Review Article

Medicinal Plants from North and Central America and the Caribbean Considered Toxic for Humans: The Other Side of the Coin

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The consumption of medicinal plants has notably increased over the past two decades. People consider herbal products as safe because of their natural origin, without taking into consideration whether these plants contain a toxic principle. This represents a serious health problem. A bibliographic search was carried out using published scientific material on native plants from Mexico, Central America, and the Caribbean, which describe the ethnobotanical and toxicological information of medicinal plants empirically considered to be toxic. A total of 216 medicinal plants belonging to 77 families have been reported as toxic. Of these plants, 76 had been studied, and 140 plants lacked studies regarding their toxicological effects. The toxicity of 16 plant species has been reported in clinical cases, particularly in children. From these plants, deaths have been reported with the consumption of Chenopodium ambrosioides, Argemone mexicana, and Thevetia peruviana. In most of the cases, the principle of the plant responsible for the toxicity is unknown. There is limited information about the toxicity of medicinal plants used in Mexico, Central America, and the Caribbean. More toxicological studies are necessary to contribute information about the safe use of the medicinal plants cited in this review.

1. Introduction

The use of herbal medicine has increased around the world due to its presumptive efficiency, availability, and general acceptance. Approximately 80% of the general population, especially in developing countries, uses medicinal herbs for primary health care [1, 2]. Worldwide, the interest in medicinal plants by patients has increased over the past two decades. The global market for medicinal plants and plant-derived drugs in 2015 was estimated at 25.6 billion dollars and is expected to rise to 35.4 billion dollars in 2020 [3]. This clearly indicates that the consumption of medicinal plants is a current topic of interest. Despite the high consumption of medicinal plants and related products, their toxicity remains to be evaluated. In addition, many medicinal plants require scientific evidence for their medicinal use, particularly those that are sold as food supplements.

Some medicinal plants might trigger undesirable side effects for human health because of (a) pharmacodynamic interaction with prescribed drugs, (b) intrinsic effects, (c) pharmacokinetic interaction with prescribed drugs, and (d) the presence of contaminants and/or pathogenic microorganisms. Other factors that impact the toxicity of medicinal plants in humans include the age of the patient, nutritional status, and the presence of chronic diseases. The concentration of toxic metabolites in plants is determined by the season
of collection, nutrients in the soil, and growth stage, among others [4].

The main reasons for focusing this review on medicinal flora with supposed toxicological effects from Mexico, Central America, and the Caribbean are as follows: (a) the ancient importance of traditional medicine in this region, (b) their great biodiversity, and (c) the current use of herbal products. This review will be useful for physicians, toxicologists, pharmacologists, and general audiences. We have tried to describe in detail some toxic symptoms reported with the consumption of the medicinal plants covered in this review.

2. Methodology

A bibliographic search was conducted from July 2016 to May 2017 of published scientific material on native plants from Mexico, Central America, and the Caribbean that describes the ethnomedical and toxicological information for medicinal plants reputed to be toxic for humans. The following keywords were searched in different scientific databases: plant extract, toxicity, Mexico, and Central America. Additional data were acquired from undergraduate and postgraduate theses, as well as published and electronic books. The admittance criteria for the selection of scientific information in this review were as follows: (i) plants native to North and Central America and the Caribbean, (ii) plants used for medicinal purposes with or without toxicological studies, (iii) plants used with experimental reports on their in vitro and/or in vivo toxicity, (iv) plants thought to be toxic for humans, (v) studies where the concentrations were presented as weight/volume relationship in international units (mg/ml, µg/ml), (vi) studies where the doses were presented as weight/weight relationship in international units (mg/kg, g/kg), and (vii) plants with information obtained from a clear source. Scientific studies reporting the combination of plant extracts were excluded. Medicinal plants considered toxic were classified into two categories: (1) plants with toxicological evidence reported in a scientific source and (2) plants without toxicological evidence. All plant names and their distributions were confirmed at the Missouri botanical garden [73]. Many of the medicinal plants cited in this review have no common name in English. Therefore, the common names were given in Spanish (Table 1).

3. Medicinal Plants Considered to Be Toxic for Humans

A total of 216 medicinal plants belonging to 77 families reported as toxic were recorded. Of these plants, 76 had been studied, and 140 plants lacked studies regarding their toxicological effects (Table 1). Aristolochia (6 plant species), Euphorbia (6 plant species), Solanum (5 plant species), and Asclepias (5 plant species) are the plant genera most often reported to induce toxicity (Table 1). Chemotaxonomic studies should be performed to identify the toxic principle in these genera. The parts of the plants considered toxic are listed in the following order: aerial parts including branches, leaves and flowers (22%), whole plant (22%), leaves exclusively (15%), seeds (14%), roots (8%), fruits (8%), bark (4%), latex (3%), and other plant parts.

The signs and symptoms of toxicity induced by medicinal plants are reported in Table 1. The main toxic effects occur in the following order: nausea and vomiting (20%), dermatitis (14%), gastritis (9%), abdominal pain (9%), abortifacient (8%), skin burns (8%), hepatotoxicity (7%), severe diarrhea (6%), cardiotoxicity (5%), nephrotoxicity (2%), numbness (2%), dizziness (2%), and hallucinations (2%), among others.

3.1. Dosages. In most of the cases, the dose for the induction of toxic effects by medicinal plants is not indicated. Usually, consumers of medicinal plants believe that increasing the consumption of these products will increase the efficacy of the treatment. In these cases, the daily dosage is exceeded, which triggers toxicity. For instance, the roots of Ipomoea purga, a purgative agent, are used at a dose of 2 g/L/day. Administration of higher doses induces vomiting and abdominal pain [15]. Fresh leaves of Prunus serotina, used for the treatment of cough, or Zanthoxylum fagara, an anxiolytic agent, each must be consumed in a maximum quantity of five leaves in 250 ml of water per day. Higher doses produce spasms and nausea [26]. Approximately 5 mL of an infusion of Picrasma excelsa (10 g/L) should be administered three times per day. Higher doses induce hypotension. This infusion should not be prepared with ethanol and orally administered. If a person consumes the hydroalcoholic infusion, the consequences could be lethal [35]. The maximum consumption of Manilkara zapota seeds should be 10 seeds per day. A higher consumption of these seeds might induce vomiting and gastroenteritis [26]. On the other hand, Sosa-Gómez [35] recommends the preparation of an infusion using approximately 1–3 g Argemone mexicana leaves in 1 L of water. This infusion should be taken 3 times per day. A higher dose might induce immobilization.

Studies analyzing the range of doses considered safe for human consumption remain to be performed. The use of natural products needs scientific evidence to corroborate the medicinal uses attributed to different plant species. Many medicinal plants sold as “food supplements” lack warnings if the suggested dosage is exceeded.

