

## SCIENTIFIC SECTION

### THE OCCURRENCE AND ALKALOIDAL CONTENT OF VARIOUS EPHEDRA SPECIES.

BY C. NIELSEN, H. McCAUSLAND AND H. C. SPRUTH.

*Native Ephedra Species.*—The following species of *Ephedra*, Gnetaceæ, are said to grow in the United States of America:

<i>Ephedra nevadensis</i> , Wats	<i>Ephedra viridis</i> , Coville	<i>Ephedra antisiphilitica</i> , Meyer
<i>Ephedra californica</i> , Wats	<i>Ephedra trifurca</i> , Torrey	<i>Ephedra pedunculata</i> , Engelm
	<i>Ephedra torreyana</i> , Wats	

These species of the Genus are found in certain localities of the Southern and Southwestern States, in arid or alkaline regions, in the deserts, on mountainous slopes, dry beds of water courses, etc.

From various sources, we are informed of their occurrence in the following localities:

*Ephedra Nevadensis*, Wats.—California, New Mexico, Arizona, Colorado, Utah, Nevada. (Honey Lake Valley, South into the Mojave Desert and the Colorado Desert, East into Utah, South to Mexico. On the Indian Reservations of the Southwest; on the North half of the White Mountains of Nevada; also Pyramid Lake, Lemmon; also Kern Valley and upper San Joaquin Valley.)

*Ephedra Californica*, Wats.—California, Colorado. (Mojave and Colorado Deserts, North as far as Western Fresno County, West to San Diego, South into lower California; on mountain slopes West of the Imperial Valley and down over the border; in Death Valley. Has also been found on North Coronado Island.)

*Ephedra Viridis*, Coville.—California, Nevada, Arizona, Utah. On mountain slopes (as high as 5000 to 7000 ft. alt.) of the desert ranges about the Mojave Desert, Owens Valley and Death Valley; North to the White Mountains and East through Nevada and Arizona to Southwestern Utah; also Ft. Tejon. In the San Bernardino Mountains East to Colorado River. In the desert region of Southern California about ten miles North of Westmoreland. Common in the coast mountains not far from Bakersfield, Coalinga, etc.

*Ephedra Trifurca*, Torrey.—Arizona, Colorado, California, perhaps Texas. (Mojave Desert, San Diego.)

*Ephedra Antisiphilitica*, Meyer.—Arizona, New Mexico, Southern California.

We have as yet no information as to the whereabouts in the United States of *Ephedra pedunculata*, Engelm, and *Ephedra torreyana*, Wats.

We have obtained samples of a few of these species from various sources. Some of these samples were identified, others were not. Their appearance is very much alike. They are shrubs, sometimes reaching a height of three to four feet, with woody trunks, green or yellowish green long-jointed stems, similar to those of the Chinese Ma-Huang, but heavier, having very small scale-like leaves at the joints. They are unisexual plants. None of the varieties received had flowers or fruits.

(A.) Figures 1, 2, 3 and 4.—*Ephedra californica*, Wats, supplied and identified by Frank A. Thackery, U. S. Dept. of Agric., Bur. of Plant Industry, gathered in August, sun-dried.

(B.) Figure 5.—*Ephedra* gathered in El Paso County, Texas, supplied by C. R. Orcutt, who was referred to us by Assistant Curator J. N. Rose of the Smithsonian Institution. Species not identified. Gathered in August.

(C.) Figures 6, 7 and 8.—*Ephedra nevadensis*, Wats, supplied and identified by Frank A. Thackery, U. S. Dept. of Agri. Bur. of Plant Industry. Gathered in August in three different localities, sun-dried.



Fig. 1.—Roots and base of *Ephedra californica*, Wats.

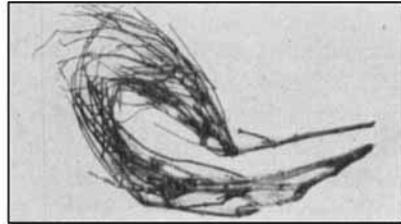


Fig. 2.—Stems and branches of *Ephedra californica*, Wats.



Fig. 3.—Branch of male plant, *Ephedra californica*, Wats.

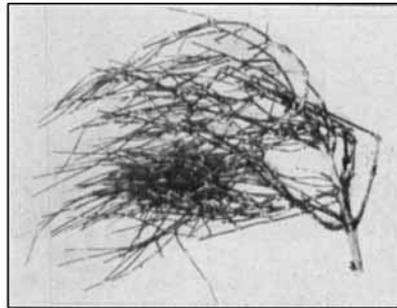


Fig. 4.—Branch of female plant, *Ephedra californica*, Wats.



