International Journal of Trend in Scientific Research and Development (IJTSRD)
Volume 7 Issue 1, January-February 2023 Available Online: www.ijtsrd.com e-ISSN: 2456 – 6470

Ephedra: Distribution, Ethnobotany and Pharmacological Properties

Dr. Ruchi Purohit[1], Dr. Sanjay Purohit[2]

[1]Associate Professor in Botany, Govt. College, Sirohi, Rajasthan, India
[2]Associate Professor in Botany, Govt. College, Abu Road, Rajasthan, India

ABSTRACT

Ephedra is one of the largest genera of the Ephedraceae family, which is distributed in arid and semiarid regions of the world. In the traditional medicine from several countries some species from the genus are commonly used to treat asthma, cold, flu, chills, fever, headache, nasal congestion, and cough. The chemical constituents of *Ephedra* species have been of research interest for decades due to their contents of ephedrine-type alkaloids and its pharmacological properties. Other chemical constituents such as phenolic and amino acid derivatives also have resulted attractive and have provided evidence-based supporting of the ethno medical uses of the *Ephedra* species. In recent years, research has been expanded to explore the endophytic fungal diversity associated to *Ephedra* species, as well as, the chemical constituents derived from these fungi and their pharmacological bio prospecting. Two additional aspects that illustrate the chemical diversity of *Ephedra* genus are the chemotaxonomy approaches and the use of ephedrine-type alkaloids as building blocks in organic synthesis. American *Ephedra* species, especially those that exist in Mexico, are considered to lack ephedrine type alkaloids. In this sense, the phytochemical study of Mexican *Ephedra* species is a promising area of research to corroborate their ephedrine-type alkaloids content and, in turn, discover new chemical compounds with potential biological activity.

KEYWORDS: *Ephedra, ethnobotany, distribution, pharmacological, chemical constituents, alkaloids, potential*

How to cite this paper: Dr. Ruchi Purohit | Dr. Sanjay Purohit "Ephedra: Distribution, Ethnobotany and Pharmacological Properties" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-7 | Issue-1, February 2023, pp.257-262, URL: www.ijtsrd.com/papers/ijtsrd52683.pdf

IJTSRD52683

INTRODUCTION

Ephedra is one of the largest genera of the Ephedraceae family, which is distributed in arid and semiarid regions of the world. In the traditional medicine from several countries some species from the genus are commonly used to treat asthma, cold, flu, chills, fever, headache, nasal congestion, and cough. The chemical constituents of *Ephedra* species have been of research interest for decades due to their contents of ephedrine-type alkaloids and its pharmacological properties. Other chemical constituents such as phenolic and amino acid derivatives also have resulted attractive and have provided evidence-based supporting of the ethno medical uses of the *Ephedra* species.[1] In recent years, research has been expanded to explore the endophytic fungal diversity associated to *Ephedra* species, as well as, the chemical constituents derived from these fungi and their pharmacological bio prospecting. Two additional aspects that illustrate the chemical diversity of *Ephedra* genus are the chemotaxonomy approaches and the use of ephedrine-type alkaloids as building blocks in organic synthesis. American *Ephedra* species, especially those that exist in Mexico,[2] are considered to lack ephedrine type alkaloids. In this sense, the phytochemical study of Mexican *Ephedra* species is a promising area of research to corroborate their ephedrine-type alkaloids content and, in turn, discover new chemical compounds with potential biological activity. Therefore, the present review represents a key compilation of all the relevant information for the *Ephedra* genus, in particular the American species, the species distribution, their ecological interactions, its ethnobotany, its phytochemistry and their pharmacological activities and toxicities, in order to promote clear directions for future research. Plant species constitute valuable

