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Systematic Review

Poisoning by Medical Plants

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Abstract

Background: Herbal medications are becoming increasingly popular with the impression that they cause fewer side effects in comparison with synthetic drugs; however, they may considerably contribute to acute or chronic poisoning incidents. Poison centers receive more than 100 000 patients exposed to toxic plants. Most of these cases are inconsiderable toxicities involving pediatric ingestions of medicinal plants in low quantity.

In most cases of serious poisonings, patients are adults who have either mistakenly consumed a poisonous plant as edible or ingested the plant regarding to its medicinal properties for therapy or toxic properties for illegal aims.

Methods: In this article, we review the main human toxic plants causing mortality or the ones which account for emergency medical visits. Articles addressing "plant poisoning" in online databases were listed in order to establish the already reported human toxic cases.

Results: The current review introduces herbal plants toxicity and herb-drug interactions to warn the health professionals about possible consequences of unconscious uses of medicinal plants. The reported cases extracted from our prepared database were classified on the basis of the main toxic effects of plants, and the most prominent constituents of the plants which are responsible for specific toxic effects.

Conclusion: Considering the long history of consumption of herbal medicines in different societies, people may wrongly think that medicinal plants are fully harmless and nontoxic. Prescription, preparation and consumption regulations of medicinal plants are not clear and strict as well as their marketing regulations that differ from country to country. The extensive and various consumption of medicinal plants without adequate observation is the most important reason for poisoning by medicinal plants.

Keywords: Medicinal plants, Poisoning, Review, Safety, Toxicity, Traditional medicine

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Introduction

The World Health Organization (WHO) has introduced traditional medicine as therapeutic remedies used historically in different societies. Chinese, Roman, Greek, Egyptian, Indian, and Syrian texts comprise the documents that indicate therapeutic remedies have been used for about 5000 years.[1,2] Even now, most of the world population, especially rural people, use herbal medicine for their common ailments due to the lack of financial resources and poor health facilities.[3]

Herbal products involve raw or processed composition of organic compounds biosynthesized by one or more different parts of plants e.g. flowers, leaves, stems, seeds, and roots and made from renewable resources of raw materials by eco-friendly prosedures.[4] These compounds are parts of physiological functions of living flora and considered to be compatible with human body.[5,6]

Herbal medicines are considered safe because they are "natural". However, studies have shown that they are not all safe for direct human use, especially in pediatric patients.[7] Findings have demonstrated that although herbal and traditional medicines may cause fewer side effects in comparison with synthetic drugs, they may considerably contribute to acute poisoning incidents in children even with fatal outcomes. There are several reports on side effects of medicinal plants including their contaminants and herb–drug interactions[8]. Studies demonstrated that continuous use of some of them may have a strong toxic effect which can be associated with respiratory failure, chronic liver injury and in some cases, liver failure.[9]

Toxicological studies of medicinal herbs in animal models have shown that some of these plants that are typically used to treat chronic eczema and other skin diseases may cause life-threatening symptoms such as

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bradycardia, respiratory and central nervous system (CNS) depression as well as nephrotoxicity and hepatotoxicity.[10,11]

There are several cases of nephropathy with the use of specific Chinese medicinal plants.[12] For example, *Aristolochia fangchi*, a Chinese herbal medicine used for weight loss, caused nephropathy and morbid cases.[13] Another common toxic effect of herbal medicines is hepatotoxicity caused by the use of PAs content of certain plants through a characteristic veno-occlusive disease that may rapidly progress and be fatal.[14]

On the other hand, since the toxicological information and antidote therapy of some medicinal herbs are not available, plant toxicity deserves greater attention. Therefore, there are great concerns about the toxicological impact of medicinal plants in humans, particularly in sensitive periods. In this study, we aim to review the toxicological impact of medicinal plants that have been investigated. In addition, we aim to introduce the herbal plants that have been reported as being poisonous to warn the health professionals of the consequences of unconscious use of herbal medicine.

Literature Search Methodology

In this review, "plant poisoning" was searched in online databases including PubMed, Cochrane library and Scopus since the year 2000 (up to October 2018). Screening of the primary 1825 resulting articles was performed to collect articles reporting toxic effects of plants. The 45 duplicate articles were excluded and 1673 articles, including phytochemical abuses, suicidal use of toxic plants, analysis of phytochemicals in plants, *in vitro* studies, plant poisoning in animals, poisoning by pesticides, herbicides and heavy metal contaminations of medicinal plants and vegetables, and treatments of toxicity with medicinal plants were omitted. From the 107 remaining, 10 non-English articles were excluded and 97 English articles were classified based on the toxic effects of plants: 8 articles based on anticholinergic effects, as well as 14 on cardiac, 7 on gastrointestinal, 5 on hepatic, 3 on renal, and 5 on respiratory toxicity. Also, 37 articles, which did not specifically address a particular effect, and 18 review articles were explored to determine the toxic effect of reported plants in different organs. The flow diagram of the literature exploration and selection and classification of search results is shown in Figure 1.

