REVIEW ARTICLE

Plant toxins and acute medicinal plant poisoning in children: A systematic literature review

Adel Ghorani-Azam[1], Samaneh Sepahi[2], Bamdad Riahi-Zanjani[1], Anahita Alizadeh Ghamsari[1], Seyed Ahmad Mohajeri[2,3], Mahdi Balali-Mood[1]

[1]Medical Toxicology Research Center, Mashhad University of Medical Sciences, [2]Targeted Drug Delivery Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, [3]Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

Background: For many years, medicinal plants and herbal therapy have been widely used in different societies for the treatment of various diseases. Besides their therapeutic potency, some of the medicinal plants have strong toxicity in human, especially in children and elderly. Despite common beliefs that natural products are safe, there have been few reports on their toxicities. **Materials and Methods:** In the present study, we aimed to systematically review the literature wherein acute plant poisoning and herbal intoxication have been reported in pediatric patients. After literature search and selection of the appropriate documents, the desired data were extracted and described qualitatively. **Results:** A total of 127 articles with overall 1453 intoxicated cases were collected. The results of this study showed that some medicinal plants can cause acute poisoning and complications such as hepatic and renal failure in children. **Conclusion:** The findings of this survey showed that acute plant poisoning can be life-threatening in children, and since a single-ingested dose of toxic plants can cause acute poisoning, parents should be aware of these toxic effects and compare the side effects of self-medication with its potential benefits.

Key words: Herbal medicine, medicinal plant, pediatrics, poisoning, toxicology

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INTRODUCTION

In terms of prevention and treatment of diseases, medicinal plans are of particular importance in medicine.[1] Given the importance of these plants in medicine, extensive researches have been performed in recent years to extract and characterize active products of herbal medicine.[2] Proven beneficial effects of these plants, cheap and low expense, and compatibility with the environment are the most important reasons of using medicinal plants.[3,4] The results of studies have shown that some active ingredients of medicinal plants are useful for pain relief.[5] Findings have also shown that some medicinal herbs have antioxidant and anti-inflammatory effects *in vitro*.[6,7] In addition, some medicinal plants are widely used for different therapeutic purposes including treatment of gastrointestinal tract and digestive diseases caused by microbial contamination.[8] In this regard, various indigenous medicinal plants such as *Cassia siamea*, *Flueggea virosa*, *Terminalia bellirica*, and *Terminalia chebula* are used in different communities for the treatment of certain diseases such as malaria and gastrointestinal disease or as remedy in infants and children.[9] It is estimated that close to 80% of people in different communities use different types of traditional medicine for the treatment of various disease.[10] Nowadays, the use of natural remedies even in developed countries has become prevalent and these herbal products are routinely used in 18% of pediatrics institutions and 94% of other communities in Canada only for the treatment of various disease in children.[11] It is shown that near to 20,000 herbal products are currently available on the market overall the world, and the annual trade turnover

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Address for correspondence: Prof. Mahdi Balali-Mood, Medical Toxicology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. E-mail: balalimoodm@mums.ac.ir; mbalalimood@hotmail.com

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of medicinal plants is approximately 4 billion dollars only in the United States.[12]

Besides their known beneficial properties, studies have shown that some medicinal plants such as *Ephedra* species, *Aconitum* species, *Datura* species, and *Lobelia* species in long-term use have strong toxic effect particularly in the children.[13-15] Toxicological studies of medicinal herbs on animal models have shown that some of these plants such as daouri and juniper tar that are typically used to treat chronic eczema and other skin diseases may have nephrotoxicity or hepatotoxicity, suggesting that the use of these plants particularly in children should be reevaluated.[16,17] Although it has been shown that natural or complementary and alternative medicines, particularly medicinal plants, have fewer side effects than chemical drugs, studies have shown that herbal medicines are not all safe for direct human use, especially in pediatric patients.[18,19] The importance of acute poisoning is greater in children and especially neonates since their digestive and immune systems are not completely evolved. On the other hand, children are not aware of the dangers associated with the ingestion of every material. Studies have shown that although the overall number of mortality due to toxic plants is low, yet they are considered as an important cause of morbidity and mortality.[20] On the other hand, since the toxicological information and antidote therapy of some medicinal herbs is not available, plant toxicity deserves greater attention.[21] Since there are great concerns about the toxicological impact of medicinal plants in human, particularly in sensitive age groups, in this study, we aimed to systematically review the literature wherein toxicological impact of medicinal plant had been investigated in children. In addition, we aimed to introduce the plants that have been reported as poisonous, at least in children, to warn the health professionals about the consequences of consciously or unconsciously use of herbal medicine.