sources of bioactive compounds. Nowadays, an increasing tendency towards to the use of natural products can be observed in a high demand from food, cosmetics and pharmaceuticals manufacturers due to the fact that phytochemicals present in the plant extracts generally show low toxicity and are effective at micromolar concentrations. In this context, in the arid and semi-arid regions of the globe there are several plants that provide a great source of phytochemicals,[3] mainly because these plants have the capability to grow under extreme climatic conditions . The *Ephedra* genus (Ephedraceae) is one of the oldest medicinal plants known to humankind and consists of 69 species mainly distributed in semi-arid environments throughout both the Palearctic and Nearctic realms, although some species are distributed through few Neotropical countries. The species grouped in this genus are among the few gymnosperms adapted to arid environments. They are perennial and dioecious and several species are rarely found shrubs and more commonly, vines (e.g., *Ephedra equisetina* Bunge).[4] Ephedras are also traditionally used to treat diseases such as allergies, bronchial asthma, chills, colds, coughs, edema, fever, flu, headaches and nasal congestion [6]. *E. sinica* Stapf is the primary species that has been used as a stimulant and as an antiasthmatic in China for more than 5,000 years and is still used in *Ephedra* preparations and extracts all around the world. In Ayurvedic medicine, *E. gerardiana* Wall. ex Stapf has been similarly employed since ancient times. In the US, at the beginning of the 20th century the use of *Ephedra* herb gained importance by its use for weight loss and performance enhancement, however, due to the possible hazards caused by misuse or abuse of the herb its use has been controlled . In the Americas, the *Ephedra* species: *E. antisyphilitica* Berland. ex C.A.Mey., *E. californica* S.Watson and *E. nevadensis* S.Watson have been used by the indigenous people since ancient times due to their properties to treat syphilis and gonorrhea. Preparations of these plants were applied either directly to the genital organs or ingested as an infusion. *E. nevadensis* S.Watson had diverse vernacular names such as Mormon tea, Brigham or whorehouse teas .Currently, some *Ephedra* species have been used for weight loss and several studies have demonstrated their potential use for several conditions.[5]

The family Ephedraceae, of which *Ephedra* is the only extant genus, are gymnosperms, and generally shrubs, sometimes clambering vines, and rarely, small trees. Members of the genus frequently spread by the use of rhizomes.[4]The stems are green and photosynthetic.[5] The leaves are opposite or whorled. The scale like leaves fuse into a sheath at the base and this often sheds soon after development.[6] There are no resin canals.[4]The plants are mostly dioecious: with the pollen strobili in whorls of 1–10, each consisting of a series of decussate[6] bracts. The pollen is furrowed. The female strobili also occur in whorls, with bracts which fuse around a single ovule. Fleshy bracts are white (such as in *Ephedra frustillata*) or red. There are generally 1–2 yellow to dark brown seeds per strobilus.[4]

The oldest known members of the genus are from the Early Cretaceous around 125 million years ago, with records being known from the Aptian-Albian of Argentina,[11] China,[12] Portugal and the United States.[13] The fossil record of *Ephedra* outside of pollen disappears after the Early Cretaceous.[14] Molecular clock estimates have suggested that last common ancestor of living *Ephedra* species lived much more recently, during the Early Oligocene around 30 million years ago.[15] However, pollen modified from the ancestral condition of the genus with branched pseudosulci (grooves), which evolved in parallel in the living North American and Asian lineages is known from the Late Cretaceous, suggesting that the last common ancestor is at least this old.[14]

Discussion

The *Ephedra* alkaloids, ephedrine and pseudoephedrine – constituents of *E. sinica* and other members of the genus – have sympathomimetic and decongestant qualities,[18] and have been used as dietary supplements, mainly for weight loss.[19] The drug, *ephedrine*, is used to prevent low blood pressure during spinal anesthesia.[18]

In the United States, ephedra supplements were banned from the market in the early 21st century due to serious safety risks.[19] Plants of the genus *Ephedra*, including *E. sinica* and others, were used in traditional medicine for treating headache and respiratory infections, but there is no scientific evidence they are effective or safe for these purposes.[19]

Ephedra has also had a role as a precursor in the clandestine manufacture of methamphetamine.[20]