Hepatotoxicity of Medicinal Plants

The liver is the most important organ in the process of metabolizing drug and food through different reactions mainly including oxidase, reductase, and hydrolase mechanisms, transforming the lipophilic chemicals to water-soluble compounds to be excreted from the body.[15] Medicinal plants may cause hepatocellular or cholestatic injury or both.[16] *Cassia occidentalis* seeds are used in composition of some medicinal plants; in two cases, poisoning of four siblings were reported for acute hepatic failure coinciding with muscular and encephalopathic damages after ingestion of the plant seeds.[17,18] Different anthraquinones in *C. occidentalis* could be responsible for plant poisoning.[18]

Xanthium strumarium is used for treatment of various problems, mostly related to the skin.[19] Ingestion of *X. strumarium* seeds caused fatigue, nausea, and vomiting in four siblings. The intensity of symptoms was related to the amount of consumed seeds and in one of the cases, liver transplantation was performed due to the massive hepatic necrosis and liver failure after *X. strumarium* ingestion. The plant contains carboxyatractyloside which is known as a potent toxic glycoside.[20]

Illicium verum is a medicinal plant used for preparation of a homemade remedy for infantile colic.[21] Microscopic characteristics of *Illicium verum* fruits are similar to *Illicium anisatum* fruits; both plants contain anethole that possesses hepatotoxicity effects but *I. anisatum* contains high amounts of anisatines which are known as lethal toxicants. It seems that the hepatotoxicity of herbal drugs prepared from *I. verum* is related to the contamination of these drugs with *I. anisatum* that could cause hepatic toxicity.[22]

Gynura segetum has been reported to be used mistakenly instead of *Sedum aizoon* for preparation of a traditional Chinese medicine which caused liver injury in a patient. The pyrrolizidine alkaloids (PAs) content of *the G. segetum* was responsible for the hepatotoxicity of traditional Chinese medicine and the absence of PAs in *S. aizoon* along with more evidences of the plants containing PAs implies the correlation between plant PAs content with liver failure.[23]

Gastrointestinal Poisoning

Gastrointestinal symptoms are very common in a variety of toxicities because ingestion is a very usual form of medicinal plant consumption. They may occur individually or simultaneously with toxicities in the other organs. Vomiting, abdominal pain, and diarrhea are considered as symptoms of gastrointestinal toxicity.

In a case of abuse toxicity, as a result of *Abrus precatorius* seed consumption which is known as an aphrodisiac in Indian folk medicine, the patient was reported to be febrile and comatose, with depressed reflexes and down-going plantars, bloody diarrhea, mild proteinuria and occasional RBC in urine. The seeds of the plant have a hard outer shell that resists digestion and is harmless. Chewing seeds before swallowing causes the release of arbin. The structure of arbin is similar to important gastrointestinal toxins such as botulinum, tetanus, cholera, diphtheria, and insulin.[24] Arbin contains two polypeptide chains A and B: chain B helps the compound to penetrate the cells and chain A causes cell death by inactivation of protein synthesis through affecting ribosomes.[25]

