii revealed its antimicrobial.[110] Nalimu et al., reported that there was no mortality or activities.[118-120]

The pharmacological studies on apparent behavioral changes at the doses tested. Thus, bioactive compounds such as rotenoids and steroids from the Median Lethal Dose (LD50) of green rind and whole T. vogelii revealed the potentiality of such compounds leaf aqueous extracts was above 5000 mg/kg. Gross for development of pesticides and insecticide.[113- 121] anatomy revealed that the rats' relative spleen weight in.

Table 1: LD50 of some medicinal plant.

Scientific name Vitex madiensis	**Local name(s) Rough finger leaf**	**Solvent(s) Water**	**LD50 value (mg/kg) 1.4 &>5000**	**LD50 Method Dragstedt and lang/ OECD**	**Reference [16,17]**
Aquilaria malaccensis	Karas, Engkaras, gaham, depu	Ethyl acetate, water	>2000, 2454	OECD 420 Thomson-well	[26,30]
Aristolochia longa	Beroustoum	Water	76g/kg	OECD 423	[34, 34, 35]
Psidium guajava	Guava gova	Methanol	>5000	OECD/ Lorkes	[41,42]
Annona squamosa	Custard apple	Ethanol	>5000	Lorkes	[45, 46]
Lagerstroemia speciosa	Banaba	Nil	>2000	OECD 423	[50]
Combretum micranthu	Kinkileba	Hydro alcohol,ethanol	>2000, 5000	OECD, Lorkes	[56, 57]
Ficus deltoidea	Kangkalibang	Nil	>2000	OECD 423	[65, 66]
Peganum harmala	Harmal	Water	1.8, 2.4, & 2.5	Kaber, Behrens &Trevane	[78, 79]
Rhizophora racemosa	Red mangrove	Methanol	573	Kaber	[81]
Mangifera indica	Mango	Methanol	3700, 4300	OECD 407	[89, 93]
Warburgia ugandensis	Kikuyu, muthigia	DMSO, ethanol	50ug/ml, >5000	Lorkes	[95, 99]
Alysicarpus glumaceus	Alyce clover	Methanol	>5000	Lorkes	[100, 101]
Abrus precatorius	Rosary pea	Water, methanol, petroleum ether, Acetone	2345, 39402, 407 & 187	Miller and Tainter	[104]
Aloe barbadensis	Aloe Vera	Water	>5000	Lorkes	[110, 111]
Tephrosia Vogelii	Fish bean	Methanol	>5000	OECD 423 & 407	[125]

LD50 assessment was carried out: the methanolic root and leaf extracts of T. vogelii at varying doses did not exhibit any mortality in the rats. However, sedation was observed as a clinical toxicity manifestation for the animals administered with both root extracts and leaf extracts at 5000 mg/kg body weight. The rotenoids especially rotenone and tephrosin are flavonoids (Isoflavonoids), mostly isolated in the T. vogelii and been reported to exhibit poisonous effects on insects, fishes, and ectoparasites.[117–120] Therefore, the observed sedation signs could be attributable to the flavonoids (rotenoids). On the other hand, the lethal dose could not be established because doses administered did not cause any death to the rats exposed to the doses. Apparently, the lethal doses for both extract types must be higher than 5000 mg/kg body weight.[122,123] Histopathological examination of liver and kidney for sub-acute toxicity test showed safety at all doses except root methanolic extracts dose of 2000 mg/kg which exhibited necrosis and vaculation of liver cells. Nonetheless, hepatic necrosis and hepatic vacuolation disappeared upon time elongation without dose administration. The conducted

toxicity evaluation of methanolic leaf and root extracts in albino rats revealed no deleterious effects,[124] Furthermore,[125] disclosed that the extract of T. vogelii has an LD50 of 134.16mg/kg, from histopathologic findings, the extract exerted toxic effect which predominantly involved neurological disorders, hepatic, renal and cardiac necrotic changes in mice.

CONCLUSION

Few of the plant species reviewed had detailed phytochemical analysis. Crude plant extracts were the most commonly used, purified/single component extracts from different plant parts were also used in most studies. The biochemical and haematological studies were the most assay carried out to ascertain lethality of the plant extract. Water, methanol, ethanol, and DMSO were the commonest solvents in above order was used. In a few instances, isolated purified compounds/ extracts such as sesquiterpenes called muzigadials from was used W. ugandensis and while magniferin for mangnifera indica. The LD50 value varied with the type of cells, extracts and solvent used, making direct comparison of the plant species difficult. Some of the plant had tolerable LD50, i.e were not toxic, two of plant species were toxic namely; Abrus precatorius and Peganum harmala in animal models, the remaining fourteen plant extract were non toxic, the crude aqueous and ethanol extracts were mainly in acute oral toxicity studies in mice. W. ugandensis decoctions were reported to cause adverse effect in humans by herbalist.