3.2. Toxic Principles. In some cases, the toxic principle is known. For instance, it is reported that cefalatin, the main toxic compound in Cephalanthus occidentalis bark, induces vomiting, anemia, and seizures, among other toxic effects. Similarly, hedergenin is the main toxic compound in Clematis dioica, which is a caustic substance [4]. Monocrotaline is the compound responsible for the toxic effects in Crotalaria sagittalis. Cianhidric acid, one of the most toxic compounds in plants, is found in Crescentia cujete fruit, Phaseolus lunatus whole plant, and Prunus serotina leaves and seeds [4]. In Phaseolus lunatus, the concentration of cianhidric acid ranges 6.8–533 mg/kg dw [74, 75]. There is limited information on the major toxic compounds cited in this review. Therefore, the identification of toxic principles in medicinal plants is necessary.
| Family | Scientific name | Common name in Spanish | Medicinal use | Signs of toxicity [plant part] | Reference |
|--------|-----------------|------------------------|---------------|--------------------------------|-----------|
| **Amaranthaceae** | *Amaranthus spinosus* L. | Quelite de Puerco | Rheumatism, diuretic, wound healing | Nephrotoxicity [whole plant] | [5] |
| **Chenopodiaceae** | *Chenopodium ambrosioides* L. | Epazote | Vermifuge, vomit | Nephrotoxicity abortifacient, hepatotoxicity [whole plant] | [6] |
| **Amaryllidaceae** | *Allium glandulosum* Link & Otto | Cebolla de monte | Cough, flu, tuberculosis | Numbness, nausea, and vomiting [bulb] | [7] |
| **Anacardiaceae** | *Metopium brownei* (Jacq.) Urb. | Chechém negro | Antiviral, Rheumatism | Skin burns [latex from leaves] | [8] |
| **Toxicodendron radicans** (L.) Kuntze | Hiedra venenosa | Headache, rheumatism | Dermatitis [latex] | | [9] |
| **Annonaceae** | *Annona cherimola* Mill. | Chirimoya | Diarrhea, dysentery | Abortifacient [aerial parts, fruits] | [10] |
| **Apiaceae** | *Conium maculatum* L. | Cicuta | Body pain | Hypertension and sweating [whole plant] | [11] |
| **Asclepias curassavica** L. | Rompemuelas | Vermifuge, cancer, wound healing, diuretic | Nausea and vomiting, muscle paralysis [whole plant] | | [12] |
| **Asclepias linaria** Cav. | Algodoncillo | Cough, fever, purgative, diuretic | Muscle paralysis [leaves] | | [13] |
| **Asclepias mexicana** Cav. | Venenillo cimarrón | Warts | Numbness [leaves] | | [12] |
| **Asclepias oenotheroides** Schtdl. & Cham | Hierba lechosa | Tooth ache | Numbness, nausea, and vomiting [leaves] | | [5] |
| **Asclepias subverticillata** (A. Gray) Vail | Hierba lechosa | Snake bite | Severe diarrhea [leaves] | | [5] |
| **Apocynaceae** | *Plumeria rubra* L. | Zacalazúchil | Stomachache, toothache | Dermatitis [latex] | [14] |
| **Rauvolfia tetraphylla** L. | Cinco negritos | Wound healing, rheumatism | Diarrhea, nausea, and vomiting, hypertension, depression [aerial parts] | | [15] |
| **Thevetia ahouai** (L.) A. DC. | Bola de venado | Toothache, headache | Cardiotoxicity [fruits and seeds] | | [8] |
| **Thevetia gaumeri** Hemsl. | Campanilla | Toothache, cancer | Tooth loss [leaves, latex] | | [16] |
| **Thevetia peruviana** (Pers.) K. Schum. | Troncomin | Stomachache | Cardiotoxicity [leaves] | | [17] |
| **Thevetia thevetioides** (Kunth) K. Schum. | Yoyote | Warts, analgesic | Cardiotoxicity [whole plant] | | [18] |
| **Aquifoliaceae** | *Ilex opaca* Aiton | American holly | Digestive | Cardiotoxicity and vomiting [fruits] | [19] |
| Family | Scientific name | Common name in Spanish | Medicinal use | Signs of toxicity | Reference |
|--------|-----------------|------------------------|--------------|------------------|-----------|
| Araceae | *Anthurium crassinervium* (Jacq.) Schott | Kiilbal chaak | Warts | Dermatitis [sap] | [8] |
| Araceae | *Anthurium pentaphyllum* (Aubl.) G. Don | Hoja de reumatismo de bejuco | Rheumatism | Dermatitis [aerial parts] | [8] |
| Araceae | *Anthurium schlechtendalii* Kunth | Hoja de piedra | Hemorrhage postpartum | Dermatitis [aerial parts] | [8] |
| Araceae | *Caladium bicolor* (Aiton) Vent.** | Heart of Jesus | Antiseptic | | |
| Araceae | *Monstera deliciosa* Liebm.** | Cerimán | Flu, rheumatism | Dysphagia [aerial parts] | [20] |
| Aristolochiaceae | *Aristolochia foetida* Kunth | Guaco | Snake bite, headache | Hepatotoxicity [whole plant] | [21] |
| Aristolochiaceae | *Aristolochia grandiflora* Sw. | Flor de pato | Stomachache, snake bite | Abdominal pain, gastritis [roots] | [15] |
| Aristolochiaceae | *Aristolochia odoratissima* L. | Guaco | Diarrhea, stomachache, belly cramps | Nephrotoxicity and hepatotoxicity [roots] | [22] |
| Aristolochiaceae | *Aristolochia pentandra* Jacq | Camotillo guaco | Fever, diarrhea | Nephrotoxicity [roots] | [22] |
| Aristolochiaceae | *Aristolochia reticulata* Nutt. | Texas dutchman’s pipe | Digestive | Nephrotoxicity [roots] | [19] |
| Aristolochiaceae | *Aristolochia serpentaria* L. | Virginia snakeroat | Digestive, diuretic | Nephrotoxicity [roots] | [19] |
| Asparagaceae | *Yucca filifera* Chabaud | Palma | Cough | Nausea and vomiting [aerial parts] | [14] |
| Asparagaceae | *Acmella repens* (Walter) Rich. | Yerba de San Pedro | Malaria | Hallucinations [aerial parts] | [23] |
| Asparagaceae | *Ambrosia confertiflora* DC. | Amargosa | Diarrhea, vomiting | Gastritis [whole plant] | [13] |
| Asparagaceae | *Ambrosia peruviana* Willd.** | Altamisa | Rheumatism, pain, fever | Neurotoxicity [whole plant] | [24] |
| Asparagaceae | *Ambrosia psilostachya* DC. | Estafiate | Stomachache | Nausea and vomiting [whole plant] | [25] |
| Asparagaceae | *Artemisia ludoviciana* subsp. mexicana (Willd. ex Spreng.) D.D. Keck | Estafiate | Vermifuge, fever | Numbness, carcinogenic [aerial parts] | [14] |
| Asparagaceae | *Barkleyanthus salicifolius* (Kunth) H. Rob. & Brettell | Jaral Amarillo | Fever, diuretic, rheumatism | Hepatotoxicity [whole plant] | [14] |
| Asparagaceae | *Conyza filaginoides* (DC.) Hieron. | Simonillo | Stomachache, diabetes, anxiolytic | Nausea and vomiting [whole plant] | [7] |
| Asparagaceae | *Eupatorium odoratum* L. | Rama de la cruz | Wound healing, anti-inflammatory | Nausea and vomiting [whole plant] | [5] |
| Asparagaceae | *Flourensia cernua* DC.** | Hojasén | Stomachache, diarrhea | Hepatotoxicity [leaves] | [13] |
### Table 1: Continued.

