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ABSTRACT
Herbal toxicity is a field that has rapidly grown over the last few years along with increased use of herbal products worldwide. The indication of herbal products is quite variable because these products are not subjected to regulation by the Food and Drug Administration and are often used without supervision by a healthcare provider. Moreover, their use is generally regarded as safe and natural by the lay-public. The objective of study is to aware the researchers about most commonly used medicinal herbs, which are known to induce various types of toxicities. A Medline search was undertaken to identify relevant literature using search terms including 'herbal', 'herbs', 'toxicities', 'cardiotoxicity', 'hepatotoxicity', 'nephrotoxicity', 'hematologic toxicity' etc. The numbers of adverse events are reported with the use of herbal products. A number of herbs, herbal drugs and herbal supplements are associated with a spectrum of toxicity events. Advances in the understanding of the pathogenesis and precautions are needed to improve herbal medicine safety.


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INTRODUCTION

There is a great raise in use of herbal medicines now days. The reason may be that herbal medicines have been used from very old times. According to WHO 2004, use of herbal products continues to increase day by day, and it has been estimated that the industry estimated at $60 billion today will significantly expand during this century. Up to 80% population of developing countries rely on traditional medicines for their primary health care [1]. Herbal remedies are not only used alone but also can be used in combination with other pharmaceutical preparations with a motive to increase efficacy and decrease side effects [2]. Long term use of herbal preparations does not indicate their complete safety. There are various cases and studies where toxicity due to herbal drugs has been reported. In China, where herbal medicines are widely used, there were 9854 known reported cases of adverse drug reactions in 2002 due to herbal drugs [1]. Herbal drugs associated toxicity can occur because of various factors viz. presence of contaminants, incomplete processing, drug-herb interactions, coexisting diseases, direct toxicity (dose/duration), improper herb identification, and preparation method [3]. The objective of the study is to aware the researchers about most commonly used medicinal herbs, which are known to induce various types of toxicities.

1. Cardiac Toxicity

1.1 Licorice (Glycyrrhiza glabra):

It is known to possess anti-inflammatory, anti-diabetic, antioxidant, anti-tumor, antimicrobial, and anti-viral properties [4]. Its prolonged use suppresses renin-aldosterone system, thus leading to sodium and water retention, hypokalemia, hypertension, cardiac arrhythmias, and myopathy which further leads to pseudohyperaldosteronism syndrome. There are cases where adverse effects were observed in people, who ingested a daily dose of 100 mg/kg. One of its constituent named as glycyrrhizic acid, inhibits 11β-hydroxysteroid dehydrogenase and is responsible for producing both hypermineralocorticidm and the onset of encephalopathy [5].

1.2 Blue cohosh (Caulophyllum thalictroides):

It is a traditional herbal medicines used for the treatment of menopausal symptoms, rheumatic pain, and as anti-inflammatory remedy. Extract prepared from roots of blue cohosh are known to exhibit anti-inflammatory and antipyretic activities [6]. It also has sympathomimetic and direct cardiotoxic effects [7]. It contains teratogenic constituent N-methylcystosine, which acts similarly to nicotine. Another constituent caulosaponin, a glycoside promotes constriction of coronary vessels and may have oxytocic activity. It has been used to promote labor. There are various case reports where blue cohosh used by mother to induce labor caused myocardial infarction, congestive heart failure, seizures, and stroke [7-9].

1.3 Ma Huang (Ephedra sinica):

It is another herbal drug which has been used as a weight loss agent. It is also used in bronchospasm, asthma, treatment of allergies, and as recreational drug [10]. Dunnick et al. reported the cardiotoxicity of Ma Huang or ephedrine (the principal active component in Ma Huang), when administered in combination with caffeine to male F344 rats. The signs of cardiotoxicity that occurred were hemorrhage, necrosis, and degeneration in the ventricles or interventricular septum [11]. Howeden et al. studied the age-dependent cardiovascular responses of ephedrine along with caffeine in Fischer 344 rats. Rise in heart rate, temperature, and corrected QT interval phenomenon were noticed in rats. Histopathological examination revealed interstitial hemorrhage and myofiber necrosis in rats, which were treated with highest concentration of ephedrine and caffeine [12].

