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Review Article

Toxic Effects of Medicinal Plants in Human and Animal Models: A Review

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Abstract

Since ancient times, people have utilized plants for therapeutic purposes. Over the past 20 years, there has been a noticeable increase in the use of medicinal plants. Due to their natural origin, people believe herbal products to be safe, but they fail to consider whether these plants have any toxic properties. This is a significant health issue. The purpose of this review is to highlight various contributions and the importance of medicinal plants that are toxic to both humans and animals. Information on the toxicological characteristics of medicinal plants and their possible impacts on both humans and animals is the goal of this review. The primary toxic medicinal plant effects on humans and animals, or those that lead to emergency medical visits, are reviewed in this article. To determine the previously documented toxicity to humans and animals, articles discussing the "medicinal plants effect in humans and animals" were found in online databases. According to the primary toxic effects of medicinal plants, the report in the current review was taken from our prepared database. According to our findings, the effects of medicinal plants that are toxic to humans and animals are reviewed in this work. To provide information regarding the safe use of the medicinal plants mentioned in this review, more toxicological research is required.

Keywords: *Medicinal Plants; Toxicity; Neurotoxicity; Reproduction; Humans and Animals*

Introduction

Since the beginning of time, man has been inseparable from nature and has depended on it for survival. In addition to fundamental needs like food, fiber, shelter, clothes, and gum, humans also depend on their environment for subsistence, livelihood, and medical treatment. Plants not only supplied his basic necessities but also fulfilled his need for medicine. Humans have started employing animal products and other natural bio- resources to make medicines in addition to plants. According to the social, cultural, and environmental conditions of the ethnic group in issue, different traditional medical systems have so evolved in different countries [1]. Toxic plants are those that contain chemical compounds or active principles that can cause harm or even death to humans and animals when they come into touch with them, breathe them in, or eat them. Among these compounds include alkaloids, glycosides, saponins, oxalates, and tannins [2]. These compounds are found in plants' secondary metabolites, and although they are harmful to people and some animals, they serve a useful function by protecting the plant against pests and illnesses. The different compounds that make up a plant are one of the many factors that affect its toxicity, which differs from one plant to another. Fruit ripening status, concentration, chemical composition, age, physical development conditions (soil type, humidity, temperature, and season), and the portion of the plant ingested are all taken into account [2].

Generally speaking, plants bearing secondary metabolites that have therapeutic potential are considered medicinal plants. Plant parts have been utilized to treat a wide range of ailments since the beginning of time. Every civilization passed on its knowledge of the curative properties of specific medicinal plants to the following generation. According to the World Health Organization (WHO), 75% of people worldwide rely on herbs for their fundamental medical needs [3]. However, interest in using medicinal plants for therapeutic purposes declined in the late 19th and early 20th centuries due to a number of processing defects and a lack of information about their negative effects. The availability of techniques for isolating pure chemicals and synthesizing new compounds with proven biomedical use has also considerably reduced interest in employing plant parts. Additionally, evidence of understanding of the toxicity of medicinal plants can be found in ancient texts such as the Ebers Papyrus (1500 BC), which mentions 800 different pharmacological compositions from 700 plant species for therapy [4]. Since the beginning of time, folk medicine has made use of a wide range of medicinal plants. For thousands of years, people all throughout the world have utilized them as natural medicines with therapeutic and other pharmacologic benefits. According to estimates from the World Health Organization (WHO), up to 80% of people globally still get their primary medical care from traditional medicine. According to the initial results of a survey carried out on behalf of WHO, the use of medicinal plants is widespread and expanding, even among young people [5]. Medicinal plants or parts of these plants (leaves, rhizomes, roots, seeds, and flowers) can be made in a number of ways, including fresh crude form and preparations like teas, decoctions, powdered plant material, or extracted forms of medicinal agents (tinctures, water or alcohol extracts, essential oils, resins, and balsams). In recent decades, there has been a significant yearning for natural goods in the industrialized world, especially in the United States. Even if the natural and manufactured exemplars are said to be chemically equivalent, the majority of people still choose the natural [6].