| Family       | Scientific name                        | Common name in Spanish | Medicinal use          | Signs of toxicity [plant part] | Reference |
|--------------|----------------------------------------|-------------------------|------------------------|--------------------------------|-----------|
| **Asteraceae** |                                        |                         |                        |                                |           |
|              | *Gymnopus glutinosum* (Spreng.) Less.** | Tatalencho              | Diuretic, rheumatism, analgesic | Sleepiness, muscle paralysis [seeds, leaves] | [5]       |
|              | *Haplopappus gymnocyclus* DC.           | Arnica morada           | Body pain, hemorrhoids  | Gastritis [aerial parts]       | [14]      |
|              | *Helenium mexicanum* Kunth              | Cabezona                | Flu                    | Gastritis and vomiting [flowers] | [15]      |
|              | *Heliopsis longipes* (A. Gray) S.F. Blake** | Chilcuague              | Analgesic              | Narcotic [roots]               | [26]      |
|              | *Montanoa tomentosa* Cerv.              | Zoapatle                | Rheumatism, cough, menstrual colic | Abortifacient, respiratory failure [aerial parts] | [27]       |
|              | *Packera aurea* (L.) Á. Löve & D. Löve | Life root               | Amenorrhea, menopause and leucorrhea. | Hepatotoxicity [aerial parts] | [19]       |
|              | *Packera candidissima* (Greene) W.A. Weber & Á. Löve | Chuca                   | Cough                  | Hepatotoxicity [aerial parts] | [28]       |
|              | *Parthenium hysterophorus* L.**         | Escoba amarga           | Stomachache, headache | Hypotensieve, bradycardia [whole plant] | [29]       |
|              | *Parthenium incanum* Kunth              | Mariola                 | Stomachache, diarrhea  | Nausea and vomiting [whole plant] | [13]      |
|              | *Psacalium decompositum* (A. Gray) H. Rob. & Brettell | Matarique              | Diabetes, rheumatism   | Neurotoxicity [roots]          | [30]      |
|              | *Tagetes erecta* L.**                   | Flor de muerto          | Diarrhea, vermifuge, diabetes, rheumatism | Gastritis [flowers] | [31]       |
|              |                                        | (cempaxochitl)          |                        |                                |           |
|              | *Tagetes lucida* Cav**                  | Pericón                 | Stomachache, diarrhea, vomit | Abortifacient [whole plant] | [32]      |
|              | *Zinnia peruviana* (L.) L.**            | Mal de ojo              | Stomachache, diarrhea  | Eye irritant                   | [14]      |
|              | **                                      |                         |                        |                                |           |
| **Berberidaceae** |                                        |                         |                        |                                |           |
|              | *Berberis moranensis* Schult. & Schult. f. | Palo amarillo          | Rheumatism             | Numbness, nausea, and vomiting [aerial parts] | [33]      |
|              | *Caulophyllum thalictroides* (L.) Michx.** | Blue cohosh            | Dysmenorrhea, rheumatism | Nausea and vomiting, gastritis [seeds and roots] | [11]      |
|              |                                        |                         |                        | Altered mental states, tachypnea, peripheral neuropathy, nausea and vomiting, hypotension, and fever [whole plant] | [19]       |
|              | *Podophyllum peltatum* L.**             | Mayapple                | Genital warts          |                                |           |
| **Bignoniaceae** |                                        |                         |                        |                                |           |
|              | *Crescentia alata* Kunth                | Cuatecomate             | Cough, asthma          | Vomiting, abdominal pain [fruit] | [21]      |
|              | *Crescentia cujete* L.**                | Güiro                   | Cough, tuberculosis    | Abortifacient, severe diarrhea [fruits] | [18]      |
| Family          | Scientific name                          | Common name in Spanish | Medicinal use               | Signs of toxicity [plant part] | Reference |
|-----------------|------------------------------------------|------------------------|-----------------------------|--------------------------------|-----------|
| Boraginaceae    | *Cordia dentata* Poir. **                | Uvita                  | Cough                       | Severe diarrhea [fruits]      | [8]       |
|                 | *Heliotropium curassavicum* L.           | Alacrancillo           | Asthma, anemia, snake bite  | Hepatitis [whole plant]       | [11]      |
| Bromeliaceae    | *Bromelia pinguin* L.                    | Piñuela                | Cough                       | Dermatitis [fruits]           | [34]      |
|                 | *Bromelia plumieri* (E. Morren) L.B. Sm. | Timbiriche             | Inflammation                | Dermatitis [fruits]           | [8]       |
| Cactaceae       | *Cereus marginatus* DC.                  | Oregano de zopilote    | Rabies                      | Cardiotoxicity [aerial parts] | [13]      |
|                 | *Coryphantha pycnantha* (Mart.) Lem.     | Falso peyote           | Rheumatism, analgesic       | Sedation in tongue [fruit]    | [14]      |
|                 | *Lophophora williamsii* (Lem. ex Salm-Dyck) J.M. Coul. | Peyote | Rheumatism, analgesic       | Hallucinations [whole plant]  | [30]      |
| Campanulaceae   | *Lobelia cardinalis* L.                  | Lobelia                | Cough, flu                  | Hypothermia, vomiting, abdominal pain [aerial parts] | [4] |
|                 | *Lobelia inflata* L. **                  | Lobelia                | Asthma, muscle relaxant     | Hypotension [whole plant]     | [35]      |
| Canellaceae     | *Canella winterana* (L.) Gaertn.         | Cúrbana                | Rheumatism, stomachache    | Edema, hemorrhage [whole plant] | [36]      |
| Caprifoliaceae  | *Lonicera periclymenum* L.               | Woodbine               | Diuretic, cough             | Cardiotoxicity and neurotoxicity [fruits] | [11] |
|                 | *Symphoricarpos albus* (L.) S.F. Blake  | Snowberry              | Tuberculosis                | Nausea and vomiting, abdominal pain [whole plant] | [11] |
| Celastraceae    | *Celastrus scandens* L.                  | Falsa dulcamara        | Diuretic, tuberculosis      | Gastritis, nausea and vomiting, diarrhea [fruit] | [11] |
|                 | *Euonymus atropurpureus* Jacq.          | Wahoo                  | Purgative                   | Vomiting [bark]               | [11]      |
| Commelinaceae   | *Commelina elegans* Kunth               | Hierba del pollo       | Conjunctivitis              | Edema, dermatitis [whole plant] | [8] |
|                 | *Tradescantia spathacea* Sw.             | Maguey morado          | Cancer, wound healing, asthma, cough | Skin burns [sap] | [8] |
| Convolvulaceae  | *Ipomoea murucoides* Roem. & Schult.    | Cazahuate              | Hair loss, wound healing, cough, diuretic | Gastritis [bark] | [37] |
|                 | *Ipomoea purga* (Wender.) Hayne          | Raíz de Jalapa         | Purgative                   | Vomiting and abdominal pain [roots] | [15] |
|                 | *Ipomoea stans* Cav.                     | Tumbavaqueros          | Epileptic seizures          | Neurotoxicity [roots]         | [38]      |
|                 | *Ipomoea tricolor* Cav.                  | Hiedra de flores grandes | Analgesic                    | Hallucinations [aerial parts]  | [14]      |
|                 | *Turbina corymbosa* (L.) Raf.            | Flor de pascua         | Fever, wound healing        | Hallucinations [seeds]        | [4]       |
| Family          | Scientific name          | Common name in Spanish | Medicinal use                      | Signs of toxicity [plant part]                  | Reference |
|-----------------|--------------------------|------------------------|-----------------------------------|-----------------------------------------------|-----------|
| Coriariaceae    | Coriaria ruscifolia L.   | Huique                 | Pneumonia                         | Hallucinations [aerial parts]                 | [33]      |
| Cucurbitaceae   | Apodanthera undulata A. Gray | Gualaista          | Gastritis                         | Vomiting and abdominal pain [roots and seeds] | [14]      |
| Dioscoreaceae   | Dioscorea floribunda M. Martens & Galeotti | Barbasco amarillo | Rheumatism, body pain          | Abortifacient [roots]                         | [8]       |
| Equisetaceae    | Equisetum hyemale L.**   | Carricillo             | Abdominal pain, urinary tract infections | Hepatotoxicity [whole plant]               | [39]      |
| Ericaceae       | Arbutus arizonica (A. Gray) Sarg. | Madroño              | Diuretic                          | Nausea and vomiting [fruit]                  | [14]      |
|                 | Comarostaphylis discolor (Hook.) Diggs | Madroño              | Diuretic                          | Nausea and vomiting [fruit]                  | [33]      |
|                 | Kalmia latifolia L.      | Ivy brush             | Syphilis                          | Neurotoxicity, cardiotoxicity [aerial parts] | [11]      |
|                 | Acalypha monostachya Cav. Cav | Hierba del cancer    | Cancer                            | Skin burns [latex]                           | [14]      |
|                 | Adelia barbinervis Schltldl. & Cham. | Espino blanco        | Body pain, wounds                 | Dermatitis [aerial parts]                    | [8]       |
|                 | Cnidoscolus chayamansa McVaugh** | Chaya                | Diabetes                          | Dermatitis [aerial parts]                    | [8]       |
|                 | Cnidoscolus souzae McVaugh | Ch’iinchay            | Rheumatism                        | Dermatitis [aerial parts]                    | [8]       |
|                 | Cnidoscolus urens (L.) Arthur** | Ortiga               | Diuretic                          | Hypotension, skin burns, nausea and vomiting [whole plant] | [24]      |
|                 | Croton ciliatoglandulosus Ortega | Hierba de la cruz    | Constipation                      | Gastritis, excessive salivation [whole plant] | [4]       |
|                 | Croton humilis L.        | ik’ja’aban             | Wounds                            | Skin burns [whole plant]                     | [8]       |
|                 | Dalechampia scandens L.  | Mool koj               | Headache                          | Edema, dermatitis [aerial parts]             | [11]      |
|                 | Euphorbia cotinifolia L. | Lechero rojo           | Purgative                         | Skin burns [seeds]                           | [24]      |
|                 | Euphorbia hirta L.**     | Hierbe de la golondrina | Stomachache                      | Skin burns [aerial parts]                    | [14]      |
|                 | Euphorbia maculata L.    | Hierbe de la golondrina | Tooth ache                        | Severe diarrhea, vomiting [seeds]            | [4]       |
| Euphorbiaceae   | Euphorbia prostrata Aiton** | Hierba de la golondrina | Pain in the kidney, wounds, diarrhea | Gastritis, abdominal pain [whole plant]    | [31]      |
|                 | Euphorbia pulcherrima Willd. ex Klotzsch** | Noche buena          | Wound healing                     | Vomiting, diarrhea, abdominal pain [whole plant] | [40]      |
|                 | Euphorbia tithymaloides L. | Redbird flower        | Asthma, skin cancer, warts        | Irritation of the mouth and throat, vomiting [whole plant] | [20]      |
| Family                      | Scientific name          | Common name in Spanish | Medicinal use                  | Signs of toxicity [plant part] | Reference |
|-----------------------------|--------------------------|------------------------|--------------------------------|--------------------------------|-----------|
| Hura crepitans L.**         | Catahua                  | Laxative               | Skin burns [seeds]             |                                | [41]      |
| Hura polyandra Baill.       | Haba                     | Stomachache, body pain,| Skin burns [latex], nausea and | Vomiting, gastritis [seeds and fruits] | [15]      |
| Jatropha curcas L.**        | Piñon                    | Fever, warts           | Dermatitis, vomiting, diarrhea|                                | [36]      |
| Jatropha dioica Sessé**     | Sangre de grado          | Cancer, rheumatism, hair loss, wound healing | Dermatitis, vomiting, muscle paralysis [stem, fruits] |                                | [13]      |
| Jatropha gossypifolia L.**  | Tua tua                  | Cough, flu, fever      | Skin burns, abortifacient [seeds, leaves] |                                | [42]      |
| Jatropha multifida L.**     | Palmeado                 | Wound healing, to purify blood | Severe diarrhea [seeds] |                                | [43]      |
| Manihot esculenta Crantz**  | Yuca                     | Wound healing, vermifuge | Poisoning and neurotoxicity [leaves] |                                | [41]      |
| Tragia nepetfolia Cav.      | Ortiguilla               | Diuretic               | Skin burns [Aerial parts] |                                | [44]      |
| Tragia yucatanensis Millsp. | Poopóx                   | Rheumatism             | Dermatitis [aerial parts] |                                | [8]       |
| Abrus precatorius L.**      | Semilla de culebra       | Diabetes, asthma       | Stomachache, diarrhea [aerial parts] |                                | [4]       |
| Andira inermis (W. Wright) Kunth ex DC. | Yaba             | Vermifuge              | Vomiting, fever, hypotension, mental confusion, respiratory insufficiency [bark] |                              | [36]      |
| Astragalus platensis Nutt.  | Garbancillo              | Diuretic               | Vomiting [leaves]             |                                | [26]      |
| Caesalpinia pulcherrima (L.) Sw.** | Clavellina colorada     | Fever, pain, cough    | Dermatitis and neurotoxicity [Aerial parts] |                              | [18]      |
| Calliandra grandiflora (L’Hér.) Benth. | Cabello de ángel | Fever                   | Dermatitis [leaves]          |                                | [45]      |
| Calliandra molinae Standl.  | Palo de corcho           | Hypertension           | Hepatotoxicity, hypotension [leaves] |                                | [46]      |
| Crotalaria pumila Ortega    | Tronador                 | Cough, diabetes        | Abdominal pain, nausea and vomiting [whole plant] |                              | [14]      |
| Crotalaria sagittalis L.    | Cocuite                  | Fever, snake bite      | Anoxia, gastritis, abdominal pain, blood in feces [Aerial parts] |                                | [4]       |
| Dalea bicolor Humb. & Bonpl. ex Willd. | Engordacabra             | Diarrhea               | Vomiting [aerial parts] |                                | [14]      |
| Diphysa robiniioides Benth. | Flor de gallito          | Fever, headache        | Nausea and vomiting [leaves] |                                | [47]      |
Table 1: Continued.