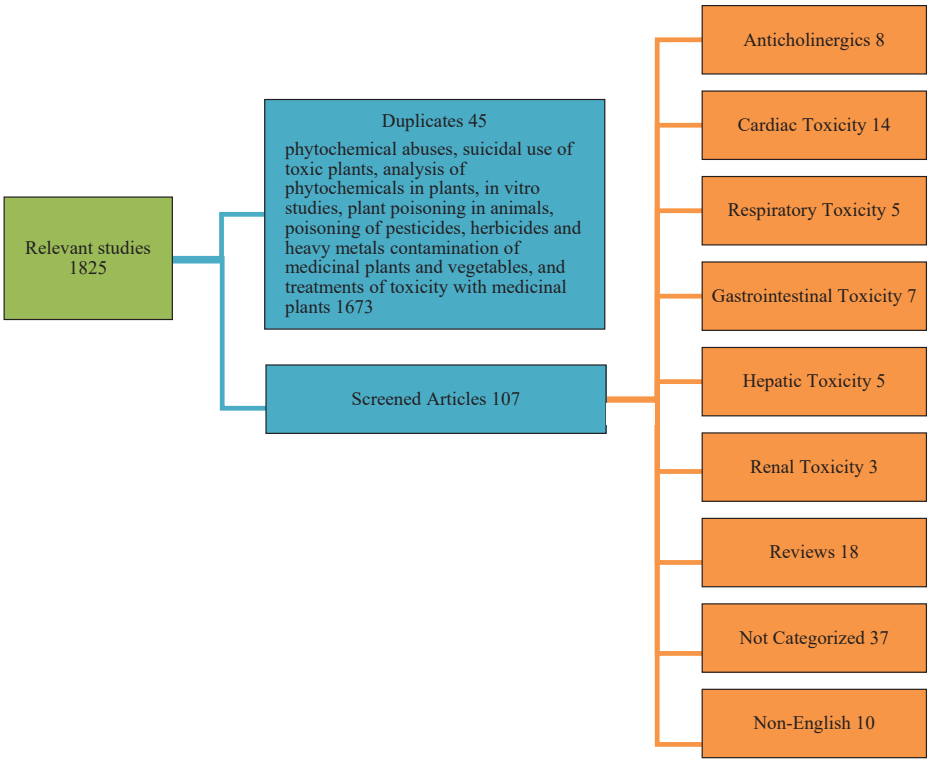

Figure 1. Flow Diagram of the Literature Exploration, Selection, and Classification. "Plant poisoning" was searched in online databases including PubMed, Cochrane library, and Scopus since the year 2000 (up to October 2018).

Colchicum autumnale was formerly used as a medicinal plant but the alkaloids extracted from the plant, mainly colchicine, have therapeutic applications in acute gouty arthritis, familial Mediterranean fever and amyloidosis.[26] Overdose of colchicine by ingestion of the plant causes severe toxic effects and even leads to death in a few cases.[27-30]

Vomiting, diarrhea, thirst, hematuria, decrease in body temperature, different organ failure and death are possible symptoms in case of colchicine poisoning. The colchicine toxicity mechanism is related to its ability in binding to tubulin and arresting cells in metaphase which causes interruption of cell functions as a result.[31]

Jatropha curcas was applied in traditional medicine for treatment of malaria and edema[32] and recently, it is used as bio-diesel fuel.[33] *Jatropha curcas* contains compounds such as curcin that is a toxalbumin, curcanoleic acid and diterpenoids. These compounds in *J. curcas* seeds are known to be responsible for gastrointestinal poisoning with vomiting, nausea and abdominal pain symptoms.[34, 35] The purgative oil of *Jatropha multifidi* was used to treat parasitic infestation, rheumatic condition, and as an abortifacient in traditional medicine in West Africa. But this plant is cultivated as a garden plant in different regions and a case of poisoning of four siblings has been reported after *J. multifidi* fruit ingestion in West Asia. *J. multifidi* contains toxicants similar to *J. curcas* and the same gastrointestinal symptoms have been reported with it.[36]

Rhododendron simsii is known as an antitussive medicinal plant in traditional medicine.[37] In one case, it was prescribed by a physician for treatment of acute bronchiolitis in a 57-day-old infant. Gastrointestinal poisoning symptoms, including nausea, vomiting, muscarinic effect, and seizure were reported after *R. simsii* powder ingestion.[38] Grayanotoxin I, the main toxicant in *R. simsii*, attaches to sodium channels of cell membranes, inhibits their inactivation, and causes depolarization of cells. In this situation, calcium entry to the cells is accelerated and it could even lead to adverse effects on the cardiovascular system.[39]

Nephrotoxicity

Nephrotoxicity is prominent among the toxic effects of traditionally used herbal extracts.[40,41] The occurrence of nephrotoxicity may be due to the following reasons: (a) consumption of herb with uncharacterized toxicity; (b) incorrect identification of a herb with a toxic nature; (c) deliberate contamination of herbal product with nephrotoxic non-herbal preparations or chemicals; (d) increased toxicity of conventional drug by interacting with other herbal preparations; or (e) interaction of herbal drug with any other drug causing adverse effects. Nephrons are the functional unit of the kidney in which urine is formed by filtering the blood. They are involved in the removal of waste products and toxic substances in the body. Small ions and water molecules as well as other small molecules

are reabsorbed back to the peritubular capillaries by reabsorption. The remaining waste molecules and ions are eliminated through the urine.

Most of the herbal drugs found to cause nephrotoxicity act through different common pathogenic mechanisms. The mechanisms can be summarized as an alteration in intraglomerular hemodynamics, toxicity of tubular cell, thrombotic microangiopathy, crystal nephropathy, inflammation, rhabdomyolysis, etc. Therefore, understanding of herbal nephrotoxins and their mechanisms in renal damage will be useful in assessment and prevention of herbal drug-induced renal injuries. The renal injuries induced by herbal preparations can be categorized into four major types, including (i) direct or immune-mediated nephrotoxicity, (ii) nephrolithiasis, (iii) rhabdomyolysis, and (iv) hepatorenal syndrome.[42] Acute renal failure caused by nephrotoxic damages can lead to loss of kidney function immediately or persistently and death, if the patients does not receive appropriate therapy.