Alkaloids obtained from the species of *Ephedra* used in herbal medicines, which are used to synthetically prepare pseudoephedrine and ephedrine, can cause cardiovascular events.[18] These events have been associated with arrhythmias, palpitations, tachycardia and myocardial infarction.[18] Caffeine consumption in combination with ephedrine has been reported to increase the risk of these cardiovascular events.[18][19] The earliest uses of *Ephedra* species (mahuang) for specific illnesses date back to 5000 BC. Ephedrine

and its isomers were isolated in 1881 from *Ephedra distachya* and characterized by the Japanese organic chemist Nagai Nagayoshi. His work to access[7] *Ephedra's* active ingredients to isolate a pure pharmaceutical substance led to the systematic production of semi-synthetic derivatives thereof is relevant still today. Three species, *Ephedra sinica*, *Ephedra vulgaris*, and to a lesser extent *Ephedra equisetina*, are commercially grown in Mainland China as a source for natural ephedrines and isomers for use in pharmaceuticals. *E. sinica* and *E. vulgaris* usually carry six optically active phenylethylamines, mostly ephedrine and pseudoephedrine with minor amounts of norephedrine, norpseudoephedrine as well as the three methylated analogs. Reliable information on the total alkaloid content of the crude drug is difficult to obtain. Based on HPLC analyses in industrial settings,[8] the concentrations of total alkaloids in dried *Herba Ephedra* ranged between 1 and 4%, and in some cases up to 6%.[21]

For a review of the alkaloid distribution in different species of the genus *Ephedra* see Jian-fang Cui (1991).[22] Other American and European species of *Ephedra*, e.g. *Ephedra nevadensis* (Nevada Mormon tea) have not been systematically assayed; based on unpublished field investigations, they contain very low levels (less than 0.1%) or none at all.[23]

Results

Recently, the idea of using Ephedra as an alternative to cancer therapy has become popular. This is particularly true of Ephedra foeminea, which many cancer patients in the Middle East region utilise because of the belief that it has cancer-curative properties [4]. Based on these observations, limited studies have investigated the effect of crude extracts of various types of Ephedra foeminea on different cancer cell lines [4-7]. In a study using an aqueous decoction of Ephedra foeminea, there were no significant effects on the viability of MDA-MB231 and SKBR3 breast cancer cell lines [5]. In contrast, another study showed that extracts and fruit juice of Ephedra foeminea significantly decreased the viability of colon cancer cells (HTC116) and breast cancer cells (MDA-MB-213), but no toxic effect was exerted on lung carcinomatous cells (A549) [7]. Likewise, Ephedra foeminea extracts exhibited a dose dependent decrease in viability of human osteosarcoma cells (U2OS) [7]. These contradictory results may be attributed mainly to differences in constituents of various types of Ephedra foeminea extracts. There are limited data on the phytochemical constituents of crude extracts of Ephedra foeminea. A recent study reported the absence of ephedrine and pseudoephedrine alkaloids from Ephedra foeminea [5]. The results obtained from the above studies are contradictory, and further investigations about anti-cancer properties and phytochemical analysis of Ephedra foeminea are required.[9]

The utilization of medicinal plants to treat infectious disease is a common practice in developing countries worldwide. The present study was aimed at evaluating the crude extracts of *Ephedra gerardiana* (root and stem) with different chemicals for antioxidant and antimicrobial (fungal and bacterial) potential. Furthermore, crude extract and fractions also revealed promising antibacterial activities against all tested microbial strains while aqueous fraction showed no activities against *Bacillus subtilis*, *Kleibsiella pneumoniae*, and *Pseudomonas aeruginosa*. Interestingly, all crude extracts and fractions were nonactive against fungal strain, *Aspergillus niger* and *Aspergillus flavus*, as compare to control. In summary, the *Ephedra gerardiana* (root and stem) extract and fraction possess antioxidant activities, which might be helpful in preventing or slowing the progress of various oxidative stresses, suggested to be a strong pharmaceutical agent.[10]