2. Renal Toxicity

2.1 Aristolochia (Aristolochia contorta):

It is a traditionally used medicinal herb which is used as antibacterial, antiviral, antifungal, and antitumor agent. One of its constituent aristolochic acids is known to have antibacterial, antiviral, antifungal, and antitumor effects [13, 14]. Debelle et al. reported progressive renal fibrosis due to aristolochia salt-depleted rats. Histological examination showed tubular necrosis associated with lymphocytic infiltrates and tubular atrophy surrounded by interstitial at higher doses of aristolochic acid [15]. Sato et al. reported aristolochic acid induced acute nephrotoxicity in mice. Severe tubular injury along with acute tubular necrosis, and rare cell infiltration into the interstitium were observed on treatment with aristolochic acid [16]. Ding et al. reported the nephrotoxicity associated with aristolochic acid in zebrafish model. Aristolochic acid was administered to zebrafish embryos by soaking them into it and results revealed existence of malformed kidney phenotypes, cystic pronephric tubes, pronephric ducts, and cases of atrophic glomeruli [17]. Zhang et al. isolated two new phenanthrene derivatives, aristololactam IVa and 9-hydroxy aristolochic acid I from stem and leaves of Aristolochia contorta along with 17 other previously reported compounds. Cytotoxic evaluation of compounds against renal proximal tubular epithelial cell line (HK-2) revealed compound aristolactolactam IVa and 7-methoxy aristolactolactam IV to be highly toxic with potency approximately equal to or even more than those of aristolochic acid I and aristololactam I [18].

2.2 Chinese yew (Taxus celebica):

The extracts of Chinese yew are used in China that contains a flavonoid sciadopitysin which is widely used as therapeutic agent for diabetes mellitus. There are two case reports of acute interstitial nephritis along with acute tubular necrosis after ingestion of 120 to 150 g of Taxus celebica [19, 20].

2.3 Bouiougui-tou: It is a herbal mixture of Chinese drugs used for curing obesity. Glycyrrhiza in Bouiougi inhibits Na+, K+-adenosine triphosphatase activity of proximal tubular cells in a case report thus causing Fanconi’s tubulopathy [21, 22].
2.4 Ma Huang (Ephedra sinica):

It is an ephedra containing herbal preparation is also known to cause renal stones. Powell et al. represented a case of 26-year-old patient, who was intaking 4 to 12 tablets/day of Ma Huang for 6 months, reported 6 episodes of nephritic colic in a period of 6 months. He was diagnosed with presence of 6 stones made of ephedrine metabolites [21, 23].

2.5 Cat’s claw:

It is a Peruvian herbal preparation named Uno degatta, which is prepared from Unicarra, a woody vine found in the Amazon basin. Cat’s claw is used to treat various diseases, such as cirrhosis, gastritis, gonorrhea, cancers of the female genital tract, and rheumatism [20]. Hilepo et al. reported a case of acute interstitial nephritis after the use of this preparation [21, 24].

2.6 Licorice (Glycyrrhiza glabra):

It is a widely used herbal medicine, used to treat duodenal ulcers and inflammation of the upper respiratory tract has known to cause an aldosterone- like effect, and large doses may precipitate hypokalemia and sodium and water retention, due to its constituents glycyrrhizic and glycyrrhetic acids [21, 25]. Velickovic-Radovanovic et al. discussed a case of acute renal failure of a 39 year old lady, who was consuming 50–100 g of herbal products that contained licorice, every day for 8 weeks in order to treat sterility [26].

3. Hematologic Toxicity

3.1 Ginkgo (Ginkgo biloba):

It is a herbal drug which is widely used for the treatment of various conditions including Alzheimer’s disease, dementia, cerebral vascular insufficiency, severe claudication, peripheral artery disease, tinnitus, ischemic stroke, and vertigo [27]. There are toxic constituents present in seeds of ginkgo, which are known to cause seizures, difficulty breathing, loss of consciousness, and shock. Ginkgo seeds contain higher quantity of ginkgo toxins than ginkgo leaf extract [10, 28]. Ginkgo increases the concentrations of endothelium-derived thrombolytics, such as nitric oxide and prostacyclin thus causing the inhibition of platelet aggregation [29]. Bent et al. published 15 case reports presenting adverse effects caused by Ginkgo biloba from which 13 case reports presented increased risk on spontaneous bleeding (advanced age, medications known to increase bleeding risk, falls, cirrhosis, and previous or present surgery) [30].