| Family          | Scientific name               | Common name in Spanish | Medicinal use       | Signs of toxicity [plant part]                                                                 | Reference |
|-----------------|-------------------------------|------------------------|---------------------|-------------------------------------------------------------------------------------------------|-----------|
| **Fabaceae**    |                               |                        |                     |                                                                                                |           |
|                 | *Entada polystachya* (L.) DC. | Bejuco de agua         | To promote hair growth | Abdominal pain and severe diarrhea [Fruits]                                                     | [4]       |
|                 | *Enterolobium cyclocarpum* (Jacq.) Griseb.** | Cascabel sonaja        | Bronchitis, sore throat | Severe diarrhea and abdominal pain [Aerial parts] Immobilization, hypotension, and respiratory paralysis [seeds] | [4]       |
|                 | *Erythrina americana* Mill**  | Colorín                | Diuretic            |                                                                                                | [15]      |
|                 | *Erythrina standleyana* Krukkoff | Cancer                | Cancer              | Somnolence, vomit [aerial parts]                                                              | [8]       |
|                 | *Gilricidia sepium* (Jacq.) Kunth ex Walp | Matarratón            | Vermifuge           | Nausea and vomiting [roots, leaves, seeds]                                                     | [24]      |
|                 | *Indigofera microcarpa* Desv. | Yaga-cohui-pichacha    | Purgative           | Severe diarrhea [leaves]                                                                       | [4]       |
|                 | *Indigofera suffruticosa* Mill.** | Añil                   | Vermifuge           | Severe diarrhea [leaves]                                                                       | [4]       |
|                 | *Leucaena esculenta* (Moc. & Sessé ex DC.) Benth. | Guaje                  | Wound healing       | Nausea and vomiting [seeds]                                                                    | [48]      |
|                 | *Myroxyylon pereirae* (Royle) Klotzsch** | Indian balsam          | Burns, wounds and ulcers | Allergies, contact urticaria and dermatitis [resin]                                              | [49]      |
|                 | *Phaseolus lunatus* L.        | Frijol ancho           | Fever, headache     | Seizures, immobilization [whole plant]                                                          | [4]       |
|                 | *Prosopis juliflora* (Sw.) DC. | Mezquite               | Fever, diabetes     | Nausea and vomiting [seeds]                                                                    | [4]       |
|                 | *Robinia pseudoacacia* L.     | Black locust           | Diuretic, laxative  | Anorexia, hypothermia, dyspnoea [bark, leaves and seeds]                                       | [4]       |
|                 | *Senna multiglandulosa* (Jacq.) H.S. Irwin & Barneby | Parral                 | Diabetes            | Abortifacient [fruit] Gastroitis, dermatitis, and conjunctivitis [fruit]                        | [33]      |
|                 | *Senna occidentalis* (L.) Link** | Frijolillo             | Fever               |                                                                                                | [4]       |
| **Garryaceae**  | *Garrya ovata* Benth.          | Cuauhchichic           | Diarrhea            | Muscle paralysis [bark]                                                                         | [26]      |
| **Gelsemiaceae**| *Gelsemium sempervirens* (L.) J. St.-Hil.** | Retama               | Stomachache, asthma, headache, rheumatism | Sedative, vertigo, hypotension, blurred vision [whole plant]                                  | [10]      |
| **Gesneriaceae**| *Moussonia deppeana* (Schlddl. & Cham.) Hanst.** | Cacahuapaxtle          | Diuretic, gastritis | Abortifacient [aerial parts]                                                                   | [50]      |
|                 | *Hedeoma drumondii* Benth.     | Drummond’s false pennyroyal | Muscle relaxing     | Abortifacient [whole plant]                                                                    | [26]      |
|                 | *Hedeoma pulegioides* (L.) Pers. | American pennyroyal    | Antispasmodic, pneumonia | Abortifacient, kidney toxicity [aerial parts]                                                  | [19]      |
|                 | *Salvia leucantha* Cav         | Lana                   | Cough, stomachache  | Abortifacient [aerial parts]                                                                   | [27]      |
| Family          | Scientific name | Common name in Spanish | Medicinal use                      | Signs of toxicity [plant part] | Reference |
|-----------------|-----------------|------------------------|------------------------------------|-------------------------------|-----------|
| Lamiaceae       | *Satureja brownei* (Sw.) Briq. | Poleo                  | Colic, cough                       | Nausea and vomiting, dermatitis, bleeding [whole plant] | [24]      |
|                 | *Scutellaria lateriflora* L. | Scullcap               | Nervousness, headache, fever, anxiety | Giddiness, stupor, confusion, twitching of the limbs, intermission of the pulse [whole plant] | [19]      |
| Loasaceae       | *Mentzelia hispida* Willd. | Pegajilla              | Rheumatism, anemia                 | Vomiting [resin]               | [14]      |
| Loranthaceae    | *Psittacanthus calyculatus* (DC.) G. Don** | Muerdago o injerto    | Hypertension, seizures, rheumatism, wound healing | Nausea and vomiting [whole plant] | [26]      |
| Lythraceae      | *Cuphea aequipetala* Cav:** | Hierba del cáncer      | Cancer, wound healing              | Numbness, nausea and vomiting [aerial parts] | [10]      |
| Magnoliaceae    | *Magnolia grandiflora* L.** | Magnolia               | Nervousness, menstrual colics       | Dermatitis [leaves]            | [51]      |
| Malpighiaceae   | *Malpighia glabra* L. | Acerola                | Dysentery, fever                   | Dermatitis [fruits]            | [19]      |
| Malvaceae       | *Ceiba pentandra* (L.) Gaertn.** | Ceiba                 | Diuretic, cough, fever             | Dermatitis [seeds]             | [24]      |
|                 | *Tilia mexicana* Schldtl.** | Tilia                 | Nervousness, menstrual pain         | Hepatotoxicity [flower]        | [39]      |
| Marantaceae     | *Thalia geniculata* L. | Kento                 | Anaemia, hemorrhoids               | Edema, gastritis [aerial parts] | [8]       |
| Martyniaceae    | *Martynia annua* L.** | Uña de gato           | Snake bite                         | Nausea and vomiting [seeds]    | [18]      |
| Melanthiaceae   | *Veratrum californicum* Durand** | California corn lily   | Cancer                             | Neurotoxicity [whole plant]    | [11]      |
|                 | *Trillium erectum* L. | Bethroot              | To prevent obstetric hemorrhage    | Skin burns [leaves]            | [19]      |
| Menispermaeae   | *Menispermum canadense* L. | Canada moonseed       | Warts                              | Cardiotoxicity [fruits]        | [11]      |
| Myrtaceae       | *Pimenta dioica* (L.) Merr.** | Pimiento              | Rheumatism, stomachache            | Neurotoxicity [whole plant]    | [19]      |
| Nartheciaceae   | *Aletris farinosa* L. | Unicorn root          | Laxative, diarrhea, rheumatism     | Narcotic [whole plant]         | [19]      |
| Nyctaginacea    | *Mirabilis jalapa* L.** | Maravilla             | Rheumatism, stomachache, fever     | Severe diarrhea [roots and seeds] | [4]       |
| Oxalidaceae     | *Oxalis alpina* (Rose) Rose ex R. Knuth | Acedera              | Gastritis                          | Poisoning [whole plant]        | [7]       |
| Papaveraceae    | *Argemone mexicana* L.** | Cardo santo           | Wound healing, fever, diuretic, analgesic | Dermatitis, abortifacient immobilizing, neurotoxicity [whole plant] | [35]      |
|                 | *Sanguinaria canadensis* L.** | Bloodroot            | Skin cancer, polyps and warts      | Narcotic [root]                | [19]      |
| Family        | Scientific name          | Common name in Spanish | Medicinal use         | Signs of toxicity [plant part] | Reference |
|--------------|--------------------------|------------------------|-----------------------|--------------------------------|-----------|
| Passifloraceae | *Passiflora caerulea* L. | Pasionaria azul        | Epilepsy, anxiolytic  | Nausea and vomiting, dizziness [flower] | [24]      |
|              | *Passiflora edulis* Sims** | Maracuya               | Relaxing              |                                 | [39, 41]  |
|              | *Passiflora quadrangularis* L. | Badea                 | Vermifuge, obesity    | Nausea and vomiting, dizziness [leaves and seeds] | [24]      |
| Petiveriaceae | *Rivina humilis* L.**     | Coralillo              | Varicose veins, snake bite, wound healing, stomachache | Nausea and vomiting, abdominal pain [whole plant] | [11]      |
| Phytolaccaceae | *Phytolacca americana* L.  | Hierba carmine        | Warts                 | Blurred vision, vomit, vertigo [whole plant] | [52]      |
|              | *Phytolacca icosandra* L.** | Mazorquilla          | Cancer, vermifuge, rheumatism | Blurred vision, vomiting, [roots] | [14]      |
|              | *Phytolacca rivinoides* Kunth & C.D. Bouché | Mazorquilla | Headache, wound healing, vermifuge | Blurred vision, vomit, vertigo [whole plant] | [30]      |
| Plantaginaceae | *Scoparia dulcis* L.** | Culantrillo           | Diarrhea, stomachache, asthma, nervousness | Hepatotoxicity [whole plant] | [39]      |
| Plumbaginaceae | *Plumbago pulchella* Boiss. | Jiricua               | Diabetes, wound healing | Skin burns, vomiting [whole plant] | [14]      |
| Polygalaceae  | *Monminia schlechtendaliana* D. Dietr. | Aguacatillo        | Dehydration           | Nausea and vomiting [fruit] | [33]      |
|              | *Polygala senega* L.       | rattlesnake root      | Cough, diuretic       | Gastritis [roots]              | [19]      |
|              | *Rumex hymenosepalus* Torr.** | Canaigre            | Wound healing         | Vomiting, abdominal pain [Aerial parts] | [19]      |
| Ranunculaceae | *Actaea alba* (L.) Mill.  | White cohosh          | Arthritis, rheumatism, dysmenorrhea | Headache, vomiting, delirium, circulatory failure [whole plant] | [19]      |
|              | *Actaea rubra* (Aiton) Willd. | Baneberry            | Dysmenorrhea          | Vomiting, abdominal pain, salivation [fruits and roots] | [11]      |
|              | *Anemone canadensis* L.    | Meadow anemone        | Body pain and wound healing | Salivation, abdominal pain, and salivation [whole plant] | [11]      |
|              | *Cimicifuga racemosa* (L.) Nutt.** | Baneberry          | To manage some symptoms of menopause | Vomiting, abdominal pain [fruit] | [19]      |
|              | *Clematis dioica* L.       | Barba de chivo        | Rheumatism, cough, diuretic | Skin burns [leaves] | [10]      |
Table 1: Continued.

| Family     | Scientific name | Common name in Spanish | Medicinal use | Signs of toxicity [plant part] | Reference |
|------------|-----------------|------------------------|---------------|--------------------------------|-----------|
|            | *Clematis virginiana* L. | Old man’s beard | For skin disorders (sores, cuts), itching and venereal eruptions | Dizziness, confusion, profuse salivation [leaves] | [19] |
|            | *Hydrastis canadensis* L.** | Sello dorado | Laxative | Gastritis, abortifacient [rhizome] | [35] |
|            | *Ranunculus geoides* Humb. Bonpl. & Kunth ex DC | Pata de león | Cough | Skin burns [seeds and fruits] | [30] |
|            | *Thalictrum strigilosum* Hemsl. | Hierba del zorro | Cough | Nausea and vomiting [whole plant] | [7] |
| Rhamnaceae | *Karwinskia humboldtiana* (Schult.) Zucc.** | Tullidora | Wound healing | Immobilization, abortifacient [fruit] | [53] |
|            | *Karwinskia mollis* Schltdl. | Capulín | Wound healing | Immobilization [fruit] | [54] |
|            | *Rhamnus kalmia* Eschsch | California buckthorn | Laxative | Gastritis [fruit and bark] | [11] |
| Rosaceae   | *Prunus serotina* Ehrh. | Capulín blanco | Cough, diarrhea, abdominal pain | Spasm, nausea and vomiting [leaves and seeds] | [7] |
|            | *Carapichea ipacuana* (Brot.) L. Andersson | Ipecac | Dysentery | Rhinitis or asthma [whole plant] | [19] |
|            | *Cephalanthus occidentalis* L. | Guayabillo | Fever | Vomiting, seizures, anemia [bark] | [4] |
| Rubarwiaceae | *Cinchona pubescens* Vahl** | Quino | Malaria, varicose veins, internal hemorrhoids | Hypoglycemia, hematologic disorders, urticaria, contact dermatitis, and other hypersensitivity reactions. | [19] |
| Rutaceae   | *Casimiroa edulis* La Llave & Lex.** | Matasanos | Hypertension, diabetes, rheumatism | Hepatotoxicity, peptic ulcer, hypotensive [leaves] | [46] |
|            | *Ruta chalepensis* L.** | Ruda | Analgesic | Dermatitis, abortifacient [aerial parts] | [18] |
|            | *Zanthoxylum fagara* (L.) Sarg. | Colima | Nervousness | Narcotic [leaves] | [26] |
| Santalaceae | *Phoradendron bolleanum* (Seem.) Eichler | Muerdago | Diuretic | Nausea and vomiting [leaves and seeds] | [55] |
|            | *Phoradendron quadrangulare* (Kunth) Griseb. | Muerdago | Cancer | Nausea and vomiting, dehydration [aerial parts] | [11] |
|            | *Phoradendron serotinum* (Raf.) M.C. Johnst.** | Muerdago | Cancer, diabetes | Nausea and vomiting, abdominal pain, dehydration [aerial parts] | [11] |
Table 1: Continued.