Various *Aristolochia* species are being utilized for preparation of herbal medicines worldwide for treatment of gout, arthritis, rheumatism, and chronic inflammatory skin diseases. Aristolochic acid, the major compound in *Aristolochia* species, is nephrotoxic as well as carcinogenic and is responsible for nephrotoxicity.[43] Interstitial nephropathy was reported after consumption of weight loss Chinese herbs mixture which were contaminated with seeds of *Aristolochia* species.[44] Exposure to aristolochic acid may lead to urothelial malignancies, and if aristolochic acid consumption increases to more than 200 g, the risk of urothelial malignancies will rise significantly.[45]

Djenkol bean is an edible fruit of *Pithecellobium lobatum* also known as Jering trees. Jering (djenkol) beans are relished as food in Java and Sumatra and are eaten raw, fried, roasted or in sprouting state. The ingestion of Jerring beans is associated with development of acute renal failure but the pathogenesis of acute renal failure following Jerring beans ingestion is yet to be established. Crystals of djenkol acid could be responsible for the obstruction of ureters, urethra and renal tubules.[46]

The impila is derived from *Callilepis laureola* tuberous roots. *C. laureola* is traditionally used by the inhabitant of specific regions in South Africa for treatment of different ailments like stomach problems, impotence, tape worm infestations, cough, blood purification, inducing fertility and for sexually transmitted diseases. Both hepatic and renal toxicity have been reported in impila which are found to be very sudden in onset. The symptoms of intoxication are marked by pain in the abdomen, vomiting, diarrhea, disturbed level of consciousness, convulsions, severe hypoglycemia, metabolic acidosis, etc.[47]

Cat's claw or *Uncaria tomentosa* is an herbal medicine that is widely used to treat many disorders in the digestive system, inflammation of the large intestine and lower bowel, gastritis, peptic ulcer, leaky bowel syndrome, etc. Bioanalytical characterization of *U. tomentosa* has led to identification of a variant form of active constituents viz. flavonoids, oxindole and indole alkaloids, carbolines, sterols, glucosinolates, and polyunsaturated fatty acids which are of toxicological, pharmacological and even nutritional interest. The nephrotoxicity potential of Cat's claw has been studied by Hilepo et al when a patient was reported to develop systemic lupus erythematosus and urinary sediment abnormalities owing to renal dysfunction upon using cat's claw.[48]

Chaparral, also known as *Larrea tridentata,* is used for general cleansing, toning, arthritis treatment, nutritional supplementation, weight loss, and cancer treatment. Nordihydroguaiaretic acid, the major constituent of chaparral, is reported to cause cystic nephropathy and carcinoma.[49]

Salix daphnoides or Willow Bark is a plant species that belong to the family *Salicaceae*. The bark extracts of this plant are used for relief of pain, myalgias, osteoarthritis, dysmenorrheal, gout, rheumatoid arthritis, common cold, and influenza. The main component of *S. daphnoides* is salicin, which is metabolized to salicylic acid. *S. daphnoides* has been reported to cause renal papillary necrosis.[50]

Ephedra sinica or Ma Huang is used as an herbal drug for weight loss. It is also used in asthma, treatment of allergies, bronchospasm, etc. It contains ephedrine and pseudoephedrine alkaloid reported to induce CNS stimulation, bronchodilation, and vasoconstriction. However, there are reports of nephrolithiasis associated with exposure to ephedra.[51]

The root of *Securidaca longepedunculata*, also known as violet tree or wild wisteria, is reported to be effective in dysmenorrhea and venereal diseases and it is also used as an expectorant and abortifacient. The root is a well-known intravaginal suicidal poison. The root of this plant contains methyl salicylate which is a nephrotoxin and causes acute renal failure.[52] The roots were also reported to contain a toxic substance called securinine.[41]

Fenugreek (*Trigonella foenum-graecum*) seeds are commonly used for decreasing blood lipid level and blood sugar level in both diabetic and non-diabetic people. Zononi et al have reported acute interstitial nephritis in a 62-year-old diabetic patient who had no prior reported kidney disease. The presence of different flavonoids in fenugreek seeds may be responsible for inducing acute interstitial nephritis accompanied by autoimmune hemolytic anemia as earlier study has also shown flavonoid-induced nephropathy in other cases.[53]

Star fruit (*Averrhoa carambola*) also known as Carambola is consumed as a low caloric exotic fruit and an important source of antioxidants, and vitamins. The fruit is used in folk medicine and provides resistance against infectious agents; it is also used as diuretic and expectorant. Contrary to its therapeutic properties, star fruit and its juice are toxic and lethal to patients with chronic kidney disease treated

with or without dialysis.[54]

Dioscorea species are tuberous plants, which belong to the family *Dioscoreaceae*. They are widely used as a staple dietary component in Asia and Africa. The tubers are prepared by being washed in water followed by being soaked in salted water, boiled for hours and roasted or squeezed for their juice. However, poisoning has occurred due to taking tubers which have been prepared improperly. The ingestion of improperly prepared tuber juice of Yam results in acute kidney injury.[55]