3.2 Dong quai (Angelica senensis):

It a medicinal herb is known to possess anticoagulation [31], vasodilatory [32], uterine effects [31], anti-constipation [33], anti-bacterial [31], immunomodulatory effects [34]. Page et al. published a case of 46-year-old African-American woman, who consumed warfarin and dong quai simultaneously and experienced a 2 -fold increase in prothrombin time and international normalized ratio (clotting time of blood). But one month after the terminating of use of dong quai, patient's coagulation values returned to acceptable levels. So, it was concluded for existance of pharmacodynamic interaction between the product and warfarin. Phytochemical analysis revealed the presence of natural coumarin derivatives along with such constituents that possess antithrombotic, antiarrhythmic, phototoxic, and carcinogenic effects [35].

3.3 Willow bark (Salix alba, Salix daphnoides, Salix fragilis, Salix nigra, Salix pentandra, and Salix purpureal):

It is a herbal drug which provides relief from pain and fever. Myalgias, osteoarthritis, dysmenorrheal, gouty arthritis, rheumatoid arthritis, gout, common cold, influenza, and weight loss are some other conditions where willow bark is used. It’s main component is salicilin which is metabolized to salicylic acid. It is known to have analgesic, anti-inflammatory, antipyretic, and antiplatelet activity due to presence of salicilin [36]. As willow bark exhibit antiplatelet effects, risk of increased bleeding can be associated with the patients taking willow bark. In order to avoid preoperative bleeding, patients are recommended to terminate the use of willow bark at least 2 weeks before going through surgery [10, 37].

3.4 Grapes (Vitis vinifera):

Grapes are used in various herbal preparations. Grapes are known to provide benefits like wound healing, prevent dental caries, treat liver cirrhosis, prevent cancer, macular degeneration, allergic rhinitis, diabetes complications, and as a mild laxative [38]. Tocopherol, one of the constituents of grapes is theoretically known to cause an increase in risk of bleeding. So the patients taking anticoagulants like warfarin along with grapes are at greater risk of bleeding. Grape seed extracts and grape leaf extracts can be safely used upto 8 weeks and 12 weeks respectively [38, 39]. It is advised for patients, who are regularly taking anticoagulant medications (grape supplements) to inform their health care professionals [38].

4. Hepatic Toxicity

4.1 Kava root (Piper methysticum rhizoma):

It is used as traditional medicine in Hawaii, Polynesia and the Fidji Islands for treatment of anxiety disorders and depression. It contains kava pyrones, including kavain, dihydrokavain, methysticin, dihydromethysticin, which are responsible for its sedation activity. These constituents act as agonist for gamma-amino-butric acid receptor that inhibits activating neurons in the reticular formation and the limbic system [40, 41]. Escher et al. published case reports in which chronic (1-3 months) use of kava kava capsules caused a marked increase in liver markers [42]. Russmann et al. reported a case where liver toxicity was caused in a patient who was ingesting alcohol along with kava supplement [43]. European Union and Canada even banned kava extracts in year 2003 [10, 42, 44].

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As kava possesses dopamine antagonistic effects, it may lead to Parkinson like syndrome. So patients suffering from Parkinson disease are advised not to take kava supplements [10, 45].