| Family       | Scientific name               | Common name in Spanish | Medicinal use                                      | Signs of toxicity [plant part]                              | Reference |
|--------------|-------------------------------|------------------------|---------------------------------------------------|------------------------------------------------------------|-----------|
| Sapindaceae  | *Sapindus saponaria* L.**     | Jaboncillo             | Diuretic                                         | Skin burns [seeds]                                         | [24]      |
| Sapotaceae   | *Pouteria sapota* (Jacq.) H.E. Moore & Stearn** | Zapote                 | To eliminate louse                               | Nausea and vomiting, dizziness [seeds]                     | [35]      |
| Scrophulariaceae | *Buddleja marrubifolia* Benth. | Azafran de campo       | Diuretic                                         | Neurotoxicity [seeds]                                      | [26]      |
| Simaroubaceae | *Picrosma excelsa* (Sw.) Planch. | Palo Amarillo          | Stomachache, diabetes                           | Hypotension [bark]                                         | [35]      |
|               | *Castella tortuosa* Liebm.    | Chaparro amargo        | Fever, amebas                                    | Hepatotoxicity [stem]                                      | [37]      |
| Smilacaceae  | *Smilax aristolochifolia* Mill. | Zarzaparilla           | Syphilis, psoriasis                             | Gastritis [whole plant]                                   | [19]      |
|              |                               |                        |                                                   |                                                            |           |
|              | *Capsicum annuum* L.**         | Chile                  | Analgesic                                        |                                                            | [35]      |
|              |                               |                        |                                                   |                                                            |           |
|              | *Cestrum fasciculatum* (Schltld.) Miers | Hierba del perro      | Vomiting                                         | Nausea and vomiting, dizziness [aerial parts]              | [10]      |
|              |                               |                        |                                                   | tachycardia, dyspnea, fever, hallucinations [leaves]       |           |
|              | *Cestrum nocturnum* L.        | Dama de noche          | Headache, stomachache                           |                                                            | [4]       |
|              |                               |                        |                                                   |                                                            |           |
|              | *Datura inoxia* Miller.**     | Toloache               | Diabetes, asthma, wound healing                 | Narcotic, anorexic, cardiotoxicity, blurred vision [seeds]| [15]      |
|              |                               |                        |                                                   |                                                            |           |
| Solanaceae   | *Solanum americanum* Mill**   | Quelite mora           | Headache, wound healing                         |                                                            | [29]      |
|              |                               |                        |                                                   |                                                            |           |
|              | *Solanum elaeagnifolium* Cav. | Trompillo              | Rattlesnake bite                                 | Dermatitis [whole plant]                                  | [13]      |
|              |                               |                        |                                                   | Narcotic, cardiotoxicity [fruits]                          | [35]      |
|              | *Solanum mammosum* L.         | Chichigua              | Diuretic, cough                                 |                                                            |           |
|              |                               |                        |                                                   |                                                            |           |
|              | *Solanum nigrescens* M. Martens & Galeotti** | Hierba mora            | Fever, rheumatism                               | Immobilization [leaves and seeds]                          | [7]       |
|              |                               |                        |                                                   |                                                            |           |
|              | *Solanum rostratum* Dunal     | Duraznillo             | Diuretic, stomachache, diarrhea                 | Dermatitis [aerial parts]                                  | [13]      |
|              |                               |                        |                                                   |                                                            |           |
|              | *Witheringia solanacea* L’Hér. | Merengena              | To purify blood                                 | Nausea and vomiting [leaves and seeds]                     | [47]      |
| Urticaceae   | *Urena baccifera* (L.) Gaudich. ex Wedd.** | Ortiga brava           | Diuretic, rheumatism, body pain                 | Dermatitis, edema [aerial parts]                           | [11]      |
|              |                               |                        |                                                   |                                                            |           |
|              | *Urtica mexicana* Liebm.      | Ortiga                 | Diabetes, rheumatism                             | Skin burns [aerial parts]                                  | [10]      |
4. Toxicology

4.1. In Vitro Studies. The Artemia salina (brine shrimp) bioassay has been widely used for the analysis of acute toxicity in vitro. Although there are no range values to consider an extract or compound as toxic in the brine shrimp test, vincristine, the positive control for toxicity, has a lethal concentration 50 (LC$_{50}$) = 0.91$\mu$g/ml [76]. Considering this value, plant extracts or compounds with LC$_{50}$ values 1000-fold higher than vincristine could be considered nontoxic.

The following plant extracts have been tested for their in vitro toxicity using the brine shrimp test and had LC$_{50}$ values higher than 1000$\mu$g/ml. The ethyl acetate fraction of Solanum nigrescens aerial parts [77], the methanol extract of Jatropha gossypifolia aerial parts [79], the methanol extract of Jatropha dioica leaves [80], the aqueous extract of Cnidoscolus urens whole plant [79], the ethanol extract of Crescentia cujete fruits [81], the aqueous extract of Enterolobium cyclocarpum bark [82], and the ethanol extract of Cordia dentata leaves and their fractions [83].

The plant extract and compounds that could be considered dangerous (LC$_{90}$ = 100–1000$\mu$g/ml) include the following: methanol and hexane proportions derived from a hexane extract of Gymnosperma glutinosum aerial parts [84], the ethyl acetate extracts of Monstera deliciosa branches [85], and icosandrin, a cyclic homoflavonoid isolated from Phytolacca icosandra [86].

The plant extract and compounds that could be considered toxic (LC$_{50}$ = 10–100$\mu$g/ml) include the following: the ethyl acetate extracts of Monstera deliciosa leaves [85], the ethanol extract of Solanum americanum fruits [87], the ethanol extract of Scoparia dulcis aerial parts [76], the methanol extract of Enterolobium cyclocarpum leaves [88], the ethanol extract of Pimenta dioica leaves [89], and the hydroalcoholic extract of Sanguinaria canadensis whole plant [90]. None of the plant extracts or compounds included in this review were considered highly toxic (LC$_{50}$ < 10$\mu$g/ml).

4.1.1. Cytotoxicity. Other plant extracts and their compounds have been tested in other in vitro models, including cytotoxicity test in nontumorigenic cells, genotoxicity using the comet assay on lymphocytes, and the mutagenic test using lymphocytes or Salmonella spp. The positive controls for cytotoxicity in nontumorigenic cells include cisplatin and Taxol. These compounds have inhibitory concentration 50 (IC$_{50}$) values ranging from 0.1 to 4$\mu$g/ml [91]. Some plants extracts have been reported to lack cytotoxic effects (IC$_{50}$ > 250$\mu$g/ml) in nontumorigenic cells. These include the ethanol extract of Phoradendron serotinum leaves tested on peripheral blood mononuclear cells [91], the aqueous extract of Cnidoscolus chayamansa leaves on baby hamster kidney (BHK) cells [92], and the aqueous extract of Enterolobium cyclocarpum bark assayed on 3T3 murine preadipocytes [82]. Additionally, the ethanol extract of Equisetum hyemale aerial parts evaluated on rabbit corneal fibroblasts (SIRC) [93], the methanol extract of Enterolobium cyclocarpum leaves evaluated on vero cells (obtained from kidney epithelial cells extracted from the African green monkey (Cercopithecus aethiops) [88], and the diterpene ent-kaur-16-en-19-oic acid, obtained from Annona cherimola, tested on rat embryo primary striatal cultures [94]. On the other hand, the hydroalcoholic extract of Hura crepitans leaves had an IC$_{50}$ = 1077$\mu$g/ml in lung fibroblasts [95].

4.1.2. Mutagenicity and Genotoxicity. Regarding mutagenicity, parthenin, isolated from Parthenium hysterophorus,
lacked mutagenicity (0.19 to 19 μM) but showed chromosomal aberrations at concentrations of 10–60 μM in blood lymphocytes [96]. These results suggested genotoxic effects of parthenin. A methanol extract of Indigofera suffruticosa aerial parts (1.25–7.5 mg/plate) showed mutagenic activity in a Salmonella microsome assay [97]. The acetone extract of Helioptis longipes roots (10–80 μg/Petri dish) and its active compound aflavin (6.25–50 μg/Petri dish) were not mutagenic, as evaluated by the Ames test [98]. Lobeline (5–10 mg/kg i.p.), an alkaloid isolated from Lobelia inflata, had no genotoxic or mutagenic effects in the comet assay, the micronucleus test in bone marrow, or the Salmonella/microsome mutagenic assay [99].