Large biological substances called phytochemicals are present in plants. They are classified as bioactive substrates and offer a variety of health advantages to humans [7]. Among the biological components found in these phytochemicals or substrates are terpenes, polyphenols, and alkaloids. Most pharmacological activity, such as anti-cancer and anti-asthma capabilities, is found in alkaloids [8]. Additionally, a number of dangerous compounds may be included in alkaloids such as atropine and tubocurarine [9]. For as long as there have been people, plants have been utilized to cure ailments. Medicinal plants are frequently recommended because of their therapeutic characteristics, which are revealed in large part by popular conceptions of their efficacy and use, even though the chemical components of these plants are not usually fully understood. Globally, but especially in South American countries, the use of medicinal plants has significantly improved primary health care [10]. Between 250 and 500 thousand plant species are thought to exist on Earth, yet only 1 to 10% of them are eaten by humans and other animals [11]. Certain medicinal plants may have negative health effects due to (a) pharmacodynamic interactions with prescription drugs, (b) intrinsic effects, (c) pharmacokinetic interactions with prescription drugs, and (d) the presence of contaminants and/or pathogenic microorganisms. Additional factors that influence how harmful medicinal plants are to humans include age, nutritional status, and the presence of chronic disorders. The concentration of hazardous metabolites in plants is influenced by a number of factors, including the stage of growth, soil nutrients, and the season of collection [12].

In general, nature offers an excellent example of significant coexisting phenomena. Human diseases are treated with natural chemicals derived from plants, animals, and minerals. Nowadays, medicinal plants are becoming more and more popular and in high demand. Since they offer vital services, plants are without a doubt vital to ecosystems. Humans and other living things cannot function properly without plants. Plants, particularly therapeutic herbs, have long been utilized as a general indicator of ecosystem health. The use of therapeutic plants has probably been considered by people since the beginning of time. Because they recognized and utilized the plants for fire, clothing, food, and shelter, early people were more or less aware of the characteristics of the plants around them before history. In countries like China, Greece, Egypt, and India, medicinal plants are one of the oldest fields of study. Plants were frequently utilized as disinfectants, medicines, and aromatic agents in ancient Persia. In fact, the usage of medicinal plants to treat illnesses dates back thousands of years, to a time when people were looking around them for ways to cure themselves of ailments. Approximately 50,000 plant species, or more than 10% of all plant species, are utilized in cosmetic and pharmaceutical goods [13].

The purpose of this study is to provide a general overview of some toxic reports pertaining to the effects of the medicinal plants that are the subject of this review.

Literature search methodology

Peer-reviewed articles, scientific reports, books, and grey literature (Springer, Wiley Online, PubMed, Google Scholar, ResearchGate, ScienceDirect, Taylor & Francis, Web of Science, MDPI, Academia.edu, Bentham, Thieme, Scopus, SpringerLink, and SciFinder) were the main sources of information used in this article.

Medicinal plants

According to clay tablets, opium and myrrh have been utilized as medicinal plants since ancient times. The ancient Egyptian Ebers Papyrus had a list of about 800 therapeutic herbs, such as juniper, castor beans, garlic, mandrake, and *Cannabis*. Since then, hundreds of these spices and herbs have been used. In those days, the Chinese used herbal treatments like ephedra and hemp to treat leprosy. In the fourth century BCE, Aristotle's pupil Theophrastus penned Historia Plantarum, the earliest systematic work on botany. In the 60th century CE, Pedanius Dioscrides, a Greek physician, proposed over 1,000 herbal medicines in his De Material Medica. These remedies were made from over 600 medicinal plants. Throughout the 17th century, herbalists consulted this invaluable book for more than 1,500 decades. Through the chemical analysis of plants and the extraction of their active substances, a new mass-scale science was established. When alkaloids like morphine were extracted from poppies and Strychnos ipecacuanha and quinine was derived from the cinchona tree, new drugs were produced. The extraction of salicylic acid in 1853 and morphine in 1826 marked the beginning of the modern age of drug development [9]. Millions of people worldwide depend on local herbal remedies, plants, and animal products to heal a variety of ailments and wounds [14].

Uses and importance of medical plants

Medicinal plants are used in alternative medicine because of their many therapeutic advantages. The use of these natural treatments is steadily increasing due to their lower cost compared to commercial synthetic pharmaceuticals. These preparations are typically drunk without a prescription. Furthermore, alternative medicine has less side effects than orthodox treatment [15]. Plants and some other species, such as fungus, are now considered to be important sources of potential drugs for a variety of diseases, including cancer, heart disease, dementia, and malaria [9].