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Conflict of Interest

None was declared.

REFERENCE

1. Ekor M. The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol, 2014; 4: 177.
2. Azis NA, Agarwal R, Ismail NM, Ismail NH, Kamal MSA, Radjeni Z. Blood pressure lowering effect of Ficus deltoidea var kunstleri in spontaneously hypertensive rats: Possible involvement of renin-angiotensin-aldosterone system, endothelial function and anti-oxidant system. Mol Biol Rep, 2019; 46(3): 2841-9.
3. Afzan A, Kasim N, Ismail NH, Azmi N, Ali AM, Mat N. Differentiation of Ficus deltoidea varieties and chemical marker determination by UHPLC-TOFMS metabolomics for establishing quality control criteria of this popular Malaysian medicinal herb. Metabolomics, 2019; 15(3): 35.
4. Irinmwinuwa OE, Emeka CI, Oyindamola J and Afonne OJ. Haemopoietic Actions of Justicia secunda Leaf Extracts in Mice. International Journal of Integrated Health Sciences, 2022; 10(2): 65–74.
5. Oyindamola JO, Akuodor GC, Obi MI, Nwachukwu EO, Chilaka KC, Irinmwinuwa OE. Comparative assessment of the anti-diarrhoeal effects of the ethanol leaf and stem extracts of lantana camara in Wistar rats. Magna Scientia Advanced Research and Reviews, 2021: 03(01): 035-045.
6. Nok AJ. Azanthraquinone inhibits respiration and in vitro Growth of long slender Blood stream forms of Trypanosoma congolense, Cell Biochemistry and function, 2002; 20: 205-215.
7. Ifeoma O, Oluwakanyinsola S. Screening of Herbal Medicines for Potential Toxicities (Chapter 4), 63 – 88 IN: New Insights into toxicity and drug Testing. Edition Sivakumar Gowder, Publisher: Intech, 2013; 252 p.
8. Bhardwaj S, Deepika G, Seth GL, Bihani SD, The International Journal of Advanced Research in Pharmaceutical & Bio Sciences, 2012; 2(2): 103-129.
9. Randhawa MA. J Ayub Med Coll Abbottabad, 2009; 21(3).
10. Gadanya AM, Sule MS, Atiku MK, Bayero. Journal of Pure and Appl. Sci, 2011; 42(2): 147-149.
11. Irvin FR, 1961. Woody Plants of Ghana. Oxford University Press, London.
12. Bakari A, Mwamba M, Lumbu S, Okusa P, Duez P, Kahumba B. Hypoglyce-mic and Antihyperglycemic Activities of Nine Medicinal Herbs Used as Antidiabetic in the Region of Lubumbashi (DR Congo). Phytother. Res, 2017; 31: 1029–1033.
13. Maydell HV. Trees and Shrubs of the Sahel. Their characteristics and Uses. Deut-sche Gesellschaft fur Technische Zusammenarbeit. 1990. Germany.
14. Guha G, Rajkumar V, Kumar RA. Polyphenolic constituents of methanolic and aqueous extracts of Vitex negundorender protection to Hep3B cells against oxidative cytotoxicity. Food Chem. Toxicol, 2010; 48: 2133–2138.
15. Ondo JP, Lekana-Douki JB, Bongui ES, Zatra R, Toure-Ndouo FS, Elomri A. In vitro antiplasmodial activity and cytotoxicity of extracts and fractions of Vitex madiensis, medicinal plant of Gabon. Trop. Med. Int. Health 2012.
16. N'Goka V, Ntandou NGF, Boumba SL, Abena AA. Chemical Screening, Acute Toxicity and Analgesic Effect of the Aqueous Extracts of Vitex madiensis Oliv. (Lamiaceae-Viticoïdeae) and Phytolacca dodecandra L'Herit. (Phy-tolaccaceae) Leaves. Int. of sci, 2018; 7(01): 1–9.
17. Ntabaza VN, Amuri B, Ompey JV, Simbi L, Byanga N Acute and sub-acute oral toxicities of aqueous leaf extract of Vitex madiensis Oliv. in guinea pig model. South African Journal of Botany, 2023; 153: 1-6

