Clinical uses and Toxicity of *Ephedra sinica*: An Evidence-Based Comprehensive Retrospective Review (2004–2017)

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INTRODUCTION

Herbs as medicines are well known and are used since long for treating various ailments. The first ever such use for any herb has been recorded by Egyptians and Ancient Chinese in medical prescription as early as 2500 BC.²,¹ The researchers found that most of the peoples are using plants in different parts of the world to treat a certain disease.³ For example, *Liujiunzi Tang* has been used to treat Phlegm–Heat syndrome.⁴ Similarly, *Ginkgo biloba* has been used to enhance memory and circulatory diseases in various parts of the world.⁵,⁶ A plethora of plants is available where they are actively used to treat disorders such as respiratory, central nervous, and cardiovascular system diseases.⁶,⁷ *Ephedra sinica* (ES) is also considered as one of the most significant plants in traditional medicine. It belongs to the family *Ephedraceae* and known with its synonym in Korea, China, and Japan, i.e., *Ma-huang*.⁸,⁹ The synonym Ma-huang in Chinese literally means a “yellow hem” or “yellow astringent” referring to its distinctive coloring.¹⁰ According to the literature, ES has been used for more than 5000 years to treat many disease,¹¹ and traditionally, the dried stems of ES as a tea was used to treat asthma, coughs, fever, problems with urination, lack of sweating, and to alleviate edema.¹² Like any other crude drug, it has an official monograph in both the Chinese and Japanese Pharmacopoeias, where it is standardized beside the main alkaloids that are analog of amphetamine: pseudoephedrine and ephedrine.¹³ It contains proanthocyanidins and phenylpropylamino alkaloids that are known as ephedrine alkaloids: (1S, 2S)-pseudoephedrine, (1R, 2S)-ephedrine, (1S, 2S)-norpseudoephedrine, (1R, 2S)-norephedrine, (1S, 2S)-N-methylpseudoephedrine, and (1R, 2S)-N-methyl ephedrine in the *Ephedra* stems.¹²,¹³ Although all parts of the ephedra plant contain ephedra alkaloids, the stem contains the highest comparative concentration, up to 3% of dry weight.¹⁴ Moreover,
according to the Japanese and Chinese Pharmacopeia, all the products, i.e., "Ephedra Herb" are extracted from the dried stems of ES, *Ephedra equisetina*, or *Ephedra intermedia*. In the ancient times, ES was used due to its alkaloid constituents for treating respiratory, central nervous, and cardiovascular diseases, as it contains about 0.7%–0.8% of alkaloids in the whole plant. In addition, some of the *Ephedra* species contain high amounts of proanthocyanidins with prominent biological activities as like alkaloids, such as bronchodilation and vasorelaxation. Proanthocyanidin oligomers too have a comparatively significant effect over alkaloids, including antimicrobial, antioxidant, anti-inflammatory, immunosuppressive, antiviral, anti-invasive, antiangiogenic, antitumor, and cytotoxic activity, especially against the cancer cell lines such as SGC-7901, HepG2, and HeLa. Recently, ES has been introduced into the United States (US) market as a supplement for weight loss energy gain, and toxicity cases up to 31% have been reported, associated with the use of products or supplements containing ephedra alkaloids. Many herbal medications have been reported with such forms of toxicities associated with the use of herbal products in any of its form and so is the dilemma with ES plant. Some of the toxicities observed for this plant are reversible that can be overcome and normalized by treatment whereas others may lead to irreversible toxicity or death in some cases. Research studies report the use of ES plant with possible complications in cardiac such as rapid ventricular contraction and atrial fibrillation, liver such as hepatitis and cirrhosis as well as at kidney level. This study aims to collect the data regarding the clinical cases observed from 2004 to 2017 and evaluate and observe them to find the association between clinical use and toxicity or adverse effects observed for ES. The study helps the health-care providers to have a glance over the main reason for toxicity, adverse effect, or deaths if reported, with the use of ES plant and to comprehend its therapeutic importance as compared to toxicity.