Advances in genetic engineering tools have enabled scientists to prepare several compounds used in medicine manufacturing, as well as to advance tissue culture for the propagation and cultivation of medicinal plants and the collection of desired bioactive compounds [16]. This innovative approach allows us to produce more active material through micropropagation and callus culture [17]. Biotechnology has recently increased interest in the manufacture of plant-based *in vitro* systems (e.g. callus cultures, cell suspension cultures, and organ cultures) and genetic modification to produce desired plants and plant products. Biotechnological *in vitro* has been employed to obtain secondary products in bigger numbers than those found *in vivo* grown plants, as more and more natural habitats are being rapidly destroyed [18].

Identifying the effectiveness of medicinal plants for human health

Humans have used plants for a number of purposes since the beginning of time, chief among them being as food for sustenance and as medicine to alleviate human and animal ailments. People have relied on plants for thousands of years to preserve, enhance, and restore human health in every culture on the planet [9].

The primary line of treatment for wounds, diseases, infections, and trauma has been medicinal plants from ancient times. For thousands of years, people have been able to identify and modify the botanical resources in their immediate environment, and as trade has expanded,

they have utilized these resources for both food and medicine. Many of these traditional and ancient medicinal plants have been shown to have therapeutic advantages, though not usually through controlled clinical experiments. One unexpected conclusion of these validation investigations is the number of medicinal plants that manufacture similar or closely related chemicals [19].

Eleven percent of the 252 essential drugs that the World Health Organization (WHO) has classified as being derived from plants are widely used and essential for optimal health. For instance, *Digitalis* spp. are the source of digoxin, *Atropa belladonna* of atropine, *Cinchona* spp. of quinidine, and *Papaver somniferum* of codeine [15]. Surprisingly, natural sources accounted for about 54% of the new anticancer drugs developed between 1940 and 2002 [20]. A study found that 73% of all pharmaceutical products made today contain chemicals derived from natural products [21] (Table 1).

S. No.	Plants	Active components	Utilization and toxic effects	Reference
	Glycyrrhiza glabra [liquorice]	Glycyrrhizic acid 18b-glycyrrhetinic acid, glabrin A and B, isoflavones	Antibacterial, anti-inflammatory, antiviral, antioxidant, and anti-diabetic activities	[22]
	Nerium oleander	Oleandrin - cardenolide and pregnatriene compounds	Arrange heart beats disorder-toxic effect	[23]
	Peganum harmala	β-carboline alkaloids	Distinctive cardiovascular impact, such as bradycardia, diminished systemic blood vessel function, toxic effect	[24]
	Strychnos ipecacuanha	Strychnos indole alkaloids	Anti-tumor alkaloids	[25]

Table 1: *Some examples of medicinal plants and their active components and utilizations.*

Poisonous medicinal plants

The biosafety of any material is the margin of safety for giving such a compound. Plants are rich in chemical components that can combine with one another to create dangerous chemicals. Furthermore, administering such substances in sufficient quantities may disrupt or interfere with the immune systems of both humans and animals. Cytotoxicity or organotoxicity in living organisms can be acute, subacute, or chronic, depending on the amount and duration of exposure. Thus, a sane approach should be used, and an herbalist should supervise administration. It is also important to look at the active components in the plant material. Tropane alkaloids and cardiac glycosides are used in traditional medicine. However, some compounds may be dangerous or have negative effects even when consumed uncooked or as plant material [26].

Furthermore, several of these medicinal herbs have poisonous properties that can be lethal when eaten in high quantities. For example, *Peganum harmala*, also known as Syrian rue, is a commonly used medicinal plant [27]. Within the Zygophyllales order, which has approximately 22 genera and more than 250 species, it belongs to the Zygophyllaceae family [28]. The primary origin of *P. harmala* is Central Asia. However, it grows in Australia, North Africa, and Southwest America and is a part of the Kingdom of Saudi Arabia's flora [29]. Additionally, it is a perennial herbaceous glabrous plant with several branches that grows between 30 and 60 cm in height. It has short creeping roots and thick, stiff, brilliant green stalks with alternating narrow leaves. The blooms are tiny, white or pale yellow, solitary, and have five petals. The fruits are capsules with three chambers that range in size from 6 to 10 mm across. The unripe fruits are green before turning orange-brown, and these capsules hold over 50 little black-brown triangular seeds [29]. The plant's main therapeutic ingredient is the seed, which has 2 - 6% pharmacologically active alkaloids, mostly b-carbolines (including harmine, harmaline, harman, and harmalol), quinazoline derivatives, vasicine, and vasicinone [27].