Fig. 5.—*Ephedra* species from El Paso County, Texas.

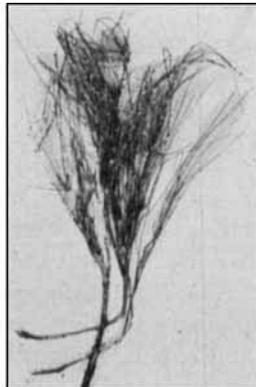


Fig. 6.—*Ephedra nevadensis*, Wats. From California.



Fig. 7.—*Ephedra nevadensis*, Wats. From California.

(D.) Figure 9.—*Ephedra nevadensis*, Wats, supplied by A. N. Woodbury, Park Naturalist, U. S. Dept. of the Interior, Zion National Park, Utah; identified by Markus A. Jones. Gathered in July.

(E.) Figure 10.—*Ephedra viridis*, Coville, gathered and identified by Dr. Albert Schneider of the North Pacific College of Oregon, School of Pharmacy, Portland, Oregon. Gathered in Southern California, ten miles North of Westmoreland.

(F.) *Ephedra*, green branches of plants gathered in Death Valley, California by Mr. W. H. Foster, Colton, California who markets these under the name of "Ephedra, locally known as Squaw or Mormon-Tea." In all probability, a mixture of *Ephedra californica* and *Ephedra nevadensis*.

For detailed botanical description of these plants, see "California Flora," part III, page 65. They are alleged to have medicinal value (1 and 2). Several of the varieties have been known for a great many years to the population in the localities where they grow. The Indians used the decoction of the green stems as a remedy for many and varied ailments and, later, the use of the drug became popular among the Whites also. The various species are known in different localities under different names, such as Squaw Tea, Mormon-Tea, Mountain Rush, Whorehouse Tea, Teamsters Tea, Canutillo, Tepopote. The Coahilla



Fig. 8.—*Ephedra nevadensis*, Wats. From California.



Fig. 9.—*Ephedra nevadensis*, Wats. From Zion National Park, Utah.



Fig. 10.—*Ephedra viridis*, Coville. From California.

Indians are said to have used the seeds also (*Ephedra nevadensis*) eating them roasted.

The most popular use of these teas as a "folk medicine" seems to have been, and still is used as a cure for venereal diseases, but they are also credited with curative properties in other ailments. *Ephedra antisyphilitica*, *californica* and *nevadensis* are said to be beneficial in syphilis and gonorrhoea, both as an injection and internally. The latter was also used by the Coahilla Indians to prepare a cooling drink. *E. trifurca* was reported years ago to be an excellent remedy for Bright's Disease. Some of the varieties have been used by the Indians in Arizona as a diuretic. In the early days, nearly all of the California pioneers traveling westward through the Desert had bunches of *Ephedra* hanging from their wagons (Teamsters Tea), using the tea for such diseases as mentioned or as a pleasant tonic. The strong decoction of the plant is also said to be beneficial for cancer sores.

Scientific pharmacologic and clinical data on the medicinal value of these plants are lacking. The information in the literature relating to their chemistry is scarce. Loew (3) reported that no organic base or alkaloid was present, that the aqueous extraction contained tannin, tartaric acid and pectin. According

to Loew "the tannin belongs to the glucoside groups, furnishing sugar on treatment with acid and various other compounds, and upon distillation pyrogallic and carbonic acids. The tannin splits up into sugar and a red amorphous powder," which he named "Ephedrin" and to which he attributed the remedial properties of the plant. Terry (4) analyzed *E. californica* and *nevadensis* and found no alkaloid present. He made some clinical experiments with the extract, fluid-extract and resin from these species, and found them to have relatively little therapeutic value, except for the tannin contained therein. Some diuretic effect was observed which he ascribed to the small amount of volatile oil in the stems.

It was of interest to us to determine whether any of these native *Ephedra* species contained ephedrine, isolated from Chinese *Ephedra* species by Nagai, Chen and others, or an alkaloid similar to it. The specimens were assayed for alkaloidal content in the order in which they are listed. The roots, stems and green branches were assayed separately whenever possible. The method employed was the U. S. P. IX method for belladonna root, using in the first step a mixture of chloroform, 1 volume and ether 3 volumes and methyl red as indicator, as suggested by Chen (5).

None of these native varieties of *Ephedra* contained any alkaloid.

We hope to obtain identified samples of *E. trifurca*, *antisiphilitica*, *pedunculata* and *torreyana* later with the view of assaying these species for alkaloidal content also.