**MATERIALS AND METHODS**

**Databases and journals searched**

Databases included in this study were PubMed, Research gate, Science Direct, Google Scholar, and Thomson Reuters. Journals searched in this article were *Journal of Ethnopharmacology, Frontiers in Ethnopharmacology, Intercultural Ethnopharmacology, Hindawi Journals, SAGE journals*, and Central library Imam Abdulrahman Bin Faisal University.

**Keywords searched**

"Ephedra Sinica," "E. Sinica poisoning," "Ma-hung major active constituents," "E. Sinica uses and toxicity," "Ephedra sinica toxicity and its treatment," "Ma-hung toxicity cases in humans," "E. sinica toxicity cases in humans," clinical trials reported, adverse effects observed for *E. sinica*.

**Review period**

The article is a review with a retrospective period of 14 years, i.e., 2004–2017, where the articles regarding the clinical cases reported for ES in humans were collected from all databases.

**Inclusion criteria**

Any clinical case related to the use of ES as well as any adverse effects, poisoning, and death reported due to its use were included in the study. The cases reported in humans only, irrespective of age, gender, and nationality were considered for the study. In addition, the cases resulted due to an overdose of ES or its concomitant use with any conventional medication and lack of medical supervision, resulting in poisoning, were included in the study. Articles from all databases, irrespective of indexed or nonindexed journals, were downloaded.

**Exclusion criteria**

The clinical cases reporting minor or less severe side effects or adverse effects were excluded from the study. Similarly, any clinical case reported in animals or research study conducted in animals resulting a toxicity or death was not included in this study. In addition, *in vitro* studies and unapproved or human studies with lack of ethical approval were excluded from this study and is presented in Table 1.

**Search results**

Following the predefined inclusion and exclusion criteria, the literature was filtered, and 11 cases were found to meet the eligibility criteria.

**LITERATURE REVIEW**

**Clinical case in 2017**

*Ephedra-containing product causes closed-angle glaucoma*

A 52-year-old female used a herbal product containing ephedra to increase weight loss. Few days later, she came to the emergency section complaining of nausea, vomiting, and headache accompanied with decreased visual acuity. The patient was diagnosed with bilateral angle-closure glaucoma and immediately treated with dorzolamide-timolol, brimonidine, and intravenous 20% mannitol. The patient was advised to stop the product, and the status improved following the complete treatment.

**Clinical case in 2016**

*Ephedra sinica long use developed renal diseases*

A patient was admitted with a complaint, consisting of nephrolithiasis and renal dysfunction. On investigation, it was found that he was previously administered with ES at a dose of 40–3000 mg/day for several months. This long-term treatment resulted in complications where no treatment was made available.

**Clinical case in 2015**

*The relation between energy-weight loss product and cardiac problems*

In the US, the Regional Poison Centers made a study that showed limitation in toxicity of ES using Food and Drug Administration (FDA) ban from 2001 to 2013. The Poison Centers reported a total of 10,326 cases related to ES poisoning in 2002. This figure continued to decrease gradually down to 180 toward the end of 2013. By 2004, FDA ban has revealed to be useful in reducing the side effects of ES related to cardiac toxicity.

**Clinical case in 2014**

*Liver toxicities related to herbal product containing ephedra*

Six patients from the US were using herbal medications, i.e., *Ma-huang* whereby they experienced an acute hepatitis. One among the patients had chronic HBV infection and two patients developed an acute liver failure; however, one of them was treated with liver transplant.