4.2 Germander (Teucrium chamaedrys):
It is used to treat diabetes mellitus, obesity, fever, diarrhea, and stomach aches. Germander contains various constituents from which diterpenoids are believed to cause hepatotoxicity. Epoxide is formed by the oxidation of diterpenoids which depletes glutathione in liver. Epoxide is also responsible for DNA fragmentation and cell apoptosis [10, 46, 47]. Kouzi et al. reported hepatotoxicity of a neoclerodane diterpenoid, teucrin A, in mice which produced toxicity due to metabolic activation of its furan ring [48]. Berardinis et al. in their study reported the human microsomal epoxide hydrolase as the target germander-induced autoantibodies on the surface of human hepatocytes [49]. Ben et al. reported two cases of chronic hepatitis and one case of active cirrhosis due to the ingestion of germander. The problem resolved after terminating the use of germander [50]. Laliberte et al. reported case of a 55 year old woman whose was suffering from jaundice, hepatomegaly and several spider angioma along with significantly increased liver enzymes. Later it was found that lady was consuming germander as weight loss supplement. Her liver enzymes levels improved 2 months after she stopped consuming germander [51].

4.3 Pennyroyal oil:
It is an herbal preparation used to treat various conditions like upper respiratory tract and ear infections, induce abortions, and act as an insect repellent [52]. Pulegone is the main constituent of pennyroyal oil which is metabolized to menthefuran by the cytochrome P450 system in liver. Many case reports have demonstrated hepatitis, hepatocellular necrosis, and hepatic failure requiring transplant due to use of pennyroyal [53, 54]. Gordon et al. also demonstrated cellular necrosis in the centrilobular regions of the liver due to pennyroyal [55]. Bakerink et al. reported a case in which an infant suffered from fulminant liver failure with cerebral edema and necrosis and ultimately died due to adverse reaction caused by menthefuran constituent of pennyroyal. Another infant developed hepatic dysfunction and a severe epileptic encephalopathy due to pulegone and menthefuran both. Liver enzymes were elevated in both infants [56].

4.4 Green Tea (Camellia sinensis):
It is enriched with a variety of components. Its components include gallocatechin gallate (GCG), galloylchoric acid (GC), catechin gallate (CG), catechin (C), and flavonoids such as kaempferol, quercetin and myricetin. Other important components include theanine, derived from amino acid, the xanthine alkaloid caffeine, theophylline, theobromine, saponins, and tannins [57]. Molinari et al. presented a case report where a 44 year old woman was taking dietary supplements that contained green tea extract (720 mg/day). Jaundice and grade I encephalopathy was reported in that lady on physical examination. Later tests were conducted and more than 50% hepatocellular necrosis was reported [57]. Gloro et al. in their case study reported fulminant hepatitis due to self-administration of herbal supplement named Exolise (80% ethanolic dry extract of green tea standardized at 25% catechins expressed as epigallocatechin gallate, containing 5-10% caffeine). Toxicity was severe and liver transplant was performed [58].

5. Endocrine Toxicity
5.1 Licorice (Glycyrrhiza glabra):
It has been reported to cause hypokalemic myopathy and hypokalemic renal tubular damage in anorexia nervosa. Ishikawa et al. presented a case of 29 year old woman who suffered from painful myopathy along with hypokalemia. It came into light that the lady was ingesting 30 tablets of licorice diuretics daily and lost 10 kg within 4 months [59]. Shintani et al. reported glycyrrhizic acid as principle toxic constituent, which performs an inhibitory action on enzyme 11-hydroxysteroid dehydrogenase thus resulting in low plasma renin activity, low aldosterone level, and normal cortisol level [60].

5.2 Bladder wrack (Fucus vesiculosus):
It is known to have anti-estrogenic effects [61], anti-lipidemic effects [62], anti-neoplastic effects [63], dermatological agent [64], and antioxidant effects [65]. It contains high amounts of iodine along with heavy metals like arsenic and cadmium [66]. Ingestion of iodine more than 150 µg/day is known to cause hyperthyroidism or exacerbate existing hyperthyroidism. If chronically consumed, iodine is responsible for reduction in organic binding of iodine by thyroid gland resulting in hypothyroidism and goitre [67]. Skibola reported a case of a woman with significantly increased menstrual cycle length (increase of 5.5 to 14 days) due to ingestion of bladder wrack [61].

CONCLUSION
A number of herbal medicinal products are associated with a spectrum of toxicity events. Advances in the understanding of the pathogenesis and precautions are needed to improve herbal medicine safety.

REFERENCES