METHODS

Methodology and selection criteria

A systematic literature search was performed in the PubMed, Scopus, and Google scholar in January 2017 to investigate the possible toxicity of medicinal plants in children from 1911 to 2017. On academic based and also according to the legal definition of the child by the UNICEF, childhood is considered as a period of time between the stages of birth and puberty. For consistency of this definition between male and female patients, and to ease the data extraction, children in this study were defined as those with <16 years old.[22] Following terms "medicinal plant OR traditional medicine" and "pediatrics" were searched in the title, keywords, and abstract of articles to find appropriate documents in which the toxicity of traditional medicine had been investigated in children. For this purpose, following search method ([[plant extract OR plant OR herbal medicine OR medicinal herb OR medicinal plant]] AND [toxicity OR toxicology OR intoxication OR poisoning]) AND (children OR child OR adolescent OR teen OR teenager OR paediatric OR pediatric OR neonate OR newborn OR infant) was used in the PubMed and Google scholar by limiting the records to article with English language. It is suggested that PubMed, Scopus, and Google Scholar cover nearly all published articles in medical topics.[23] However, to find potentially eligible documents, Scopus, Irandoc, Ovid, and ScienceDirect were also searched using a similar but customized method in which "medicinal plant OR traditional medicine" was searched as the main search term and then "children AND toxicity" was searched within the records.

With no strict inclusion criteria, all potentially eligible documents were included. Thus, almost all articles relevant to the purpose of this review wherein toxicological impact of medicinal plant had been investigated in children were included in this literature review and used for data synthesis. No time limitation was defined for the selection of eligible articles; however, to avoid misconception as well as to ease data extraction, the results were limited to articles with English languages, unless the desired data are extractable from the English abstract of those articles with languages other than English. Moreover, documents with duplicated data were excluded from further evaluation. In addition, articles with inadequate data, as well as editorials, conference papers, and review articles, were also excluded from additional assessment. Hence, according to aforementioned, the exclusion criteria in this review were as follows:

I. Article with language other than English
II. Documents with duplicated data
III. Editorials, conference proceedings, and review articles
IV. Irrelevant articles or articles with inadequate data.

All procedures of literature search, article selection, and data extraction were performed by two reviewers independently according to the modified PRISMA Checklist 2009, a protocol for systematic reviews, in which the checklist has been modified to assess the nonrandomized trials.[24] For this purpose and to avoid possible misinterpretation during data analysis, any probable discrepancies between the authors were resolved in each step before further data processing.

Data synthesis and the variable in the included literature

All necessary data including the name of author, sex ratio, date and origin of the publication, as well as the total number of studied population in the selected literature were recorded. Furthermore, other useful information including methods of assessment, study variables, and the main findings of each study was collected and used for qualitative

data assessment. The variable of interests included blood metal, alcohol and electrolytes level, arterial blood gases, records of clinical features, patient outcome, and mortality rate. The reports of included manuscripts were qualitatively described after recording the desired data.

RESULTS

Literature search and study selection

A total 7509 documents were found, of which 4126 articles were in the PubMed, 3237 articles were in the Scopus, and additional 146 documents were also found through search in Google scholar, Ovid, ScienceDirect, and manual reference list screening. Irandoc was also searched as a local Iranian database for plant toxicity in children. Afterward, among the collected documents, 5501 articles were excluded due to subject irrelevancy. Further 766 documents were also disqualified after excluding the articles that had been performed on animals or cell lines. Additional 772 articles were further omitted due to language irrelevancy. Furthermore, 343 review articles were also excluded from additional data processing. The documents were then reviewed, and after duplication removal and exclusion of irrelevant articles, finally, 127 papers were fully met the inclusion criteria. Due to the nature and sensitivity of the study and also ethical issues for study on newborns and children, most of the studies were case reports. Afterward, full text of 127 appropriate documents was collected and used for data extraction. The full process of literature selection is demonstrated in Figure 1.