**Clinical case in 2012**

*Drug-herb interaction causes irreversible neurodegenerative disorder*

A 29-year-old male has been injected with an intravenous mixture of pseudoephedrine (extracted from ephedra), potassium permanganate, and acetylsalicylic acid two to three times a day for 9 years and a half. Drug-herb interaction causes irreversible neurodegenerative disorder due to the long exposure to ES. He used to take fluoxetine, amitriptyline, diazepam, and
Table 1: Clinical cases reported about *Ephedra sinica* (Ma-hung)

<table>
<thead>
<tr>
<th>Case number</th>
<th>Form of ephedra used</th>
<th>Age</th>
<th>Gender</th>
<th>Clinical manifestation</th>
<th>Treatment protocol</th>
<th>Reason for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Medication</td>
<td>52</td>
<td>Female</td>
<td>Nausea, Vomiting, Headache, Decreased visual acuity</td>
<td>Dorzolamide + timolol, Brimonidine, Mannitol (20% IV), Stop the medication</td>
<td>To lose weight</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>-</td>
<td>Male</td>
<td>Nephrolithiasis, Renal dysfunction</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>-</td>
<td>Male and female</td>
<td>Cardiac dysrhythmias, Stroke, Seizure, Hypertension, Death</td>
<td>Standard therapy</td>
<td>To induce energy and to lose weight</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Acute hepatitis/chronic HBV infection/liver failure</td>
<td>Liver transplant</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Ephedra (IV)+other drugs</td>
<td>29</td>
<td>Male</td>
<td>Speech disturbance, Inability to walk, Postural instability, Tremor, Dystonia</td>
<td>Fluoxetine, Amitriptyline, Diazepam, L-Dopa</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>17</td>
<td>Male</td>
<td>Jaundice, Hyperbilirubinemia, Elevated aminotransferases, Hepatomegaly</td>
<td>Cholestyramine, Ursodeoxycholic acid, Stop the medication</td>
<td>For physical performance</td>
</tr>
<tr>
<td>7</td>
<td>Medication/placebo</td>
<td>20–30</td>
<td>Females and males</td>
<td>Imbalance on the autonomic nervous system</td>
<td>-</td>
<td>To evaluate the effect of ephedra on the autonomic nervous system</td>
</tr>
<tr>
<td>8</td>
<td>Medication</td>
<td>21</td>
<td>-</td>
<td>Complete muscle failure, Hypotensive Tachycardia</td>
<td>Fluid-containing bicarbonate</td>
<td>To improve physical performance</td>
</tr>
<tr>
<td>9</td>
<td>Dietary supplement/medication</td>
<td>-</td>
<td>-</td>
<td>Cardiovascular toxicity</td>
<td>Stop the supplement</td>
<td>To improve performance and lose weight</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>45</td>
<td>Females</td>
<td>Cardiac collapse, Severe headache, Vomiting, Loss of awareness</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>-</td>
<td>19</td>
<td>Male</td>
<td>Chest pain, Breathing difficulty</td>
<td>Medication for heart failure</td>
<td>-</td>
</tr>
</tbody>
</table>

IV=Intravenous, HBV=Hepatitis B virus

L-Dopa to recover from this toxicity; however, no improvement was observed even after 2 years of treatment.²²

**Energy supplement-induced liver injuries**

A 17-year-old student from Guerrero, Mexico, was using energy supplements and natural product to enhance physical performance. Subsequently, he developed acute mixed liver injury with other symptoms including jaundice, hyperbilirubinemia, elevated aminotransferases, and apparent hepatomegaly, after taking a lot of these supplements. His liver test returned to normal after a treatment with cholestyramine and ursodeoxycholic acid.²²

**Clinical case in 2010**

*Autonomic nervous system imbalance caused by Ephedra sinica extract*

Twenty healthy adults (10 females and 10 males) participated in a study of the effects of ES on autonomic nervous system (given either 1 g of ES dry extract or a placebo). The treatment was taken once a day for 2 weeks with 1 week in between as a washout period. Heart Rate Variability analysis, to evaluate the results of the medical trial, revealed both acute and chronic effects on the autonomic nervous system balance. The effects may be due to an increase in the sympathetic nervous system activity and decrease in the parasympathetic activity. There is no specific treatment for this toxicity.²²