Ma-huang is the drug isolated from *Ephedra,* used in Chinese medicine for 5000 year to cure various human diseases such as fever, nasal congestion, and asthma [2]. In Japan, ephedra genus is used at a rate of some 300 tons a year due to their addition as a crude drug in several Sino-Japanese medicine; preparations have been widely used as a treatment for fever, nasal congestion, and asthma [3]. Furthermore, the ephedra genus contains bronchial dilator, ephedrine, and other ephedrine alkaloids.[11] It has been also used for many years in traditional medicine to treat allergies, bronchial asthma, chills, colds, coughs, edema, fever, flu, headaches, and nasal congestion and has been a natural source of alkaloids such as ephedrine, pseudoephedrine, pseudoephedrine, and other related compounds [4]. Similarly, the extracts with various chemicals from medicinal plants have been tested and showed the effectiveness of traditional herbs against microorganisms; as a result plants are one of the bedrocks for modern medicine to attain new principles [5]. Thus, medicinal plants can offer a wealth for their biological activities, such as antimicrobial, antioxidants, antimalarial, and anticancer activities.[12]

Therefore, the exploration of plants needs attention to isolate compounds that can act as suitable antioxidants and antimicrobial agent instead of synthetic compounds [6]. Recently, the natural antioxidants have significantly increased in food and cosmetic and therapeutic products, since they have

multifacetedness in their mass and amount of activities and provide huge scope in modifying imbalance [7]. Similarly, the aqueous extract of the *Ephedra aphylla* is used as strong inhibiter against malarial parasitic protozoan, *plasmodium falciparum* [8], and the compounds which were isolated from *Ephedra aphylla* have no estrogenic activity but most of the Lignans exhibited moderate antioxidant activity without any cytotoxicity. [13]Up to now, some species of genus ephedra were screened for antimicrobial activities including, *E. altissima* [9], *E. transitoria* [10], *E. breana* [11], and *E. gerardiana* (leaf) [12], while, as for their antioxidant potential, *E. laristanica, E. sarcocarp* [13], and *E. gerardiana* (ethanol extract) [14] were investigated. In the light of this previous study, we sought to evaluate the crude extracts and fractions of *E. gerardiana* (root and stem) for free radical scavenging potential and antimicrobial (fungal and bacterial) activities.[14]

Conclusions

The distribution pattern of *E. gerardiana* in the Himalayan region considered as critically endangered using IUCN criteria (Samant and Pant 2006) and endangered in Trans-Himalayan cold desert of Ladakh and Lahaul-Spiti (Chaurasia and Gurmet 2003). It is locally known as Tsepat, and mTshe-lDum in Sowa-Rigpa (Gurmet and Rath 2020) and popular trade name is Somlata. Himalayan region medicinal plants have occupied an important values spiritually, culturally, and health benefits of the peoples. More than 34% of total plant wealth have known to have medicinal value (Ved 2008). The genus Ephedra belonging to member of Ephedraceae, is a group of plants that inhabit temperate regions in Asia, Eurasia, Northern Africa, South-western North America, and western South America. Due to its xerophytic characters, it is a drought and frost resistant. It is represented by 50-65 species of shrubs, rarely small trees (Stevenson 1993; Sharma and Uniyal 2008; Sharma et al. 2010). Three species were reported from Ladakh including *E. gerardiana, E. intermedia* and *E. regeliana* (Dvorsky et al. 2018). In India, its distribution extends from Sikkim in Eastern Himalaya to North-West in Uttarakhand, Ladakh, Himachal Pradesh, and Jammu & Kashmir. Genus Ephedra have eleven species that distributed in the Indian sub-continent,[15] mostly in higher elevations of Himalaya preferring alkaline soils. Different species that occur in various regions of country are markedly different from each other in term of their habitat preferences that promote diversity within the genus (Sharma and Uniyal 2008; Sharma et al. 2010). The drug Ephedrine and many active compounds such as ephedrine, pseudoephedrine, norephedrine, norpseudoephedrine, methyl ephedrine, methyl pseudoephedrine, alkaloids, phenoles, terpenoids are obtained from the *E. gerardiana* and is one such important endangered medicinal plant. In trans-Himalaya of Ladakh the *E. gerardiana* is being used by local healears (Amchis) and ethnic people to cure various diseases such as chronic fever, wounds, tumours, discomfort in breathing, cough, sweating, urine obstructions (Gurmet and Stobgais 2016). The fruit and shoot is also used for the treatment of asthma, rheumatism and heart stimulant in Sowa-Rigpa by local healears (Amchis) of High altitude of Ladakh (Kunzes et al. 2012). The decoction of areal part is used against bronchial problems and liver disorders. It is also cure menstrual irregularities (Navchoo and Buth 1992). *E. gerardiana* is also used in Ayurveda, Unani, Siddha, Homeopathy Chines medicines,[16] folk medicine and other traditional m edicines. Due to its resinous smell and taste it is used with tobacco after drying and making powder called Sotak, a pinch of which local people place under the tongue in Ladakh. Twigs used as a tooth brush (Bhattacharyya 1991). The *E. gerardiana* has been also used for other purposes by ethnic communities, where fruit is eaten in high altitude areas, whole plant used for fuel, aerial part is used for washing utensils and also used for religious purposes in cold desert (Samant and Lal 2019). Owing to its many fold medicinal properties and their folk uses, *E. gerardiana* is in high demand by pharmaceutical industries and traditional healers. Lack of suitable and effective conservation management, over exploitation, habitat degradation the genus is under brink of extension. [17]For long-term conservation management of this genus, a better and comprehensive understanding of the species remains a top priority, for which detailed studies on its habitat ecology, biology, and agro-technology are not done so far (Samant and Lal 2019). *E. gerardiana* is an erect shrub of varying sizes, bears cylindrical, striated, often curved branches arising in whorls, dark green in colour.[18] The internodes of branchlet measure 1-5 cm in length and the fruits are 1-3 mm in width are red in colour, sweet in taste and edible. The ovoid fruits contain 1-3 seeds covered by bracts. The rhizomes have large knobs. It is found scattered in the drier regions of temperate and alpine Himalayas from Kashmir to Sikkim at altitude range 2100-4800 m amsl (meter above mean sea level) and similar heights at Pangi (Chamba), Lahaul and Spiti, Chini and Kilba Kailash ranges of Kanawar (Kinnaur), Shali hills (Shimla), Kashmir and Ladakh. The habitat preference of the plant are sandy slopes, rocky slopes, sandy places and driers area of Himalayas. [19]