18. Lim TW, & Noorainie AA. Wood for the Trees: a review of the agarwood (gaharu) trade in Malaysia. TRAFFIC Southeast Asia. Petaling Jaya, Selangor, Malaysia. 2010.
19. Mitra R, Orbell J, Muralitharan MS. Medicinal plants of Malaysia. Asia-Pacific Biotech News, 2007; 11(2): 105–110.
20. Vakati K, Rahman H, Eswaraiah MC, Dutta AM. Evaluation of hepatoprotective activity of ethanolic extract of Aquilaria agallocha leaves (EEAA) against CCl4 induced hepatic damage in rat. Scholars Journal of Applied Medical Sciences, 2013; 1(1): 9–12.
21. Ibrahim AH, Al-Rawi SS, Abdul Majid AMS, Ab. Rahman NN, Abo-Salah KM, & Ab Kadir MO. Separation and fractionation of Aquilaria malaccensis oil using supercritical fluid extraction and the cytotoxic properties of the extracted oil. Procedia Food Science, 2011; 1: 1953–1959.
22. Zulkifle NL, Mohd Omar NA, Tajudin SN, & Shaari MR. Antidiabetic activities of Malaysian agarwood (Aquilaria Sp.) leaves extract. In Conference on Industry- Academia Joint Initiatives in Biotechnology. 2013.
23. Dahham SS, Tabana YM, Iqbal MA, Ahamed MBK, Ezzat MO, Majid ASA., & Majid AMSA. The anticancer, antioxidant and antimicrobial properties of the sesquiterpene β-caryophyllene from the essential oil of Aquilaria crassna. Molecules, 2015; 20: 11808–11829.
24. Kamonwannasit S, Nantapong N, Kumkrai P, Luecha P, Kupittayanant S, & Chudapongse N. Antibacterial activity of Aquilaria crassna leaf extract against Staphylococcus epidermidis by disruption of cell wall. Annals of Clinical Microbiology and Antimicrobials, 2013; 12(20): 1–7.
25. Zaridah MZ, Nor Azah, MA, & Rohani A. Mosquitocidal activities of Malaysian plants. Journal of Tropical Forest Science 2006; 18(1): 74–80.
26. Redzuan NR, Suzanah AR, Asmah HH, Roszaman R, Muhammad LM, Hussin M, Nik FH. Evaluation of acute and sub-acute oral toxicity of the aqueous extract of Aquilaria malaccensis leaves in Sprague Dawley rats. AsPac J. Mol. Biol. Biotechnol, 2018; 27(1): 20-32
27. Adamson RH. The acute lethal dose 50 (LD50) of caffeine in albino rats. Regulatory Toxicology and Pharmacology, 2016; 80: 274– 276.
28. Schlede E, Genschow E, Spielmann H, Stropp G, & Kayser D. Oral acute toxic class method: A successful alternative to the oral LD 50 test. Regulatory Toxicology and Pharmacology, 2005; 42: 15–23.
29. Organisation for Economic Co-operation and Development. 2001b. Test No. 420: Acute Oral Toxicity - Fixed Dose Procedure, 420: 1–14.
30. Rizky Y, Santi P, Barmi H, Lia A, Lili A, Lesra I, Lara S, Suci R, Nadia M. Acute Toxicity LD50 Fraction Ethyl Acetate Aquilaria malaccensis, Ficus benjamina, Mikania micrantha, and Fraction Water Cinnamomum burmanii in Mus Musculus. Biology, Medicine, & Natural Product Chemistry, 2023; 12(1): 55-60
31. Pacheco AG, Machado de Oliveira P, Piló-Veloso D, Flávio de Carvalho Alcântara A. 13C-NMR data Of diterpenes isolated from Aristolochia species. Molecules, 2009; 14:1245–62.
32. Latha S, Selvamani P, Dhivya PS, Benaseer BR. A review on pharmacological activities of Aristolochia species. European journal of biomedical and pharmaceutical sciences, 2015; 2(5): 160-167.
33. Merouani N, Belhattab R. Acute toxicity of Aristolochia longa L. of aqueous extract in mice. Journal of Drug Delivery & Therapeutics. 2020; 10(3): 4-10.
34. Benaddi FZ, Ouahbi A, Bellahmar M and Said Chakir. The acute toxicity of the aqueous extract of aristolochia longa prepared by the traditional method. World Journal of Pharmaceutical and Life Science, 2020; 6(2): 29-33.
35. El Omari N, El Blidi O, Bouyahya A, Sayah K, Bakrim S, Fettach S, Tahri R, Taghzouti K, Chokairi O, and Barkiyou M. Toxicological Investigations of Aristolochia longa Root Extracts. Journal of Toxicology, 2020; 10(11): 1-11.
36. Biswal B, Kimberly FM, Dwaye D, Anand Y. Antimicrobial activity of leaf extracts of Guava (Psidium guajava) on two Gram positive and two Gram negative bacteria. International Journal of Microbiology, 2013; 2: 7.
37. Morton JF. Fruits of warm climates, 2004; 425-428.
38. Gbile ZO. Vernacular names of Nigerian plants; Yoruba forestry research institute of Nigeria Ibadan in: Okujagu TF. (2005). Book of Abstract of Published Research finding on Nigerian Medicinal plants, 1984.
39. Okujagu TF, Etatuvie Sam O, Ifeyinwa E, Jimoh B, Nwokeke. Book of Abstract of Published Research finding on Nigerian Medicinal Plants and Traditional Medicine Practice, 2005; 1: 90.
40. Kumar M. A study of antibacterial activity of Psidium guajava Linn fruit extracts against Gram-positive and Gram- negative bacteria. International Journal of Institutional Pharmacy and Life Sciences, 2015; 5(2): 231-239.
41. Igwe JO, Abone HO, Ezea MC, Ejikeugwu CM and Esimone CO. Acute and chronic toxicity evaluation of methanol leaf extract of Psidium guajava (Myrtaceae). GSC Biological and Pharmaceutical Sciences, 2021; 16(03): 120–128.
42. Yamssi C, Payne VK, Noumedem ACN, Tateng Ngouateu A, Megwi L and Kuiate JR. Acute Toxicity of Pentaclethra macrophylla and Psidium guajava Use as Antiprotozoan Medicinal Plants. J Drug Discov Develop and Deliv, 2020; 6(1): 01-05.