Description of included studies

In the present review, 127 articles with a total of 1453 study population were included and used for qualitative data assessment. The number of studied patients in the included documents varied from 1 to 220. The age of patients also varied from 21-day-old baby to 16-year-old children. The results of this study revealed that the use of traditional medicines, particularly medicinal plants such as *Karwinskia humboldtiana, Lavandula angustifolia, Cannabis,* and cinnamon oil, may lead to acute poisoning and central nervous system (CNS) toxicity in children.[25,26] Depending on the route of exposure, the symptoms of acute poisoning differ; however, it has been reported that nausea, abdominal pain, dehydration, arrhythmia, vomiting, and bradycardia are the most prevalent symptoms. Rush or sensation of warmth, facial flushing, and/or oral burning are also reported when the plants are ingested orally.[27,28]

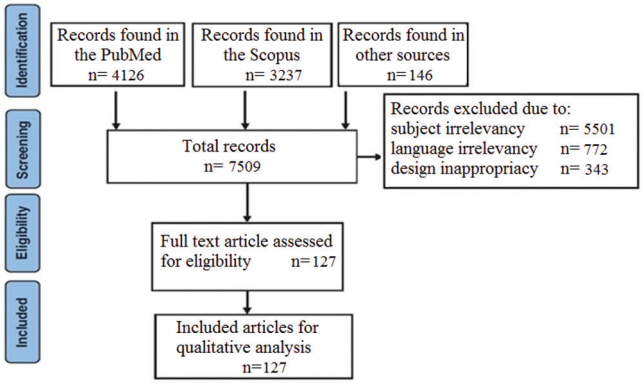

Figure 1: Flowchart of the literature search and strategy for the selection of relevant document

Findings have shown that intoxication with wild berries (*Vaccinium* species) and elephant' ear (*Colocasia* species), deadly nightshade (*Atropa belladonna*), and impila (*Callilepis laureola*) are more prevalent in Africa. Reports show that cutaneous application of cade oil (juniper tar) from *Juniperus oxycedrus* as mildly irritant oil, which is considered as a plant with antiseptic, antimicrobial, and fungal properties, can also cause serious acute poisoning in children. Medical records have shown that acute poisoning of the cade oil may also manifest as convulsions, acute pulmonary edema, renal failure, and hepatotoxicity.[17] On the other hand, intoxication following oral ingestion of jimson weed (*Datura stramonium*) is reported from Asia, Africa, America, and Europe. Studies have also shown that *Salvia officinalis* (sage oil) is an epileptogenic plant, and even a single-ingested dose of this plant can cause seizure.[29] Castor bean from *Ricinus communis* was also shown to have hepatotoxicity in children.[30] Castor beans also contain ricin, which is a highly toxic and is used as chemical and biological weapon.[31] Depending on the type of intoxication and the organs involved, mild-to-severe symptoms were reported in the literature. These symptoms include abdominal pain, diarrhea, vomiting, dermatitis, jaundice, decreased level of consciousness, tachycardia, dry mouth, confusion, incoherent speech, visual disturbances, hearing and visual hallucinations, coma, and deaths. The plants, type of intoxication, and clinical symptoms of acute plant poisoning are summarized in Table 1.

DISCUSSION

Native traditional medicine has been widely used in the treatment of various diseases in different cultures.[8] Nowadays, medicinal plants have largely been used even in children, but the toxic effect and adverse reactions of these plants are an important and challenging issue in safety monitoring of these products.[148] Although most of medicinal plants have traditionally been considered safe, many reports and medical data demonstrated that continuous use of these plants may be associated with respiratory, chronic liver injury, and in some cases liver failure.[37,71] Clinical reports have shown that some herbal products such as Jin Bu Huan, a Chinese herbal remedy, can cause life-threatening symptoms such as bradycardia and respiratory and CNS depression in the users.[149] According to a 10-year