For genotoxicity, the ethyl acetate/n-hexane extract of Zinnia peruviana aerial parts tested using 5 and 20 mg/ml extracts showed genotoxic effects in PBMC compared to the positive control of copper sulfate (1%) [100]. A butanol fraction of Ureia bacifera roots at a 1.8 mg/g concentration of oxalic acid decreased leukocyte number significantly and increased cell death and DNA damage in primary cultures of leukocytes in comparison to the control treatment [101]. The methanolic extract of Pistacia lentiscus calyculatus aerial parts (200 and 400 mg/kg i.p.) did not induce chromosomal damage in peripheral blood erythrocytes obtained from mice after 72 h of exposure [102]. An ethanol extract of Heliopsis longipes roots (3–100 mg/kg i.p.) did not induce chromosomal damage in peripheral blood erythrocytes obtained from mice after 72 h of exposure [103]. The methanolic extract of Pistacia lentiscus calyculatus aerial parts (200 and 400 mg/kg i.p.) did not induce chromosomal damage in peripheral blood erythrocytes obtained from mice after 72 h of exposure [102]. An ethanol extract of Heliopsis longipes roots (3–100 mg/kg i.p.) did not induce chromosomal damage in peripheral blood erythrocytes obtained from mice after 72 h of exposure [102].

4.2. In Vivo Acute Studies

4.2.1. Lethal Dose 50 (LD50). The guideline 423 of the Organization for Economic Cooperation and Development (OECD) establishes that substances with an LD50 < 5 mg/kg are highly toxic, whereas LD50 values from 5 to 50 mg/kg are very toxic, LD50 values from 50 to 300 mg/kg are toxic, LD50 values from 300 to 2000 mg/kg are dangerous, and LD50 values higher than 2000 mg/kg are not dangerous [104].

Some plant extracts showed LD50 > 2000 mg/kg p.o. in mice: ethanol extracts of leaves of Casimiroa edulis [105] and Cnidoscolus chayamansa [106], ethanol extracts of aerial parts of Moussonia debpeana [107], Equisetum hyemale [93], and Rutu chalepensis [108], as well as methanol extracts of leaves of Chenopodium ambrosioides [109] and Rauwolfia tetraphylla [110]. The same pattern was also shown in aqueous extract of Cuphea acupetala aerial parts [111], ethanol extract of Plumeria rubra flowers [112], aqueous extract of Larrea divaricata leaves [113], ethanol extract of Caesalpinia pulcherrima leaves and bark [114, 115], aqueous extract of Euphorbia prostrata whole plant [116], aqueous-methanol extract of Ceiba pentandra leaves [117], petroleum ether, chloroform, and methanol extracts of Gelsemium sempervirens roots [118], acetone extract of Capsicum annuum fruits [119], and aqueous and ethanol extract of Scoparia dulcis leaves and whole plant [120, 121].

The following extracts have shown LD50 > 2000 mg/kg p.o. in rats: aqueous extract of Pouteria sapota seeds [122], methanol extract of Martynia annua leaves [123], ethanol extract of Ficus verna leaves [124], aqueous extract of Enterolobium cyclocarpum bark [82], ethanol and aqueous extract C. pulcherrima aerial parts [125], aqueous extract of Passiflora edulis leaves [126], hydroalcoholic extract of Magnolia grandiflora seeds [127], and ethanol extract of Crescentia cujete fruits [128]. The same pattern was also shown in methanol extracts of leaves of Americanus spinosus [129], and Rauwolfia tetraphylla [130], chloroform-methanol extract of Cnidoscolus chayamansa leaves [131], aqueous extract of R. humilis fruits [132], a chloroform fraction from an ethanol extract of Tagetes erecta flowers [133], aqueous extract of Karwinskya humboldtiana seeds [134], and hydroalcoholic extract of Senna occidentalis aerial parts [135], as well as lutein and lutein ester, obtained from Tagetes erecta [136], and ethanol extract of Jatropha gossypifolia aerial parts [137], and aqueous extract of Caladium bicolor [138].

Other plant extracts showed LD50 > 2000 mg/kg i.p. in mice: hexane extract of Tilia mexicana inflorescences [139], aqueous extract of Tagetes lucida aerial parts [140], ethanol extract of Mirabilis jalapa aerial parts [141], and aqueous extract of Ureia bacifera leaves [142]. Some plant extracts and plant compounds had LD50 values from 300 to 2000 mg/kg, which is considered dangerous [104]. These plant extracts were intraperitoneally administered to mice: the ethanol extract of Tagetes lucida aerial parts (LD50 = 970 mg/kg) [140], the aqueous extract of Caladium bicolor leaves (LD50 = 1778.28 mg/kg) [138], and the ethanol extract of Tagetes lucida aerial parts (LD50 = 970 mg/kg i.p.) [140]. On the other hand, the ethanol extract of Phoradendron serotinum leaves had an LD50 = 375 mg/kg p.o. in mice [143], and sanguinarine, an alkaloid isolated from Sanguinaria canadensis, had an LD50 = 1658 mg/kg p.o. in rats [144]. Methanol extracts of Tilia mexicana inflorescences had LD50 values of 375 mg/kg i.p. in mice [139].

Other plant extracts and plant compounds had LD50 values varying from 50 to 300 mg/kg, which is considered toxic [104]. Ethanol extract of Phoradendron serotinum leaves had an LD50 = 125 mg/kg i.p. in mice [143], whereas capsacin, the main active principle of Capsicum annuum, had an LD50 = 190 mg/kg p.o. [145]. The acetone extract of Heliopsis longipes roots had an LD50 = 62.14 mg/kg p.o. in mice, whereas its active compound affinin had an LD50 = 113.13 mg/kg p.o. in mice [98]. The ethanol extract of Heliopsis longipes roots had an LD50 = 288 mg/kg p.o. in mice [103]. The following plant extracts and compounds can be considered very toxic (5–50 mg/kg) [104]: the free alkaloid fraction in hexane and methanol extracts from Erythrina americana seeds (LD50 = 38.54 to 40.37 mg/kg i.p.) in mice [146], Jatropha curcas oil (LD50 = 23.34 mg/kg p.o.) in mice [147], and α-solamargine, isolated from Solanum americanum, with an LD50 = 42 ± 2 mg/kg i.p. in rats [148]. The alkaloid N-methylsicoscordinum, obtained from Magnolia grandiflora trunk wood, had an LD50 = 10 mg/kg i.p. in mice [149] and y-conconicine, isolated from Convium maculatum, had an LD50 = 12 mg/kg p.o. in mice [150]. Parthenin, the toxic compound of Parthenium hysterophorus, had an LD50 = 42 mg/kg i.p. in rats.
Capsaicin had an LD₅₀ = 8 mg/kg i.p. and 7.80 mg/kg i.m in mice [152]. Sanguinarine, an alkaloid isolated from *Sanguinaria canadensis*, was toxic at 29 mg/kg i.v. in rats [144].

The following plant compounds had LD₅₀ values < 5 mg/kg, which is considered highly toxic [104]. Capsaicin had an LD₅₀ = 0.56 mg/kg i.v. [152].

### 4.2.3. Toxicity to Reproduction and Pregnancy.

#### 4.2.3.1. Biochemical and Hematological Parameters.

Treatment with plant extracts in short-term studies have effects on biochemical and hematological parameters, as well as the levels of the hepatic enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). An aqueous extract of *Larrea divaricata* aerial parts (0.5–200 mg/kg i.p.) did not affect the levels of ALT in mice after 2 days [153]. Aqueous extract of *Karwinskia humboldtiana* fruits (1250 mg/kg p.o.) administered to rats for 3 days increased the levels of hepatic enzymes compared to the untreated group [154]. An aqueous extract of *Passiflora edulis* (30 mg/kg p.o.) did not affect motor coordination in mice or change the biochemical measurements in serum after 4 days [155]. α-Solamargine (15–35 mg/kg i.p.) did not affect hematological parameters or the levels of hepatic enzymes in rats after 5 days [148], whereas an aqueous extract of *Karwinskia humboldtiana* fruit (5000 mg/kg p.o.) in rats for 5 days induced weight loss (15%) in rats, as well as toxicity in the pancreas [156]. An aqueous extract of *Passiflora edulis* leaves (100–400 mg/kg p.o.) did not affect organ body weight or hematological parameters but decreased the levels of ALT in rats after 7 days of treatment at all doses [126]. A methanol extract of *R. tetraphylla* leaves (1000 mg/kg p.o.) decreased body weight change and food consumption and increased total bilirubin in rats after 7 days [157]. An aqueous extract of *K. humboldtiana* (1000–2000 mg/kg p.o.) administered for 7 days in rats induced alterations in membrane fluidity and ATPase activity in liver subcellular particles [158]. An ethanol extract of *Euphorbia hirta* leaves (60.4–483 mg/kg i.p.) [159] and a chloroform fraction from an ethanol extract of *Tagetes erecta* flowers (200–400 mg/kg p.o.) [133] did not affect hematological or biochemical parameters in rats after 14 days. An aqueous extract of *Euphorbia hirta* whole plant administered at a single dose of 2000 mg/kg p.o. significantly decreased the levels of ALP and ALT after 14 days in broiler chickens [160]. Lobeline (5–10 mg/kg i.p.) did not affect the levels of AST, ALT, ALP, and LDH after 4 days of exposure [99].

#### 4.2.3.2. Dermal Tests.

A diethyl ether extract of *Jatropha multifida* showed the presence of 16-hydroxyphorbol. This compound showed an irritant dose 50 (ID₅₀) of 0.05 μg/ear [165].

### 4.3. In Vivo Subacute and Chronic Studies

#### 4.3.1. Biochemical and Hematological Parameters.

Some plant extracts and their active compounds have been tested for their effects on biochemical and hematological parameters in rodents for at least 18 days of exposure. A histological study has also been included in some reports. A hydroalcoholic extract of *Senna occidentalis* aerial parts (100–2500 mg/kg p.o.) [135] and a hydroalcoholic extract of *Sapindus saponaria* leaves (44.76 mg/kg p.o.) and fruits (45.0 mg/kg p.o.) [166] did not change the biochemical profile or hematological parameters or alter body weight and organ weight for 30 days in rats. An ethanol extract of the pod of *Plumeria rubra* (50–200 mg/kg p.o.) [167] and an aqueous-methanol extract of *Ceiba pentandra* leaves (250 and 500 mg/kg p.o.) [117] did not alter hematological or biochemical parameters in rats and mice, respectively, after 21 days [167]. A chloroform-methanol extract of *Cnidoscolus chayamansa* leaves (1000 mg/kg p.o.) [131] and an ethanol extract of *Moussonia deppeana* aerial parts (1000 mg/kg p.o.) [107] did not affect biochemical or hematological parameters in mice after 28 days of daily administration. In addition, histological examinations of the spleen, kidney, and liver showed no abnormalities. Capsaicin (5–100 mg/kg p.o.) [168], obtained from *Capsicum annum*, and lutein and lutein ester (4–400 mg/kg p.o.) [136], obtained from *Tagetes erecta*, did not affect hematological or biochemical parameters, growth, food consumption, or body weight in mice and rats, respectively, after 28 days. An aqueous extract of *Rivina humilis* fruits (2500 and 5000 mg/kg p.o.) administered daily for 35 days showed no changes in the hematological profile or in the relative organ weight, whereas the same extract administered daily for 90 days at 0.5–2 g/100 g in a powdered diet did not affect hematological parameters, biochemical determinations, or the levels of hepatic enzymes [132].