43. Johns T, Windust A, Jurgens T, Mansor SM. Antimalarial Alkaloids isolated from Annona squamosa, phytopharmacology, 2011; 1(3): 49-53.
44. Mohammad S, Thattakudia SU, Ramkath S, Azagusundharam M, Gnanaprakash K, Angala PS. Protective effect of methanolic extract of Annona squamosa Linn. in Isoniazid –rifampicin induced hepatotoxicity in rats, Pak. J. Pharm. Sci, 2011; 2: 129-134.
45. Saleh J, Olowoniyi F, Emmanuel E, Abdullateef A, Bolanle MK, Acute Toxicity Assessment of the methanolic leaf extract of Annona squamosa Bark in Male Albino Rats. J Phytopharmacol, 2021; 10(3): 151-155.
46. Utami AD, Khairunnisa, Marianne. Study on Acute Oral Toxicity of Ethanolic Extract of Annona squamosa Leaves in Mice (Mus musculus). Indonesian Journal of Pharmaceutical and Clinical Research, 2028; 01(01): 56 – 63.
47. Carew DP, Chin TF. Constituents of Lagerstroemia Flos-reginae Retz. Nature 1961; 190: 1108–1109.
48. Thakur RS, Devaraj E. Lagerstroemia speciosa (L.) Pers. triggers oxidative stress mediated apoptosis via intrinsic mitochondrial pathway in HepG2 cells. Environ. Toxicol, 2020; 35: 1225–1233.
49. Singh TR, Ezhilarasan D. Lagerstroemia speciosa (L.) Pers. ethanolic leaves extract attenuates leaves extract attenuates dapsone-induced liver inflammation in rats. Drug Chem. Toxicol, 2021; 1–10.
50. Alkahtani S, Hasnain M, Algamdy H, Aljarba HN, AlKahtane A. Acute and sub-acute oral toxicity Lagerstroemia speciosa in Sprague-Dawley rats. Saudi Journal of Biological Sciences, 2022; 29: 1585–1591.
51. Clemente M, Miguel M.D, Felipe KB, Gribner C, Moura PF, Rigoni AGR, Fernandes LC, Carvalho JLS, Hartmann I, Piltz MT. Acute and sub-acute oral toxicity studies of standardized extract of Nasturtium officinale in Wistar rats. Regul. Toxicol. Pharmacol, 2019; 108: 104443.
52. Kunimatsu T, Yamada T, Miyata K, Yabushita S, Seki T, Okuno Y, Matsuo M. Evaluation for reliability and feasibility of the draft protocol for the enhanced rat 28-day subacute study (OECD Guideline 407) using androgen antagonist flutamide. Toxicology, 2004; 200: 77–89.
53. Park SJ, Lim KH, Noh JH, Jeong EJ, Kim YS, Han BC, Lee SH, Moon KS. 2013. Subacute oral toxicity study of Korean red ginseng extract in Sprague-Dawley rats. Toxicol. Res, 2013; 29: 285–292.
54. Kpemissi M, Eklu-Gadegbeku K, Veerapur VP, Potârniche AV, Adi K, Vijayakumar S, Banakar SM, Thimmaiah N, Metowogo K, Aklikokou K, Antioxidant and nephroprotection activities of Combretum micranthum: a phytochemical, in-vitro and ex-vivo studies, Heliyon, 2019; 5(3): 1365.