Table 1: The plants, type of intoxication, and clinical manifestations of plant poisoning in children

References	Plant name (common name)	Number of reports (*n*=127)	Number of patients (*n*=1453)	Poisoning	Symptoms
[32-34]	*Abrus precatorius* (jequirity bean)	3	3	Cholinergic toxicity	Abdominal pain, diarrhea, vomiting
[35]	*Vaccinium* and *Colocasia* species (wild berries)	1	32	Fatal toxicity	Deaths, ND
[36]	*Narcissus tazetta* (cream narcissus)	1	10	Cholinergic toxicity	Nausea, severe vomiting, diarrhea, dermatitis
[37]	*Camellia sinensis* (green tea)	1	1	Liver failure	Jaundice
[38]	*Albizia julibrissin*	3	10	CNS toxicity	Decreased level of consciousness
[38-48]	*Cannabis*	11	132	CNS toxicity	Coma, hypotonia, mydriasis and seizure
[38,49-51]	*Nerium oleander*	4	16	Cardiac toxicity	Tachycardia, vomiting
[52-55]	*Atropa belladonna* (deadly nightshade)	4	52	Anticholinergic toxic syndrome	Dry mouth, confusion, incoherent speech, visual disturbances, hearing and visual hallucinations
[56]	*Gaultheria* species	1	1	Salicylate toxicity	Vomiting, tonic–clonic seizures
[17]	*Juniperus oxycedrus* (juniper tar or cade oil)	1	1	Renal failure and hepatotoxicity	Convulsions, collapses, hypotension, hypothermia, tachypnea, tachycardia
[29]	*Salvia officinalis* (sage oil or apple oil)	1	2	Epileptogenic	Tonic–clonic seizures
[57-60]	*Jatropha curcas* (ratanjyot or jungli erandi)	4	102	Cholinergic toxicity	Abdominal pain, diarrhea, vomiting
[61-67]	*Prunus* species (apricot seeds)	7	72	Cyanide intoxication	Hyperglycemia, coma, hypotension, metabolic acidosis, convulsions
[25]	*Lavandula angustifolia*	1	1	CNS toxicity	Depression and confused state
[26,68-70]	*Karwinskia humboldtiana* (buckthorn, coyotillo, or tullidora)	4	21	Neurotoxicity	Flaccid, symmetric, progressive, ascending palsy, bulbar palsy and death
[71]	*Retama raetam* (white weeping broom)	1	1	Respiratory failure	CNS depression
[72]	*Ficus insipida*	1	20	Cerebral edema	Vomiting, nausea, psychomotor excitation, unconsciousness, convulsions, death
[30,73-77]	*Ricinus communis* (castor bean)	6	14	Hepatotoxicity	Vomiting
[78-81]	*Callilepis laureola* (impila)	4	230	Atractyloside poisoning, hepatotoxicity	Abdominal pain, semi-coma, restlessness, vomiting, diarrhea, fatal liver necrosis, death
[82-92]	Eucalyptus oil	11	264	CNS toxicity	Slurred speech, ataxia and muscle weakness
[93-129]	*Datura stramonium* (jimson weed or thorn apple)	37	360	Anticholinergic toxicity	Mydriasis, tachycardia, agitation, disorientation, delirium, hallucinations, restlessness
[27,130]	Cinnamon oil	2	33	Gastrointestinal and dermatotoxicity	Rush or sensation of warmth, facial flushing, oral burning, nausea or abdominal pain
[131-138]	*Digitalis purpurea* (foxglove plants leaves)	8	8	Digitalis poisoning and cardiotoxicity	Dehydration, arrhythmia, vomiting, bradycardia
[28,139-147]	*Azadirachta indica* (margosa oil, neem oil)	10	67	CNS and hematotoxicity	Vomiting, drowsiness, metabolic acidosis, polymorphonuclear leukocytosis, anemia, and encephalopathy