Yohimbe (*Pausinystalia yohimbe* (K. Schum.) Pierre ex Beille), belongs to the family *Rubiaceae* and it was used traditionally as a tonic for men and as treatment for erectile dysfunction and other sexual problems. Herbal preparations made from this plant were also reported for their psychoactive effects. The plant contains a pharmacologically active alkaloid component called yohimbine.[56] Yohimbine is reported to induce systemic lupus erythematosus resulting in renal dysfunction.[57]

Aloe capensis (Cape aloe), traditionally used as a laxative, contains phytochemicals like aloins and aloinosides, which are reported to cause parenchymatous nephritis. The lethal dose of the *A. capensis* is estimated at about 8 to 20 g for adults. Acute renal failure was caused due to ingestion of *A. capensis* for treatment of constipation. Hemorrhagic gastroenteritis and parenchymatous nephritis are reported after consumption of the plant and the renal injury is suggested to be secondary to dehydration.[58]

Glycyrrhiza glabra (Licorice) is known as an anti-inflammatory, antidiabetic, antioxidant, antitumor, antimicrobial, and antiviral plant. Traditionally, licorice is used to cure sore throats, carbuncles, bronchitis, cough, colic, arthritis, and hepatitis. However, associated nephrotoxicity is observed in many cases of licorice ingestion followed by hypokalemia and severely damaged tubular cells with intense vacuolar formations. Licorice produces rhabdomyolysis-induced renal dysfunction because of potassium diuresis. It contains glycyrrhetinic acid, which is extensively bound to tissues, and as its urinary elimination is negligible, its toxicity may take weeks to resolve.[59]

Aristolochic acid is detected in the species of *Aristolochia* and *Asarum* genera belonging to the family *Aristolochiaceae*. Aristolochic acids structurally belong to a family of nitrophenanthrene carboxylic acids. Aristolochic acid I and aristolochic acid II are two important derivatives of these acids and are mutagenic in nature.[60] After metabolic activation, aristolochic acid forms DNA adducts in tissues such as kidney. These DNA adducts are responsible for causing genotoxic mutations resulting in development of urothelial carcinoma leading to interstitial fibrosis and loss of cortical tubules.

Djenkolic acid is a sulfur-rich cysteine thioacetal of formaldehyde and causes severe necrosis of tubular cells and minor necrosis of glomerular cells. In the concentrated acidic urine, djenkolic acid shapes sharp pointed crystals in distal tubules that cause obstruction and induce stone formation.[61]

Atractyloside is a compound which exists in several plants in Asia, Europe, Africa and South America. This diterpenoid glycoside inhibits the transport of ADP and ATP competitively based on its ability to bind specifically to the adenine nucleotide translocator of the inner mitochondrial membrane. ATP synthesis is stopped, leading to energy depletion and consequently cell death.[62] In addition, atractyloside is reported to induce the permeability of transition pores of mitochondrial membrane, cytochrome-c release, and caspase-activating proteases triggering the apoptosis.[63] The renal damage caused by Atractyloside is recognized by inflamed renal cortex and congested medulla and also acute proximal convoluted tubule and loop of Henle necrosis.

Nordihydroguaiaretic acid, the main secondary metabolite of *Larrea tridentata* (chaparral), has been shown to cause cystic nephropathy. δ-Quinone, the major metabolite of nordihydroguaiaretic acid, increases the fragility of lysosomal membranes by lipid peroxidation and causes autolysis, desquamation of necrotic proximal tubular epithelial cells, and accumulation of cellular debris leading to blockage of the tubules.[64]

Salicin is the active constituent of *Salix daphnoides*. It is first metabolized to saligenin, which is then further metabolized to salicylate. The salicylates are nephrotoxic in nature and cause renal dysfunction and reduction in renal blood flow.[50]

The glycyrrhizic acid content of *Glycyrrhiza glabra* (Licorice) root is hydrolyzed to glycyrrhetinic acid that causes inhibition of renal 11-hydroxysteroid dehydrogenase. It prevents the inactivation of cortisol to cortisone; thus, cortisol accumulates in the kidney and further stimulates the aldosterone receptors in cortical cells of collecting duct to reabsorb sodium ions. Another constituent of licorice is glycyrrhizin which is nephrotoxic in nature and was reported to cause hypokalemic nephropathy. Severe hypokalemia may lead to rhabdomyolysis and can cause acute renal injury.[65] Renal failure is a rare adverse event associated with licorice ingestion but studies on nephrotoxicity secondary to hypokalemia have been reported.[66]

A few important clinically proven nephrotoxic herbal medicines are summarized in Figure 2.