55. Romanucci V, Agarwal C, Agarwal R, Pannecouque C, Iuliano M, De Tommaso G, Caruso T, Di Fabio G, Zarrelli A, Silibinin phosphodiester glyco-conjugates: synthesis, redox behaviour and biological investigations, Bioorg. Chem, 2018; 77: 349–359.
56. Kpemissi M, Metowogo K, Melila M, Veerapur VP, Negru M, Taulescu M, Potârniche AV, Suhas DS, Puneeth TA, Vijayakumar S, Eklu-Gadegbeku K, Aklikokou K. Acute and subchronic oral toxicity assessments of Combretum micranthum (Combretaceae) in Wistar rats Toxicology Reports, 2020; 7: 162–168.
57. Mohammed OA, Soliu AA, Quadri AO, Eniola OO, Akeem IO. Assessment of anxiolytic potential and acute toxicity study of Combretum micranthum G. Don. leaves (Combretaceae) Journal of Medicinal Plants for Economic Development, 2020; 4(1): 97.
58. Auwalu M, Lawan JA and Muhammed SS. Toxicological Studies of the Aqueous Leaves Extracts of Combretum micranthum on Rats. International Journal of Biotechnology and Biochemistry, 2016; 12(2): 167-171.
59. Lorke D. A new Approach to Practical Acute Toxicity Testing. Archives of Toxicology Journal, 1983; 54: 275 – 287.
60. Salleh N, Ahmad VN. In vitro effect of Ficus deltoidea on the contraction of isolated rat's uteri is mediated via multiple receptors binding and is dependent on extracellular calcium. BMC Complement Altern Med, 2013; 13: 359.
61. Mustaffa NA, Hasham R, Sarmidi MR. An in vitro study of wound healing activity of Ficus deltoidea Leaf extract. J Teknol, 2015; 77(3): 1-6.
62. Asis J, Yusoff N, Nashriyah M. Allelopathic assesments of Ficus deltoidea jack varieties and Ficus microcarpa L.f. (Moraceae) on Lactuca sativa L. Seed. J Agrobiotechnol, 2018; 9(15): 214-21.
63. Isa MN, Ajit A, Naila A, Sulaiman A. Effect of Microwave Assisted Hydro distillation Extraction on Extracts of Ficus deltoidea Materials Today, 2028; 5: 21772-9.
64. Bodeker G, Shekar S. Health and Beauty from the Rainforest: Malaysian Traditions of Ramuan. USA: Didier Millet, Csi; 2009.
65. Nugroho RA, Aryani R, Manurung H, Rudianto R, Prahastika W, Juwita A, Alfarisi AK, Pusparini AOP, Lalong A. Acute and Subchronic Toxicity Study of the Ethanol Extracts from Ficus deltoidea Leaves in Male Mice. Macedonian Journal of Medical Sciences, 2020; 8(1): 76-83.
66. Farsi E, Shafaei A, Hor SY, Ahamed MB, Yam MF, Asmawi MZ, Ismail Z. Genotoxicity and acute and subchronic toxicity studies of a standardized methanolic extract of Ficus deltoidea leaves. Clinics (Sao Paulo), 2013; 68(6): 865-75.
67. Sanae A, Naima R, Asmae K, Hayat L, Abdelrhan M, Abdelmajid S, Alain T, Rachida SB. Peganum harmala L. Poisoning in Morocco: about 200 Cases, 2012; 67(1): 53–58.