P. harmala works best as an emmenagogue stimulant and a well-known medicine to treat a number of conditions, including lumbago, asthma, colic, and jaundice. The anticancer effects, intestinal sickness treatment, antileishmanial, anti-spasmodic, antihistaminic, and vasorelaxant qualities of *P. harmala* are also remarkable. In addition to its anti-inflammatory, hypoglycemic, immunomodulatory, and antinociceptive properties, it also aids in hepatoprotection, wound healing, leukemia recovery, pain management, and antioxidant movement [28]. *P. harmala* contains β-carboline alkaloids, which have a special cardiovascular effect that includes lower blood weight, bradycardia, and decreased systemic blood vessel activity. It has been shown to contribute to peripheral vascular resistance, have anti-platelet aggregation capabilities, and be utilized to treat nervous system illnesses including Parkinson's disease [27]. However, the entire plant is considered toxic. According to Asgarpanah and Ramezanloo (2012) [28], *P. harmala* is harmful to both people and animals. Typical symptoms of poisoning in animals include anorexia, hypersalivation, vomiting, diarrhea, clonic muscle spasms, rapid respiration, and an accelerated pulse [30]. When it comes to human toxicity, *P. harmala* is usually used by women to cure amenorrhea; nevertheless, it only turns harmful when consumed in considerable amounts. Typical symptoms include bradycardia, hallucinations, neurosensorial syndromes, and gastrointestinal disorders such as nausea and vomiting [28]. In some cases, symptoms of an overdose include vomiting blood and experiencing gastrointestinal trouble. Low blood pressure, a high pulse rate, convulsions, facial and limb tremors, visual hallucinations, abdominal pain, and a minor rise in body temperature are all observed during the physical examination [30].

Medicinal plant overdose causing human death

Plants include a variety of physiologically active phytochemicals that affect humans and other living organisms, including terpenoids, glycosides, and alkaloids. These substances may interact chemically, antagonistically, or synergistically to produce unknown physiological effects that may be beneficial or detrimental. There is a wide range of safety for several of these phytochemicals. Some don't affect biological function, but others should be used carefully since they can damage or disrupt a person's biological functioning. There are two types of toxic doses: acute, which act rapidly, and chronic, which act gradually. However, the majority of medicinal herbs are only utilized under the supervision of professionals or informed individuals due to their recognized harmful or poisonous side effects [9].

Toxicity of medicinal plants

Within and between species, bioactive chemicals in medicinal plants usually differ in kind and content. Because of the potential toxicity of their chemical elements, several plants employed in traditional medicine are intrinsically toxic. Several plants are recognized to be toxic or dangerous in traditional medicine, including *Atropa belladonna, Datura* spp., and *Digitalis* spp. [31].

Many plants used in traditional medicine or as food have been demonstrated to have some toxicity (mutagenic and carcinogenic) effects [32]. The possible mutagenic, genotoxic, and/or toxic consequences of herbs used in traditional medicine have been highlighted by the review [33]. However, some poisonous plants, such as *Datura* (tropane alkaloids), *Digitalis* (cardiac glycosides), and *Pyrethrum* (pyrethrin insecticides), are useful to humans as pesticides, medicines, and hunting poisons. Well-known therapeutic herbs have been shown to be poisonous in both laboratory and field experiments. For example, it has been demonstrated that *Lantana camara*, which is used to treat malaria and other ailments, is hepatotoxic in several animal species, which calls into doubt its long-term usage in humans [34].