Based on present study *E. gerardiana* is an important plant species for local dwellers and Amchies who

take care of health of the inhabitants of the region, and other part of the world. Many important active compounds are obtained from the species having high demand globally. Owing to its many important medicinal and folk importance leads to over exploitation and habitat degradation, due to which it may extinct from the wild of cold desert of Ladakh, study also confirm that the species has very low density individual/m^2 in the region, study conducted by Samant and Pant (2006) using IUCN criteria in the Himalayan region also confirmed that it is on brink of extinction on distribution of *E. gerardiana* therefore, it's very important to conserve the species. On the basis of density of the species in the region and ethno-botanical study, optimization of cultivation techniques was made, for standardization of the packages and practices we opt for the simple seeds treatments with hot water with different timing and used high cost and low cost greenhouses to raise the nurseries so that distinguish farmers can afford for the cultivation of the *E. gerardiana*.[20] The study revealed that freshly harvested seeds can be used to raising the nursery which required quite moist and warm temperature, therefore different protective conditions is recommended coupled with hot water treatment is highly recommended. The freshly harvested seeds collected from the wild has 70-80 germination percentage in the protective condition and nurseries are ready to transplant in 3 months were they get the average temperature 35.52 ^{o}C and relative humidity was 56.49 percentage. As the density of the species is very low in the wild due to poor germination percentage and survival of the species in the open condition. Non-favourable environmental condition in open condition where annual maximum average temperature is 12 ^{o}C and annual average relative humidity was 2.24 % as study revealed that for the maximum germination of the seeds of *E. gerardiana* it required maximum temperature of 35 ^{o}C and relative humidity of 57 %.[21] The study also revealed that the approach for the cultivation and conservation of *E. gerardiana* is very simple it does not required any rocket science. For maximum survival and in-situ, ex-situ conservation we recommended to transplant the nurseries from protective condition to poly-nursery bags in open condition under maximum care for one year for proper development of roots and then can be transplant in open field for maximum survival.[22] Study on packages and practices and population census on the *E. gerardiana* is the first hand information and this can be used as base for the cultivation and conservation of the species ex-situ, in-situ in the region and other part of India and the world with similar topography[23]

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