**Clinical case in 2006**

*Cardiovascular problems due to herbal supplement*

A 21-year-old healthy adult was using herbal supplement containing ES to enhance the performance; however, the patient was found to have complete muscle failure. Before the use of ES, the patient had hypotension and tachycardia which progressed to acute renal failure with the elevation of creatine kinase (426 U/L to 241.418 U/L in 6 days). A treatment with...
fluids containing bicarbonate for 1 month recovered the renal function and creatine kinase to normal; however, the muscle biopsy was negative for underlying neuromuscular disease.  

**Clinical case in 2005**

**Cardiovascular toxicity among athletes using ephedrine supplement**

Athletes in the US developed cardiovascular toxicity with the use of drugs and dietary supplements containing ES to improve athletic performance and loss weight. No specific treatment for such toxicity was reported except to stop the use of drug.

**Death due to myocardium degeneration after using ephedra product**

A 45-year-old female using ES died due to cardiac collapse. Initially, she had a complaint of severe headache and used painkiller (aspirin). After a short time, she was suffering from vomiting and loss of awareness. The medical history revealed a degenerative myocardium such as lipofuscin associated with caspase activation, myocyte apoptosis, and extensive cleavage of myofibrillar proteins (α-actinin, α-actin, and cardiac troponin-T), associated with the use of ES.

**Clinical case in 2004**

**Adverse reaction leading to death**

A 19-year-old patient was admitted to the emergency department with major complaint of intermittent chest pain extending to the left arms with breathing difficulty. Left heart catheterization revealed a significant coronary artery disease, global hypokinesis, and dilated left ventricle. Following some standard therapies for heart failure, the patient was discharged; however, a death was reported for the patient after 5 weeks. An objective causality assessment probability scale disclosed the use of ES in the same patient, whereby cardiomyopathy was resulted as an adverse reaction to ephedra use.

**DISCUSSION**

ES, known as Chinese *Ma-hang*, is a part of traditional Chinese medicine (TCM) used for many conditions due to its alkaloid content. The plant is used mainly for the treatment of central nervous, cardiovascular, and respiratory system diseases. For ES, an increase in use (18% to 32%) has been observed particularly in two groups, i.e., athletes and cancer patient. In the US, it has been estimated that people spend around 30 million dollars for weight loss products without seeking medical advice, among which few products are allowed by FDA without verifying their safety and efficacy. Usually, traditional drugs commonly used as energy supplement resulted in nephrotoxicity, liver injuries, and extreme release of catecholamine in the form of dopamine, epinephrine, pseudoephedrine, and norepinephrine. As per the literature reports, these conditions are caused by using some known materials such as usnic acid, *Ma-Huang* (ES), anabolic steroids, *Morinda citrifolia* (Noni Juice), Hydroxycut, kava, Vitamin A, Germander, and *Camellia sinensis* (green tea). The toxicity may take place by different mechanisms such as hypersensitivity reaction, autoimmunity, accumulation of toxic metabolite, and drugs interaction.

ES as a medicinal product, though, has more widespread uses; however, it may induce many adverse effects besides its therapeutic purpose. This literature review highlights the therapeutic uses for ES along with the adverse effects or toxicity associated with its use and extracts out the causes and reasons leading to such unwanted conditions. This will enable the end user to keep in mind the comparative value of ES in treating a particular disease. Following an in-depth literature search, we found the following undesired effects resulting with the use of ES.

**Effect on sympathetic nervous system and toxicity**

ES stimulates the sympathetic nervous system and pushes the body into a fight or flight mode. This adrenaline-like effect increases heart rate and blood pressure and stimulates lipolysis; thus, it makes the body to burn more calories. Various fat-burning supplement contains ephedra in combination with caffeine to potentiate its effect; however, the adverse reactions posed from these products are life threatening such as brain hemorrhage, seizures, chest pain, tremor stroke, and possibly death.