In addition to its anti-diabetic and antimalarial qualities [35], *Momordica charantia*, a plant used as an abortifacient in Ghana, has also been reported to cause deadly hypoglycemia in children [36]. According to Organization for Economic Cooperation and Development (OECD) guidelines, special toxicity studies are carried out, including eye irritation tests, skin sensitization tests, neurotoxicity studies, carcinogenicity studies, prenatal developmental toxicity studies, and reproductive toxicity studies, including one-generation and two-generation reproduction toxicity studies.

Acute eye irritation/corrosion test

The ocular corrosivity of a drug can be evaluated *in vivo* using the albino rabbit acute eye irritation test. Following systemic analgesia (subcutaneous buprenorphine 0.01 mg/kg) and topical ocular anesthetic (0.5% proparacaine hydrochloride or 0.5% tetracaine hydrochloride), the test medication is injected as a single dosage into the conjunctival sac of one eye, while the other eye serves as a control. One hour following the administration of the test chemical, the eye is inspected for the presence or absence of identifiable ocular lesions. The observation periods of 24-h, 48-h, 72-h, 7, 14, and 21 days come next. Clinical signs of pain or anxiety, like increased blinking and frequent eye rubbing, are also observed twice a day. The animals are killed at the end of the designated observation period and rated for their eye irritation reaction in addition to their ocular lesions and corneal perforations in order to assess the test substance's corrosive nature [37].

Skin sensitization test

In addition to ocular lesions and corneal perforations, the animals are rated for their eye irritation reaction and killed at the end of the designated observation period to assess the corrosive nature of the test material [37]. The Magnusson and Klingman grading scale (0-no visible change; 1-discrete or patchy erythema; 2-moderate erythema; 3-intense erythema and swelling) must be used to assess erythema after 24 hours after the patch test is removed [38,39].

Prenatal developmental toxicity

The toxic effects of a substance on prenatal development can be investigated in female rodents (rats) or nonrodents (rabbits) by continuously administering the test substance via oral gavage tube (intubation) from the day of fertilized ovum implantation (i.e. day 5 of postmating) until the day before cesarean sectioning. Mortality, behavioral changes, body weight, and food and drink consumption are usually observed before and after exposure to the test chemical. At the end of the study period, the animals are killed, and the numbers of living and dead fetuses as well as the contents of their uteruses are counted. The body weight, sex, soft tissue, and skeletal anomalies of the fetuses are also recorded [40].

Neurotoxicity studies

Neurotoxicity tests are carried out to detect notable neurotoxicological and neuropathological alterations when a chemical is administered to rodents (rats) via the mouth, skin, or lungs. Depending on the requirements of the research, the study duration can be as short as 28 days or as long as a year. Both before and after exposure to the test material, neurobehavioral function tests and clinical observations are frequently carried out for auditory and proprioceptive stimuli, motor activity, changes in body weight, food and water consumption, and ophthalmological examination. After the designated amount of time has elapsed, the animals are sacrificed and histopathological alterations are examined to determine the study's conclusion [41].

Carcinogenicity studies

In this investigation, the carcinogenicity of a test drug is assessed in rodents, preferably rats or mice. The test drug is usually administered orally, but if the study calls for a 6-hour daily exposure duration, topical and cutaneous methods are also recommended. Depending on the animal selected, the study's duration can vary from 18 months for some mouse strains (AKR/J, C57 BL/6J) to 24 months for rats. At the end of the study time, the animals are put down and checked for any odd signs of toxicity, like neoplastic developing lesions. The onset time, location, size, appearance, and course of each physical tumor must be recorded [42].

Reproduction toxicity studies

One-generation [43] and two-generation reproduction toxicity studies use either mice (8 weeks of treatment for one generation and 56 days for two generations) or rats (10 weeks of treatment for one generation and 70 days for two generations) [44]. Female animals

are measured for body weight, gestation duration, length of estrus cycle, number and sex of pups, number of dead pups, and physical and behavioral abnormalities of pups, while male animals are measured for sperm mobility, testicular and epididymal weight, and prenatal and F1 animals.

Conclusion

Although plants are recognized for their therapeutic qualities, they also contain harmful substances known as active components that can harm both people and animals. A medicinal herb that is widely utilized worldwide is believed to be both cost-effective and efficient. It is unclear how harmful therapeutic plants are to both people and animals. Toxic medicinal plants could be considered a public health concern. According to this study, poisonous therapeutic plants had an impact on both people and animals.

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