68. El Bahri L, Chemli R. Peganum harmala L: a poisonous plant of North Africa. Vet Hum Toxicol, 1991; 33: 276–277.
69. Lamchouri F, Settaf A, Cherrah Y, Zemzami M, Lyoussi B, Zaid A, Atif N, Hassar M. Antitumor principles from Peganum harmala L. seeds. Therapie, 1999; 54(6): 753–8.
70. Wang C, Zhang Z, Wang Y, He X. Cytotoxic constituents and mechanism from Peganum harmala L. Chem Biodivers, 2016; 13(7): 199–212.
71. Trevan. The Error of Determination of Toxicity. 1927; 484.
72. Karber C, Brehrens B. Wie sind Reihenversuche furbiologische Auswertungen am Zweckmässigsten Anzuordnen Arch. Exp. Path. Pharm, 1938; 177: 379-388.
73. Bliss CI. The determination of the dosage mortality curve from small numbers. Quart Pharm, 1938; 192-216.
74. Horn HJ. Simplified LD50 (or ED50) calculations. Biometrics, 1956; 12: 31l-322.
75. Rezzagui A. Evaluation de l'effet toxique de l'extrait brut et de l'activité antioxydante des différents extraits des graines de Peganum harmala L, 2012; 49(22): 84–86.
76. Lamchouri, F, Settaf, A, Cherrah, Y, El Hamidi, M., Tligui, N. S, Lyoussi, B, & Hassar, M. Experimental toxicity of Peganum harmala seeds. Annales Pharmaceutiques Françaises, 2002; 60(2): 123–9.
77. Marua H, AL-Hammoshi. Effects of Crude Alkaloids Isolated from Peganum harmala Seeds on the Growth and Metabolism of Leishmania tropica Promastigotes, 2010; 22(1): 17- 32.
78. Muhi-eldeen Z, Al-Shamma KJ, Al- Hussainy TM, Al- Kaissi EN, Al-Daraji AM, Ibrahim H. Acute Toxicological Studies on the Extract of Iraqi Peganum Harmala in Rats, 2008; 22: 494-500.
79. Zahra BF, Abdelilah O, Bellahmar M and Chakir S. the acute toxicity of the aqueous extract of peganum harmala « morocco » prepared by the traditional method World Journal of Pharmaceutical, 2019; 5(3): 15-19.
80. Ishibashi FC, Satasook MB, Isman GH, Neil T. Insecticidal 1H-Cyclopentatetrahydro Benzofurans from Aglaia odorata, Phytochemistry, 1993; 32: 307-31.
81. Aliu YO, Nwude N. Veterinary Pharmacology and Toxicology Experiments. A.B.U. Press, Zaria, 1982: 104-110.
82. WHO. Epidemiology and control of African trypanosomiasis. Report of a WHO Expert Committee. Technical Report Series No. 739, Geneva, 1986.
83. Clarke EGC, Clarke M. Veterinary Toxicology. E.L.B.S./Baillière Tindall, London, 1975: 268.
84. Mwaurah P, Kumar S, Kumar N. Physicochemical characteristics, bioactive compounds and industrial applications of mango kernel and its products: A review. Compr Rev Food Sci Food Saf, 2020; 19(2): 1-26.
85. Awad El-Gied AA, Joseph MRP, Mahmoud IM, Abdelkareem AM, Al Hakami A, Hamid M. Antimicrobial Activities of Seed Extracts of Mango (Mangifera indica L.). Adv Microbiol, 2012; 2: 571-576.
86. Torres-Leon C, Rojas R, Contreras-Esquivel JC, Serna-Cock L, Belmares-Cerda R, Aguilar CN. Mango seed: functional and nutritional properties. Trends Food Sci and Technol, 2016; 55: 109-117.
87. Irinmwinuwa EO, Mbah CA, Ibeabuchi KC, Godwin OB. Evidence based medicinal plant possessing anti-diarrhea activity: A review. National Journal of Advanced Research, 2023; 9(1): 1-6.
88. Abdel-Aty AM, Salama WH, Hamed MB, Fahmy AS, Mohamed SA. Phenolic-antioxidant capacity of mango seed kernels: Therapeutic effect against viper venoms. Rev Bras Farmacogn, 2018; 28: 594-601.
89. Nwachukwu KC, Ibe C, Nwachukwu NC, Ugbogu OC. Hematological, biochemical and histopathological assessment of the toxicity potential of seed kernel extracts of Mangifera indica Linn. varieties in mice. Discovery, 2022; 58(322): 1117-1127.
90. Organization for Economic Co-operation and Development (OECD). Guidelines for Testing of Chemical, Guideline 423. Acute Oral Toxicity-Acute Toxic Class Method (Paris). 2001.
91. Organization for Economic Co-operation and Development (OECD). Test No. 407: repeated dose 28-day oral toxicity study in rodents, 2008.
92. Prado Y, Merino N, Acosta J, Herrera JA, Luque Y, Hernández I, Prado E, Garrido G, Delgado R, Rodeiro I. Acute and 28-day subchronic toxicity studies of mangiferin, a glucosyl xanthone isolated from Mangifera indica L. Stem bark Journal of Pharmacy & Pharmacognosy Research, 2015; 3(1): 13-23.
93. Buhari TR and Muhammad A. Phytochemical screening, heavy metals evaluation and acute toxicity studies of Azadirachta indica and Mangifera indica methanol leaves extract. Bayero Journal of Pure and Applied Sciences, 2022; 13(1): 97 – 101.
94. Anywar G, Kakudidi E, Byamukama R, Mukonzo J, Schubert A, and Oryem- Origa H. (2020a). Indigenous traditional knowledge of medicinal plants used by herbalists in treating opportunistic infections among people living with HIV/ AIDS in Uganda. J. Ethnopharmacol, 2020a; 246: 112-205.
95. Mwitari PG, Ayeka PA, Ondicho J, Matu EN, and Bii CC. (2013). Antimicrobial activity and probable mechanisms of action of medicinal plants of Kenya: Withania somnifera, Warbugia ugandensis, Prunus africana and Plectrunthus barbatus. PLoS One, 2013; 8(6): 65619.