ND=Not described; CNS=Central nervous system

retrospective study of forensic autopsy cases, it is estimated that near to 7% of poisoning deaths in China are due to the use of poisonous plants.[150] Medicinal plants and herbal remedies such as *Thespesia acutiloba* and *Bersama abyssinica* are currently used in South African for the treatment of various diseases, especially to combat pediatric infections. Toxicological studies have shown that most of these plant extracts have strong cytotoxicity and therefore cannot be

considered as appropriate pediatric remedies.[151] Other toxicological assessments have shown that some plants such as *Pelargonium sidoides*, *Salvia officinalis*, *Datura stramonium*, and eucalyptus can be hepatotoxic, epileptogenic, and hallucinogenic, and consumption of any part of these plants may result in hepatotoxicity, seizures, and severe acute anticholinergic poisoning, respectively.[29,30,93] Furthermore, it is reported that death can occur from respiratory failure in *Salvia officinalis* poisoning.[29]

Due to immature metabolic enzyme system, children and infants can be more susceptible to the toxic and side effects of these plants.[152,153] Studies on some medicinal plants show that most of these herbal products are contraindicated during pregnancy and early age, and even some of these products can cause abortion, contraception, or severe intoxication.[154] Although the results show that herbal intoxication occurs in all age groups, children as a sensitive groups are more susceptible to acute plant poisoning. Intoxication with plant toxins is a global health issue especially in sensitive age groups. Many case reports have described the toxicity of medicinal plants in human, particularly in pediatric patients. Findings show that children aged below 13 years comprises the majority (69.8%) of cases intoxicated with poisonous plant. Moreover, it is reported that about 60% of acute poisoning occurs in children younger than 20 years in Botswana and South Africa.[35] Reports have also demonstrated that ingestion of *Jatropha curcas* seeds or fruits is an important cause of acute plant poisoning in Thailand and Paris, and *Manihot esculenta* is the most common cause of death in children in Thailand.[155,156] Cyanide and salicylate toxicity has also been reported from ingestion of apricot seeds and *Gaultheria* species, respectively, and many of these intoxicated patients require intensive care therapy.[56,61] The results of a 5-year retrospective study have shown that of 867 plant-intoxicated pediatric patients, 260 cases were due to apricot seed poisoning.[157]

Findings have demonstrated that although herbal and traditional medicines may cause fewer side effects in comparison with synthetic drugs, medicinal plants may considerably contribute to acute poisoning incidents in children even with fatal outcomes.[35] Many of these plants have some active components that may cause side effects or adverse reaction with neurotransmitters or other medicines; hence, the use of herbal remedies needs precaution at least in certain illnesses or during pregnancy and breastfeeding.[158] The results of this survey and other studies suggest that adverse reactions of herbal medicines could be avoided by controlling the defined dose and also preventing self-medication.[11] Since supportive therapy is the only therapeutic approach for the treatment of acute intoxication with plant, and there is no specific therapy for most plant poisonings, medicinal plants should be used with caution. Furthermore, because children are at a greater risk of ingesting poisonous plants, and since the major type of exposure to these plants was unintentional ingestion and the consequences could be fatal particularly in children and elderly, parents and health-care professionals should be aware of the safety and the toxic properties of medicinal plant. It is also shown that the community awareness regarding the risk factors associated with plant poisoning is limited. Similarly, findings have shown that the awareness is also limited among health-care workers regarding the plant poisoning in children.[159] On the other hand, due to easily availability and increasing use of herbal products, health authorities should be aware of plant poisoning and the people should compare the side effects of self-medication with its potential benefits. Studies suggest that, like other drugs on the markets, medicinal plants must obey a well-established rule, wherein the dose per kilogram body weight, ingredients, suggested method of use, and possible side effects of the herbal products should be provided on the products.[160]

CONCLUSION

The results of this literature review show that although medicinal plants and herbal remedies may have potential benefits for the treatment of certain diseases, they may cause acute poisoning, including CNS disorders and hepatotoxicity in children as a sensitive age group. In addition, findings showed that since a single ingested dose of toxic plants can cause acute poisoning, health professionals and parents should be aware of these toxic effects and compare the side effects of self-medication with its potential benefits. In addition, it is suggested to establish a local database in each country including the library and toxic profiles of medicinal plants with easily accessible for the parents and health-care workers.

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Conflicts of interest
There are no conflicts of interest.

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