Respiratory Toxicity

A detailed overview of European poisonous plants provides information about the different types of plant toxins and their mode of action.[67] Toxins were grouped into five categories: cytotoxins, neurotoxins, alkylating and intercalating DNA toxins, inhibitors of cellular respiration, and toxins of skin and mucosal tissues. All of them could affect the respiratory system, but most often,

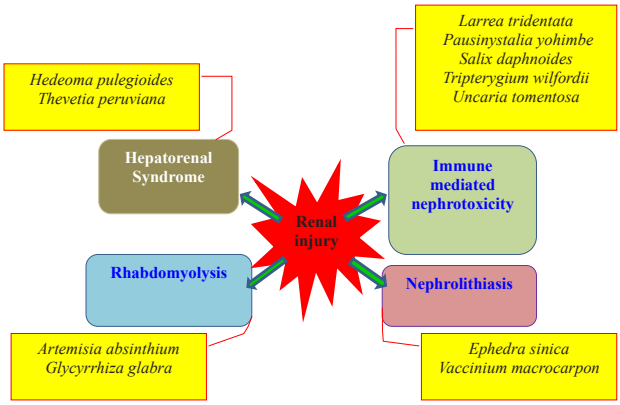

Figure 2. Types of Nephrotoxicity in Herbal Drugs.

the causes were associated with neurotoxin intoxication. In fact, the poisonous substances do not affect the respiratory system alone, but act simultaneously on other important parts of the human organism.

The genus *Strychnos* (*Loganiaceae*) is always associated with one of the most poisonous substances – strychnine. As detailed in a review in 2004, toxicity of some species of the genus, mostly from the phytochemical point of view was described. *Strychnos nux-vomica* L., commonly known as kuchla is a shrub or small tree containing strychnine and its analogue brucine as main constituents.[68,69] *S. nux-vomica* is used in treatment of musculoskeletal injuries, limb paralysis, and rheumatism.[54] Due to its high alkaloid content, the herb (the seeds are the part used) can cause strychnine poisoning which is characterized by muscle spasms or convulsions; deep and rapid respiration are observed, followed by respiratory arrest and asphyxia, ending in death.[68,70]

Another plant species, *Gelsemium elegans* (Gardner & Chapm.) Benth. (*Gelsemiaceae*) induces poisoning with muscle spasm and tetanic convulsion symptoms like strychnine[71] and causes death due to depression of the nervous and respiratory systems.[72]

Conium maculatum L. (Apiaceae) is a common toxic plant and its active components coniine and γ–coniceine (piperidine alkaloids) are responsible for its neurotoxic properties. The coniine alkaloids cause respiratory failure, preceded by paralysis, muscular tremors and weakness that can lead to death.[73-77]

Colchicine, the toxic alkaloid from *Colchicum autumnale* L. (autumn crocus, wild saffron, and naked lady), is antimitotic and also blocks mitosis by preventing DNA synthesis and tubulin polymerization.[78] *C. autumnale* can be mistakenly considered as *Allium ursinum* L., an edible plant, and used in its place. Consumption of *C. autumnale* can cause severe poisoning (starting with gastroenterocolitis) which may be fatal.[79] There are many cases of fatal colchicine poisoning in the literature.[80-87] In most cases, respiratory failure, cardiovascular collapse or leukopenia with infection are the main reasons for death.

Cleistanthus collinus (Roxb.) Benth. ex Hook.f. (*Euphorbiaceae*) is a toxic plant which causes many deaths in India, Malaysia, and Africa.[88-90] No specific antidote is available for it yet. Cardiac and respiratory toxicities of the plant are the main causes of mortality in consumers.[91]

Diterpene grayanotoxins are the constituent of several poisonous plants (mostly members of the *Ericaceae* family). In humans, grayanotoxin intoxication is rarely lethal and the toxic effects involve dizziness, hypotension and atrial-ventricular block.[92] One case with the intake of a decoction of *Rhododendron simsii* showed respiratory distress, bradycardia, hypotension, constricted pupils, salivation, and muscle twitching.[93] Laboratory studies of grayanotoxin mechanism of action[94,95] have shown respiratory depression and bradycardia in anaesthetized albino rats injected with a small dose.

Cardiac Poisoning

Consumption of *Thevetia peruviana* (yellow oleander) has been a common mode of self-harm in South India. It contains cardiac glycosides, and its consumption has effects similar to digitalis poisoning. These glycosides exert their primary pharmacological effect by inhibiting the Na^+/K^+ ATPase channel that extrudes sodium and imports potassium into cardiomyocytes in a vicious cycle.[96] Patients may develop arrhythmia and become hypotensive, interfering with the intracellular production of ATP through glycolysis by inhibiting the rate-limiting enzyme phosphofructokinase. In addition, increased vagal tone causes bradycardia. Ventricular tachycardia and fibrillation seen in cardiac glycoside toxicity are usually resistant to defibrillation.