96. Maroyi A. The genus Warburgia: a review of its traditional uses and pharmacology. Pharm Biol, 2014; 52(3): 378-91.
97. Anywar, G. Ethnopharmacology, cytotoxicity, antiviral and immunomodulatory profiles of medicinal plant species used by herbalists in treating people living with HIV/AIDS in Uganda. PhD thesis. 2020. Uganda: Makerere University
98. Olila D, Opuda-Asibo J, and Olwa O. Bioassay-guided studies on the cytotoxic and in vitro trypanocidal activities of a sesquiterpene (Muzigadial) derived from a Ugandan medicinal plant (Warburgia ugandensis). Afr. Heal Sci, 2001; 1(1): 12–(15.)
99. Karani LW, Tolo FM, Karanja SM, and Khayeka−Wandabwa C. Safety of Prunus Africana and Warburgia ugandensis in asthma treatment. South Afr. J Bot, 2013; 88: 183–190.
100. Khan F, Sani MA, Olorunkooba AM, Danraka SN, Magaji MG, Abdu-Aguye I, Hussaini IM. A safety profile of aqueous methanol aerial extract of Alysicarpus glumaceus in mice: acute and subacute administration. Journal of Current Biomedical Research, 2022; 2: 224-243
101. Bawa B, Pateh UU, Hassan HS & Yaro AH. Phytochemical and Central Nervous System Activity Study of Alysicarpus glumaceaus. Biotropic Research International Journal, 2012; 3(1): 20–24.
102. Sudipta R, Rabinarayan A. A Review on Therapeutic Utilities and Purificatory Procedure of Gunja (Abrus Precatorius Linn.) as Described In Ayurveda Journal of Ayush : Ayurveda, Yoga, Unani, Siddha and Homeopathy, 2013; 2(1): 1-11.
103. Ogbuehi IH, Omotayo OE and Atuboyedia WO. Oral acute toxicity (LD50) study of different solvent extracts of Abrus precatorius Linn leaves in wistar rats. European Journal of Experimental Biology, 2015; 5(1): 18-25
104. Saganuwan S, Onyeyili PA, Suleiman AO, Herba Polonica. Comparative toxicological effects of orally and intraperitoneally administered aqueous extracts of Abrus precatorius leaf in Mus musculus, 2011; 57(3): 33-44.
105. Adams K, Eliot T, Gerald A. Extent of use of Aloe vera locally extracted products for Management of Ailments in comunities of Kitagata subcounty in Sheema District, Western Uganda. Intern J Sci Basic Appl Res, 2014; 15(1): 1.
106. Kumar S, Yadav JP. Ethnobotanical and pharmacological properties of Aloe vera: a review. J Med Plant Res. 2014; 8(48): 1387–98.
107. Gumisiriza H, Birungi G, Olet EA, Sesaazi CD. Medicinal plant species used by local communities around Queen Elizabeth National Park, maramagambo central forest reserve, and ihimbo central forest reserve, Southwestern Uganda. J Ethnopharmacol, 2019; 239: 111926.
108. Tugume P, Kakudidi EK, Buyinza M, Namaalwa J, Kamatenesi M, Mucun- guzi P, Ethnobotanical survey of medicinal plant species used by communities around Mabira central Forest reserve, Uganda. J Ethnobiol Ethnomed, 2016; 12(1): 1–28.
109. Anywar G, Kakudidi E, Byamukama R, Mukonzo J, Schubert A, Oryem- Origa H. Indigenous traditional knowledge of medicinal plants used by herbalists in treating opportunistic infections among people living with HIV/AIDS in Uganda. J Ethnopharmacol, 2020; 246: 112-205.