In contrast, some plant extracts have altered biochemical and/or hematological parameters. An aqueous extract of *Abrus precatorius* leaves (400–1600 mg/kg p.o.) was administered to rats for 18 days. Only the highest dose (1600 mg/kg p.o.) decreased levels of hematological parameters and increased the levels of hepatic enzymes [169]. An aqueous extract of *Scoparia dulcis* leaves (250–500 mg/kg p.o.) showed mild vascular and portal congestion in the heart and the number of fetal resorptions was also increased, and the fetuses showed skeletal malformations [162]. Additionally, an aqueous extract of *R. chalepensis* leaves (0.8 and 1.6 g/kg p.o.) administered to mice from day 1 to day 14 post coitum caused perinatal changes in mice such as righting reflex, cliff avoidance, and swimming ability, among others [163].
liver, respectively, of rats treated daily with this extract for 30 days. Nevertheless, there were effects in the lungs and testis [120]. A methanol extract of *Rauvolfia tetraphylla* leaves did not affect hematological parameters. However, a significant decrease in the total bilirubin and glucose levels was observed in the mice treated at 100 and 300 mg/kg, with a significant increase in triglycerides at doses of 10–300 mg/kg after 28 days in mice [130]. An ethanol extract of the aerial parts from *Jatropha gossypifolia* (135 mg/kg p.o. or higher doses) reduced the activity in the central nervous system and showed hepatotoxicity, pulmonary damage, and digestive disturbances in rats over 13 weeks of treatment [170]. The lethality was 46.6% and 13.3% among male and female rats under the highest tested dose (405 mg/kg), respectively [170].

### 4.3.2. Toxicity during Reproduction and Pregnancy.

Yao et al. [171] reported that an aqueous extract of *Hydrastis canadensis* (1.86 g/kg p.o.) containing 9.6 mg/ml of berberine and 8.4 mg/ml of hydastine did not affect fetal development in pregnant rats over 20 days of treatment. A *Prosopis juliflora* seedcase added at 70% to the diet of pregnant rats resulted to be teratogenic (13-fold) compared to the untreated group [172]. Aqueous and ethanol extracts of *Plumeria rubra* pods (200 mg/kg p.o.) had 51% and 100% abortifacient activity, respectively, in female albino rats from day 11 to day 15 of pregnancy [173]. The hydroalcoholic extract of *Lantana camara* leaves (1000–7000 mg/kg p.o.) administered during premating, mating, pregnancy, and lactation (56 days in total) in rats did not affect mating, pregnancy, delivery, and live birth. Nevertheless, the two highest doses tested (3000 and 7000 mg/kg p.o.) produced an increase in the resorption rate and parallel increases in the postimplantation loss index, as well as embryotoxicity characterized by skeletal abnormalities [174].

### 4.3.3. Carcinogenicity.

Only one plant extract has been tested for its carcinogenic effects. Rats (treated with doses ranging 136–1175 mg/kg p.o.) and mice (treated with doses ranging 375–3275 mg/kg) received an aqueous extract of *Hydrastis canadensis* root for 2 years (106 weeks). At the end of the treatment, the doses of 1175 mg/kg in rats and the doses varying from 1120 to 3275 mg/kg in mice showed hepatocarcinoma [175].

### 4.4. Clinical Cases.

The toxicity of sixteen species plants has been reported in clinical cases. Fourteen of the sixteen plants are enlisted in Table 2. The other two plants are described in Section 4.4.1. The Naranjo algorithm [176], which consists of 10 questions that address the factors considered to determine the causal relationship in case reports, was used to assess causality. A score is obtained (maximum 13) and the results are classified as doubtful or unlikely (0), possible (from 1 to 4), probable (from 5 to 8), and clear or definite (score > 9). The event must be definitive from a pharmacological or phenomenological point of view, using, if necessary, a conclusive procedure of reexposure [177].

Those cases that report hepatic damage were also evaluated using the method proposed by the Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method (CIIOMS/RUCAM) [178], which is an organospecific instrument designed for the assessment of hepatotoxicity. This method evaluates the temporal relationship between the consumption of a substance (drug or natural remedy) and the appearance of hepatic damage, the absence or presence of risk factors, the exclusion of alternative causes of liver injury, among others. The sum of the scores leads to a final score between −8 and 14 points, which results in the following categories: highly probable or definite, probable, possible, or excluded. The amount of information of each clinical case considered for this review was classified as enough (number of criteria: 5-6), regular (number of criteria: 3-4), and poor (number of criteria: 1-2). The following criteria were used to evaluate the amount of information: (1) clear information regarding the intake and time elapsed for the onset of symptoms, (2) information of the dose ingested, (3) explanation and clinical management of the intoxication, (4) information for the exclusion of other causes that might induce the toxic effect, (5) information of the withdrawal of the plant substance, and (6) time of recovery from the toxicity or death of the patient.

The toxicity presented in clinical cases was mainly due to the accidental consumption of toxic medicinal plants, especially by children. In all the cases, the toxic effects occurred after the administration of the plant. The symptoms of toxicity were confirmed using objective evidence. None of the reports provided information about the presence of similar toxic effects compared to a previous experience. Improvement of symptoms occurred in some cases (i.e., [58, 62–64, 69, 71, 72]). The information about the number of ingestion with the plant is only reported in some cases (i.e., [43, 57, 59, 60, 65, 67, 70]).

#### 4.4.1. Case Series.

Krenzelok et al. [179] gathered information about *Euphorbia pulcherrima* exposure during an 8-year period in the United States of America. The results showed that children accounted for 93.3% of cases of exposure, which were accidental (98.9% of cases) and by ingestion (94.5% of cases). No deaths were reported. However, this study did not report the symptomatology. The toxicity of *Cimicifuga racemosa* has been extensively studied. The reviews of Borrelli and Ernst [180] and Teschke et al. [181] can be consulted for more information regarding the adverse effects of *Cimicifuga racemosa* in other clinical cases. The prevalence of allergy to *Myroxylon pereirae* resin has been reported in many countries, ranging from 5.4 to 11.8% (i.e., [49, 182–185]). From a total of 27815 patients recorded over 5 years in Croatia, 8.4% were positive to contact dermatitis upon exposure to *Myroxylon pereirae* bark [186]. In another case, the prevalence of toxicity by medicinal plants was also reported. *Jatropha curcas, Andira inermis,* and *Canella winterana* were the third, the fourth, and the fifth most cited plant species, respectively, associated with cases of toxicity in Cuba from 1998–2007 [36]. Eddleston et al. [187] reported 351 patients with a history of *T. peruviana* consumption for 2 years. No deaths were reported.
Table 2: Evaluation of causality and exclusion of alternate causes in clinical cases of medicinal plants from Mexico and Central America considered as toxic.

| Information of the patient (age, gender, country of residence) | Plant, way of administration, dose and part of the plant consumed, time of consumption if indicated | First symptoms (onset, in days, of the first symptoms) | Toxic effects (onset, in days, of the toxic effects) | Clinical complications | Evaluation of causality (score) | Amount of information | Outcome (days) | Alternate causes excluded | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| 9, M, Israel | *Jatropha multifida* Oral: >10 fruits | Vomiting, watery diarrhea, and abdominal pain (1 h) | Gastroenteritis (1) | Hepatic enzymes elevation | Naranjo (5): probable | Enough | Recovered (5) | ND | | [43] |
| 8, M, Israel | *Jatropha curcas*, Oral: 1–4 seeds | Vomiting (95%) Headache (40%) Fever (40%) Diarrhea (50%) | Gastroenteritis (1) | Hepatic enzymes elevation | Naranjo (5): probable | Enough | Recovered (5) | ND | | [57] |
| 20 children; 8–13 years old, India | *Jatropha curcas*, Oral: 1–4 seeds | 1–2 h | Vomiting (95%) Headache (40%) Fever (40%) Diarrhea (50%) | ND | Naranjo (6): probable | Regular | Recovered (6 hours) | ND | | [57] |
| 4, M, United States of America | *Conium maculatum* (piperidina 850 U/g plant), ND | Drowsiness (0.5 h) | Central nervous system depression (3 hours) | ND | Naranjo (6): probable | Regular | Recovered (6) | ND | | [58] |
| 19, F, Turkey | *Conium maculatum*, ND | Headache, blurred vision, and difficulty speaking (0.5 h) | Central nervous system depression (ND) | Difficulty breathing | Naranjo (5): probable | Regular | Recovered (1) | ND | | [59] |
| 5, M, India | *Argemone mexicana* Oral: oil | Abdominal pain, loss of movements and swelling throughout the body (20) | Epidemic dropsy (ND) | ND | Naranjo (6): Probable | Regular | Fatal (4) | Thalassemia and sickle cell disease (postmortem) | [60] |
| 10, M, India | *Chenopodium ambrosioides*, Oral: oil 80 ml (1,560 mg ascaridol) | Abdominal pain, fever, and shortness of breath (20) | Multiple organ dysfunction syndrome (ND) | Seizures, periods of apnea | Naranjo (6): probable | Enough | Fatal (3) | Encephalopathy due to lead poisoning and organophosphates | [61] |
| Information of the patient (age, gender, country of residence) | Plant, way of administration, dose and part of the plant consumed, time of consumption if indicated | First symptoms (onset, in days, of the first symptoms) | Toxic effects (onset, in days, of the toxic effects) | Clinical complications | Evaluation of causality (score) | Amount of information | Outcome (days) | Alternate causes excluded | Reference |
|---|---|---|---|---|---|---|---|---|---|
| 64, F, United States of America | Cimicifuga racemosa, Oral: capsules (80 mg/day/2 months) | Painful nodules on her left foot (ND) | Cutaneous vasculitis (42) | ND | Naranjo (5): Probable | Regular | Recovered (90) | ND | [62] |
| 54, F, United States of America | Cimicifuga racemosa, Oral: capsules (80 mg/day/4 months) | Ulcers (ND) | Cutaneous vasculitis (90) | ND | Naranjo (4): Possible | Regular | Recovered (90) | ND | |
| 57, F, United States of America | Cimicifuga racemosa, Oral: capsules (without more specifications) | Lethargy and fatigueness (14) | Autoimmune hepatitis (21) | ND | RUCAM (6) probable (Hepatocellular) Naranjo (7): Probable | Enough | Recovered (14) | Hepatic disease, serology of negative hepatitis, normal Antinuclear antibodies | [63] |
| 16, F, United States of America | Podophyllum peltatum, Topical; 20% of the resin in tincture | Vomiting, watery diarrhea, and abdominal pain (7 h) | Multiple organ dysfunction syndrome (<1) | Neurological toxicity and respiratory complications | Naranjo (6): probable | Enough | Recovered (120) | ND | [64] |
| 18, F, United Kingdom | Podophyllum peltatum, Topical; 25% of the resin in tincture (75 ml = 1.88 g) | Hypokalemia and peripheral neuropathy (<1) | Hypokalemia and peripheral neuropathy | Naranjo (5): probable | Regular | Recovered (90) | Previous cesarean anesthesia not discarded | [65] |
| 21, F, United States of America | Caulophyllum thalictroides, ND | Nicotinic toxicity (<1) | Tachycardia, diaphoresis, abdominal pain, vomiting and muscle weakness | Naranjo (5): probable | Poor | Recovered (1) | ND | [66] |
| 40, M | Thevetia peruviana, Oral: seeds | ND | Atroventricular block (1) | Hyperkalemia, bradycardia | Naranjo (3): Possible | Regular | Recovered (3) | No cardiac history or vascular risk factor | |
| 25, F | Cinchona pubescens, Oral: leaves | ND | Atroventricular block (1) | Hyperkalemia, bradycardia | Naranjo (3): Possible | Regular | Recovered (2) | ND | [67] |
| 75, F | Cinchona pubescens, Oral: infusion | ND | Multiple organ dysfunction syndrome (ND) | Naranjo (3): Possible | Poor | ND | ND | |
| 20 patients: 9–50 years old, Mexico | Metopium brownie, ND | 1–4 | Erythema (95%) Vesicles (60%) Papules (4%) Blebs (2%) | ND | Regular | Recovered (ND) | Poison ivy | [68] |
Table 2: Continued.