Anandhi et al reported a case of cardiac poisoning in a 37-year-old man who consumed yellow oleander seed. Initially, he was asymptomatic for 4 hours, following which, he developed vomiting, dizziness and cardiotoxic manifestations.[97] The toxicity was not related to the number of yellow oleander seeds taken.[98]

Dwivedi et al reported cardiotoxic and neurotoxic manifestations in a 30-year-old female complaining of

vomiting, drowsiness, hyperkalemia and bradycardia after ingesting five seeds of yellow oleander.[99]

Rhododendron mucronulatum (azalea), from the *Ericaceae* family, is widely grown in Asian countries such as Korea, Japan, China, and Mongolia. Grayanotoxins in *R. mucronulatum* attach to sodium channels in cell membranes and increase membrane sodium permeability.[95] In addition, grayanotoxins prohibit cardiac and respiratory actions within the CNS by exhibiting bradycardia effect on the heart, which is mediated by vagal stimulation at the periphery in proportion to the amount absorbed.[100]

Choi et al reported a case with major symptoms of dizziness and general inertia, who had taken about 10 azalea blossoms approximately 1 h before his admission to the hospital.[100] Cardiotoxicity was caused by Azalea blossom which is a selective M2-muscarinic receptor antagonist without respiratory rate depression.[101]

Aconite, from the *Ranunculaceae* family is a toxic plant that contains aconitine alkaloids and the aconitines. Aconite poisoning has occurred in Japan and China. The common causes are ingestion of aconitine-containing Chinese herbal medicine and mistaken ingestion of aconite instead of edible wild plants. Aconite poisoning often results in death due to cardiac arrest caused by a fatal arrhythmia such as ventricular fibrillation.[102]

Fujita demonstrated alkaloid toxicokinetic parameters in patients poisoned by aconite with ventricular tachycardia and ventricular fibrillation, premature ventricular contraction and accelerated idioventricular rhythm, AIVR, and non-sustained ventricular tachycardia symptoms.[103]

Besides, Chinese herbal medicine, such as *Tripterygium*, has been suggested for treatment of various autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus but its toxicity with the therapeutic dosage is close to the minimal toxic dosage. Huang reported that two cases died of acute cardiogenic shock caused by myocardial damage and hydropic degeneration of the myocardial cells in the papillary muscles; two other patients died of severe acute renal failure due to severe acute toxic nephrosis. Using the crude *Tripterygium* in clinics should be prohibited, and its preparation should be produced by pharmaceutical companies regulated by the government.[104]

One of many plants containing cardiac glycosides is Foxglove, (including *Digitalis purpurea* and *Digitalis lanata*) that exerts potent inotropic and electrochemical effects on cardiac tissue. The cardiac glycosides of medical importance are extracted from *D. purpurea* and *D. lanata*, yielding digitoxin and digoxin, respectively. Cardiac glycosides are believed to affect the autonomic nervous system by suppressing sympathetic activation and increasing vagal tone.[105]

It has been suggested that ingestion of foxglove (*Digitalis purpurea*) can cause cardiac toxicity. Janssen et al reported two cases who presented to the emergency department with notable bradycardia (53 beats/min) with normal electrolyte levels, renal function and complete blood count after consuming foxglove (*Digitalis purpurea)*. The ECG showed sinus bradycardia with nonspecific ST-segment changes and lateral T-wave inversion and developed refractory ventricular arrhythmias.[106]

On the other hand, Wu *et al*. (2017) reported a case with bradycardia (54 beats/min) and hyperkalemia (7.6 mEq/L), nausea, vomiting and generalized weakness eight hours after drinking "comfrey" tea. First-degree atrioventricular conduction block with premature atrial contractions was found on electrocardiogram and ventricular fibrillation.[105]

Lavandin from the *Lamiaceae* family is a hardy, evergreen shrub, and is one of the most useful medicinal plants. Commercially, the *Lavandula* species provides several important essential oils to the fragrance industry, including soaps, colognes, perfumes, skin lotions, and other cosmetics. Recently, *Lavandula* is used in aromatherapy as a relaxant as well as antibacterial, antifungal, carminative, sedative, and antidepressive plant.[107]

Linalool (an unsaturated tertiary alcohol), linalyl acetate (an ester), lavandulyl acetate and terpinen-4-ol are main constituents of Lavandin and *L. angustifolia* extract. Linalool and terpineol toxicity showed similar central depressive and narcotic effects (linalool in particular). Acute poisoning from linalool includes ataxia, decreased spontaneous motor activity and lateral recumbence.

Landelle et al reported a case with hypertrophy of the adenoids, otitis media, and moderate hearing loss with normal levels of blood glucose, electrolytes, calcium, amino acids, urine amino acids and cerebro-spinal fluid analyses caused by ingestion of small amount of lavandin extract. The neurological state was normalized spontaneously within approximately 6 hours.[107]

"Torikabuto" or *Aconitum* genus contains a deadly poison and its main ingredients are aconitine alkaloids. Ohuchi et al reported a 41-year-old male who had taken "Torikabuto" with aconitine poisoning, demonstrating fatal arrhythmia, ventricular tachycardia, fibrillation and cardiogenic shock soon after his admission.[103]