**Liver toxicity**

The use of products containing ephedra may develop health issues. Few of the user have reported liver problems such as chronic hepatitis B infection and acute liver failure which required a transplant in a few cases.

Herein, we mentioned 11 different cases in our study which reported toxicities associated with the use of ES. Few of the cases mentioned liver toxicity whereas others reported cardiac problems and hypertension along with neurological problems. However, it is noteworthy to mention here that after an in-depth study of the reported cases for the possible reasons of toxicity, we ended with a conclusion that the toxicity resulted due to drug interaction, i.e., a concomitant use of ES with conventional medications, long-term use of ES plant in a particular disease, overdose, misuse of ES, i.e., as an energy source or supplement to enhance performance, use of the plant with lack of proper medical supervision, and lack of knowledge about its complications. Moreover, lack of proper regulation from FDA also adds to the disadvantages as they are easily available in the form of over-the-counter drugs and supplements at any drug store which makes it easily accessible to end user. Thus, to claim ES as a toxic plant is not justifiable at this stage.

Moreover, the use of ES plant with proper dose and in specific conditions as directed along with use under proper medical supervision provides more advantages and therapeutic effects as discussed in the forthcoming section.

**Ephedra sinica used for nasal congestion**

ES contains ephedrine and pseudoephedrine, the two oldest agents known for their efficacy in nasal congestion. Pseudoephedrine is used...
orally alone or in combination with other drugs such as antihistamine (H1) to treat allergies and common cold. On the other hand, ephedrine applied to the nasal mucosa reduces nasal congestion more strongly and quickly than oral pseudoephedrine but with a short duration of action.31

Bromchodilator effect of Ephedra sinica

Ephedrine is a crude powdered extract from the stem of ES, used in TCM for over 5000 years to treat asthma. Ephedrine has an adrenaline-like effect on the nervous system, and its benefits in asthmatic patients are achieved through the activation of B2 receptor found on the smooth muscle of the airways which is responsible of relaxation effect.32

Anti-inflammatory and immunosuppressive properties

Polysaccharide, purified from the stems of ES, is considered to be an important contributor to immunosuppressive and anti-inflammatory effects in the plant. The most effective polysaccharide is ESP-B4 which shows activity against cytokines (monocyte chemotactant protein-1, tumor necrosis factor-a, and interleukin-6 [IL-6], IL-1β, and IL-8) and inflammatory mediators (prostaglandin E2), and within the serum, it is suggested that ESP-B4 is effective to treat adjuvant-induced arthritis.33

Nutritional value of Ephedra sinica

In addition to the above medical uses, Chinese people used ES fruit part as a food (eaten dried or fresh, raw or cooked) and consumed safely through different ways, such as in cheese condiment, tea substitute, and refined sugar. The nutritional components responsible in fruit are carbohydrates, protein, fibers, fatty acids, and mineral. However, there are only a few reports related to the fruit, and it has been stated that the fruit part of ES is nontoxic for birds or rodent even.34

The discussion provides an insight regarding the comparative value of ES. It is evident from the mentioned clinical cases and literature reports that ES may have adverse effects or toxicity, leading to deaths in extreme cases even. However, it was observed that long-term use, overdose, misuse, ES, and conventional drug interactions, as well as lack of medical supervision for ES in a particular treatment are the factors which favor such unwanted effects. On the other hand, the number of reported cases during the last 14 years, i.e., 11, is not a sufficient explanatory proof to rule out ES for being used in the treatment of various specified disease. Furthermore, the untoward effects are very less for ES as compared to its beneficial effects in different treatment and conditions.

CONCLUSION

ES may lead to serious side effects, including cardiac, renal, and liver complications. However, a proper use of the plant with suggested dose, frequency, and duration, under a proper monitoring and medical supervision, may avoid such complications and may result in the utilization of ES for an effective therapeutic plan.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

REFERENCES