| Information of the patient (age, gender, country of residence) | Plant, way of administration, dose and part of the plant consumed, time of consumption if indicated | First symptoms (onset, in days, of the first symptoms) | Toxic effects (onset, in days, of the toxic effects) | Clinical complications | Evaluation of causality (score) | Amount of information | Outcome (days) | Alternate causes excluded | Reference |
|---------------------------------------------------------------|-------------------------------------------------|--------------------------------------------------|--------------------------------------------------|----------------------|-------------------------------|---------------------|----------------|----------------------------|-----------|
| 27, M, United States of America | *Larrea tridentata*, Oral: 500 capsules (3–7/day/10 months) | Vomiting, watery diarrhea, and abdominal pain (ND) | Hepatic damage (ND) | ND | Naranjo (4): Possible, RUCAM (4): Possible (Hepatocellular) | Regular | ND | Hepatic disease, serology of negative hepatitis, (cytomegalovirus positive, ingestion of other plants and history of alcohol abuse) | [69] |
| 13, M, Sri Lanka | *Abrus precatorius*, Oral: 1 seed | Vomiting, watery diarrhea, and abdominal pain (5) | Pulmonary edema associated with hypertension (1) | Early renal parenchymal disease | Naranjo (5): probable | Enough | Recovered (3) | Organophosphate poisoning, acute glomerular nephritis, viral myocarditis, and dengue | [70] |
| 17, F, India | *Abrus precatorius*, Oral: 10 seeds | Gastrointestinal (4) | Idiopathic intracranial hypertension (6) | Hepatic failure, hyponatremia, and hypokalemia | Naranjo (5): Probable | Enough | Recovered (21) | ND, intentional intake | [71] |
| 28, F, India | *Abrus precatorius*, Oral: 7 seeds | Gastrointestinal (20) | Idiopathic intracranial hypertension (4) | Seizures and respiratory failure | Naranjo (5): Probable | Enough | Fatal (4) | | |
| 18, M, United States of America | *Datura inoxia*, Oral: seeds | Incoherences and hallucination (ND) | Anticholinergic intoxication (<1) | ND | Naranjo (4): Possible | Enough | Recovered (4) | Methamphetamine intake, and intake of other unknown substances | [72] |

Age is given in years old; ND, not described; F, female; M, male.
5. General Considerations

The identification of the compounds responsible for the toxicity has been reported only in some cases. Urushiol might be the compound responsible for the dermatitis reactions to Metopium brownei [188], whereas sanguinarine is the compound associated with the toxicity of Argemone mexicana. Eddleston et al. [189] reported six fatalities in patients who ingested between 1 and 10 seeds of T. peruviana. These fatalities occurred due to high concentrations of cardiac glycosides (neriifolin, thevetin A, thevetin B, and oleanadrin) in seeds. Three toxins (T-544, T-514, and T-496) have been reported in Karwinskia humboldtiana [190]. Manihot esculenta, an important dietary staple, is toxic because of the presence of cyanogenic compounds. Linamarin, the predominant cyanogenic glycoside in Manihot esculenta, can be accumulated in a range of concentrations between 100 and 500 mg/kg in roots and leaves. The content of HCN in Manihot esculenta has been reported 0.1–1 mg/g fresh weight in the leaves [191]. Several intoxications have been described in humans. The clinical pattern consists of neuropathy and hyperthyroidism [192].

The mechanism of toxicity is also unknown in many cases. The mechanism of toxicity of Argemone mexicana oil might be explained by the inhibitory effects of sanguinarine on Na+/K+ ATPase, induction of cell membrane damage by reactive oxygen species and lipid peroxidation, and inhibition of DNA polymerase activity, among other effects [193]. Larrea tridentata and nordihydroguaiaretic acid, its active compound, generate acute hepatotoxicity by the inhibition of cyclooxygenase and cytochrome P-450 [194].

Special attention should be given in medicinal plants such as Argemone mexicana, Chenopodium ambrosioides, and Thevetia peruviana. Effects in humans have been reported due to the consumption of these medicinal plants. Other plant species, including Abrus precatorius, Capsicum annum, Conium maculatum, Erythrina americana, Heliopsis longipes, Hydrastis canadensis, Jatropha curcas, Jatropha gossypifolia, Karwinskia humboldtiana, Larrea tridentata, Magnolia grandiflora, Parthenium hysterophorus, Phoradendron serotinum, Plumeria rubra, Prospis juliflora, Ruta chalepensis, Sanguinaria canadensis, Solanum americanum, and Veratrurn californicum, have shown effects considered highly toxic, including hepatotoxicity, teratogenic, and cardiotoxicity, or with high toxicity in acute studies. Therefore, a total of 22 plants of 216 cited in this review should be extensively studied in terms of their toxicity. Regarding the hepatotoxicity induced by medicinal plants, Valdivia-Correa [39] reported 15 medicinal plants commonly used in Mexican traditional medicine that induce hepatotoxicity. Five (Equisetum hae- male, Tilia mexicana, Passiflora edulis, and Scoparia dulcis) of these fifteen medicinal are considered as toxic, according to our bibliographic research. The induction of hepatotoxicity induced by herbal products represents a serious problem in Mexico since the symptoms and signs might be confused with other diseases, and the diagnosis can be incorrect [39].

Some aspects that influence the toxicity of medicinal plants reported in this study are: (a) time of exposure, (b) misidentification of medicinal plants, and (c) adulteration of medicinal plants. Most of the acute symptoms reported in this review appear in the first 24 h after exposure. Nevertheless, more studies, including subacute and chronic assays, as well as the quantitation of hepatic enzymes, should be performed. In other cases, such as the intoxication of Crotalaria sagittalis, the toxic symptoms appear 2 to 6 months after the exposure [4]. However, chronic poisoning induced by medicinal plants is not easily detected since the symptoms are multiple and variable and a diagnosis cannot be made. Many poisonings caused by medicinal plants are classified as of unknown origin because most of the patients deny the consumption of herbal products. For instance, the clinical picture of intoxication with Karwinskia humboldtiana might be confused with poliomyelitis [190]. In addition, in most of the cases, the plants are not taxonomically identified [36]. The misidentification of medicinal plants represents a serious problem for human health. The adulteration of medicinal plants sold as food products should be considered as a risk of intoxication by medicinal plants.

Another aspect to consider for further studies is the evaluation of mixtures of medicinal plants and the combination of medicinal plants with allopathic medications. It is thought that the combination of medicinal plants might result in higher beneficial effects compared to those found with single preparations. Nevertheless, it might be the case that two toxic plants are combined and their toxic effects might result in a synergistic action. The self-medication of drugs along with the consumption of medicinal plants is a common practice among patients with chronic diseases [195], which can be considered as an alternative cause of intoxication. In the clinical record, it is not indicated whether the patient consumes medicinal plants. The interaction of herbal extracts and drugs remains to be studied. There are few documented cases that report the toxicity of the combination of plant extracts and drugs. For instance, the combination of Picrasma excelsa coumarins are reported to potentiate the activity of warfarin [196]. The toxicity of mixtures of medicinal plants and the combination of medicinal plants with allopathic medication requires further investigation.

6. Conclusions

There is limited information about the toxicity of medicinal plants used in Mexico, Central America, and the Caribbean. The molecular mechanisms by which medicinal plants induce toxic effects should also be addressed. In many cases, intoxication by medicinal plants might be confused with other diseases. The detection of intoxication with medicinal plants could be difficult because the symptoms might be confused with other diseases.

The prevention of poisoning in humans can be avoided if the chemical composition of medicinal plants is known.

Conflicts of Interest

The authors declare that there are no conflicts of interest.
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