Yew (*Taxus Baccata*) leaves have been used as a means of deliberate self-harm. Cardiotoxic effects may result in rhythm alterations and ultimately ventricular fibrillation. Taxine-derived alkaloids (e.g., taxine A and B, isotaxine B, paclitaxel), taxane-derived substances (e.g., taxol A and B), and glycosides (e.g., taxicatine) are the main toxic compounds of *Taxus* spp. that may cause dizziness, nausea, vomiting, diffuse abdominal pain, tachycardia and convulsions followed by bradycardia, respiratory paralysis, and eventually death. Minimum lethal doses (LDmin) of yew leaves in human and animals have varied from 0.2 to 0.4 g/kg body weight (bw) for the sensitive horses, 0.6–1.3 g/kg bw for humans to the less sensitive chicken (LDmin=16.5 g/kg bw).[108] Pietsch et al reported a 23-year-old woman diagnosed with *Taxus* poisoning who had been

found dead in her flat. In postmortem investigation, the duodenum and colon contained 200 g of green-brown plant particles, identified as leaves of *Taxus baccata.*[109]

Five fatal cases have been reported in *Taxus* poisoning. Another case was a 20-year-old man with lungs and brain blood congestion as well as dilated cardiac ventricles in forensic autopsy. *Taxus* intoxication was found with 150 g of green leaves.[109] Another case was a 26-year-old man with nonspecific signs of intoxication and high-grade swelling of the brain (1750 g) in autopsy. Furthermore, yew needles were found in the greenish plant material of the stomach content by their characteristic stoma in microscopic analysis leading to the hypothesis of a fatal *Taxus* ingestion.[109]

Mandragora from the solanaceous (nightshade) family can be found in Greece, particularly on Crete and Amorgos Islands. *Mandragora* has been suggested as a sedative and aphrodisiac plant and it was used as an analgesic, emetic and also anesthetic for surgical purposes. Alkaloids of *Mandragora* (solanum and tropane alkaloids) demonstrate anticholinergic properties. These anticholinergic properties can cause severe symptoms such as nausea, mydriasis, blurred vision and supraventricular tachycardia. Tsiligianni et al reported two cases who had consumed *Mandragora* as a vegetable meal with persistent supraventricular tachycardia, nausea, dizziness, blurred vision, dryness of mouth, headache, instability in walking and vomiting. [110]

Castilla elastica from the *Moraceae* family known as 'Panama rubber' and 'castilloa rubber' is a common plant growing in the coastal region of Western Colombia and Western Ecuador. Branches of the tree are wide-spreading with large leaves. Witharana et al a reported a case of a 76-year-old man with Panama rubber (*Castilla elastica*) poisoning with severe cardiac toxicity and nodal bradycardia. The patient had developed vertigo in the morning and decided to take herbal medication made from the leaves of a wild plant (Panama rubber). This resulted in accidental ingestion of the plant extract of Panama rubber which was misidentified as thebu (*Costus speciosus*). Thebu is a plant used by villagers as food and as an herbal medication.[111]

Veratrum album is a poisonous plant that can be mistaken for the yellow gentian, *Gentiana lutea*, used in beverages. Severe poisoning with toxic plants has been reported in eight cases due to *Veratrum album* (White *veratrum*; *Rhizoma veratri*, *Radix hellebori albi*) with bradycardia and circulatory shock. *Veratrum* alkaloids are known to stimulate the vagal afferents and cause significant bradycardia and hypotension. Hypotension and bradycardia are common symptoms of ingestion of homemade gentian wine. Zagler et al reported two adult men with nausea, vomiting and headache followed by diarrhea with normal vital signs and heart rates of 42 and 45 beats per minute with sinus bradycardia. Retrospective investigation confirmed that *Veratrum album* was mistaken for *Gentiana lutea* in the beverage they had taken. Patients with clinical toxicity following unintentional ingestion of *Veratrum album* should be given appropriate supportive care.[98]

In conclusion, considering the long history of consumption of herbal medicines in different societies, people mainly assume medicinal plants to be harmless and non-toxic. Moreover, prescription, preparation, and consumption regulations of medicinal plants as well as their marketing regulations are not clear and strict. The extensive and diverse consumption of medicinal plants without adequate observation are some of the most important reasons for medicinal plant poisoning. Recently, the number of famous medicinal plant toxicities have diminished because of the improvement in practitioners' and patients' general knowledge about medicinal plants. However, there are still abundant sales of medicinal plants by street corner herbalists without enough knowledge of instruction and caution regarding consumption, side effects, toxicity, and contaminants. Moreover, in some plant poisoning cases, self-medication of patients without awareness of cautions in medicinal plant consumption, mistaken use of plants containing toxic compounds instead of the medicinal plants, or accidental use have been reported.

The composition of herbal medicines is not constant and it varies by different factors such as time, place, temperature, etc. In addition, people consider herbal medicines to be side effect free and the tendency to use them is increasing greatly. Therefore, adopting more strict regulations on the use of plants for medical and even supplementary purposes is necessary.

Authors' Contribution
All authors contributed equally.

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