110. Nalimu F, Oloro J, Peter EL, and Ogwang PE. Acute and sub-acute oral toxicity of aqueous whole leaf and green rind extracts of Aloe vera in Wistar rats. BMC Complementary Medicine and Therapies, 2022; 22(16): 2-15.
111. Dhar ML, Dhar MM, Dhawan BN, Mehrotra BN, Ray C. Screening of Indian plants for biological activity: Indian J Exp Biol, 1968; 6: 232–247.
112. Orwa C, Mutua A, Kindt R, Jamnadass R, Anthony S. Tephrosia vogelii Hook.f. Fabaceae - Papilionoideae. Agroforestry Database. 2009; http: //apps. world agro forestry. org / treedb /AFTPDFS / Tephrosia vogelii.
113. Makoshi M, Arowolo ROA. Therapeutic effects of Tephrosia vogelii ointment in the treatment of bovine dermatophilosis. J Vet Med Anim Health, 2011; 3: 51–5.
114. Gadzirayi CT, Mutandwa E, Mwale M, Chindundu T. Utilization of Tephrosia vogelii in controlling ticks in dairy cows by small-scale commercial farmers in Zimbabwe. African J Biotechnol, 2009; 8: 4134–6.
115. Li W, Huang C, Wang K, Fu J, Cheng D, Zhang Z. Laboratory evaluation of aqueous leaf extract of Tephrosia vogelii against larvae of Aedes albopictus (Diptera: Culicidae) and non-target aquatic organisms. Acta Trop, 2015; 146: 36–41.
116. Russell DA, Freudenreich JJ, Ciardiello JJ, Sore HF, Spring DR. Stereocontrolled semi-syntheses of deguelin and tephrosin. Org Biomol Chem, 2017; 15: 1593–6.
117. Dzenda T, Ayo JA, Adelaiye AB, Adaudi AO. Ethnomedical and veterinary uses of Tephrosia vogelii hook. F: a review. Niger Vet J, 2008; 28: 24–39.
118. Inalegwu B, Sodipo OA. Antimicrobial and foam forming activities of extracts and purified saponins of leaves of Tephrosia vogelii. Eur J Exp Biol, 2015; 5: 49–53.
119. Mwaura L, Stevenson PC, Ofori DA, Anjarwalla P, Jamnadass R, Smith P. Pesticidal Plant Leaflet: Tephrosia vogelii Hook. f: World Agro forestry Centre; 2013. http: // apps. world agro forestry. org /downloads /Publications/PDFS/ LE13137.pdf.
120. Stevenson PC, Belmain SR. Tephrosia vogelii: a pesticide of the future for African farming. Boletín SEEA, 2017; 2: 19–22.
121. Kalume MK, Losson B, Angenot L, Tits M, Wauters JN, Frederich M. Rotenoid content and in vitro acaricidal activity of Tephrosia vogelii leaf

extract on the tick Rhipicephalus appendiculatus. Vet Parasitol, 2012; 190: 204–9.

122. 122. Nanthini K, Kanakavalli K, Kaliyamurthy V. Acute and sub acute toxicity study on siddha drug Mandoora Chooranam. Int J Pharm Biol Arch, 2014; 5: 86–91.
123. 123. Olaniyan JM, Muhammad HL, Makun HA, Busari MB, Abdullah AS. Acute and sub acute toxicity studies of aqueous and methanol extracts of Nelsonia campestris in rats. J Acute Dis, 2016; 5: 62–70.
124. Mlozi SH, Juma A. Mmongoyo and Chacha M. The in vivo toxicity evaluation of leaf and root methanolic extracts of Tephrosia vogelii Hook.f using animal model. Clinical Phytoscience, 2020; 6: 73.
125. Dzenda T, Ayo JO, Adelaiye AB, Adaudi AO, and Ibrahim NDG. Preliminary investigation into the acute oral toxicity of leave in mice. Nigerian Journal of vertinary journal, 2007; 28(2): 4