*Mexican Ephedra Species.*—From the "Secretaria de Agricultura y Fomento," Bio. Dept. Botanical Section, Mexico, we are informed by Prof. Alfonso L. Herrera, Dir. of Biologic Studies, that the following species of *Ephedra* grow in Mexico.

*Ephedra antisiphilitica*, Berland. In Coahuila and Durango.

*Ephedra aspera*, Engelm. In Coahuila.

*Ephedra pedunculata*, Engelm. In Coahuila, San Luis Potosi and Chihuahua.

*Ephedra californica*, Wats. In lower California. (Canutillo).

*Ephedra trifurca*, Torr. In Chihuahua.

*Ephedra Sp.* (?). On the Isle of Cedros.

*Chinese Ephedra Species.*—The drug (Fig. 11) commonly known in China for centuries under the name of Ma-Huang (astringent-yellow) contains ephedrine and pseudo-ephedrine, and is the chief source, perhaps the only source for ephedrine at present. This alkaloid was subjected to a very careful investigation in recent years by Chen, Read and co-workers. The description of Ma-Huang and of the chemical and pharmacologic character of its alkaloids, the clinical value of ephedrine with its important advantages over epinephrin has been given in detail by Chen, Read and co-workers (6), and need not be repeated here. Soon after these authors published the results of their preliminary investigations, ephedrine attracted a great deal of attention and a number of clinical reports, recommending its use, have since then appeared. This resulted in a rapidly increasing demand out of proportion to the limited supply, and it was in the hope of obtaining a more convenient source for ephedrine that our investigation of the native ephedras

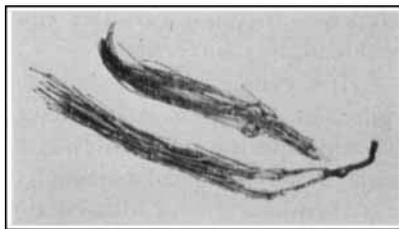


Fig. 11.—Ma Huang—from China.

was undertaken. In the meantime, the scarcity of supply has been overcome. Large quantities of chemically pure Ephedrine hydrochloride (free from pseudoephedrine) from Ma-Huang, are now manufactured in U. S.

Chinese Ma-Huang may consist of more than one variety of Ephedra. Nagai, Chen and co-workers, Read *et al.* refer to their Ma-Huang as *E. vulgaris*, Rich. var. *helvetica* Hook. and Thomson. The Council on Pharmacy and Chemistry of the A. M. A. in their preliminary report on Ephedrine (7) refer to Ma-Huang as *E. equisetina*, Bunge and some other species of Ephedra. Holmes (8) considers it likely that the species sold at Peking would be *E. intermedia*, Schrenk and C. A. Meyer, var. *Tibetica*, Stapf., *E. equisetina* Bunge and *E. monosperma*, C. A. Meyer and states that *E. vulg.*, Rich. var. *helvetica*, Hook. and Thomson has been identified with *E. intermedia* S. and M. var. *Tibetica*; that *E. monosperma*, C. A. Meyer has been examined and does not yield the same alkaloid as Ma-Huang; and that *E. equisetina*, Bunge, therefore, requires examination as to its alkaloidal content, presuming that Ma-Huang consists chiefly of *E. intermedia* var. *Tibetica*, Stapf.

In the later communication Holmes (11) reports that a sample of Ma-Huang sent to him for examination has the characteristic appearance of *E. equisetina*, Bunge, adding that according to Professor Bernard F. Read, this is the plant now imported by the ton into the United States for the extraction of ephedrine. It comes from Peking.

The European variety identified by Arthur Meyer in 1902 as *E. vulgar.* var. *Helvetica*, according to Miller (6), yielded pseudo-ephedrine only. Chen (5) states that the European variety is not the same as the Asiatic and does not contain ephedrine; the alkaloid isolated from it and named pseudo-ephedrine by Merck (9) is an isomer of ephedrine; in a later article Chen and Kao suggest the possibility that *Ephedra vulgaris* var. *helvetica* yields ephedrine when grown in China, but pseudo-ephedrine when grown in Europe. They call attention to an analogous difference between the *l*-pinene in the French and Spanish oil of turpentine and the *d*-pinene in the Greek oils.

Merck's index for 1902 gives *Ephedra helvetica (gracilis)* as their source for ephedrine, and *Ephedra vulgaris* as the one for pseudo-ephedrine. In their Index for 1910, however, *Ephedra helvetica* C. A. Meyer is given as their source for both isomers. If these varieties contain pseudo-ephedrine only, was the ephedrine obtained by conversion?

It is evident that our knowledge of the species containing ephedrine or pseudo-ephedrine or both is in a state of confusion at present and will remain so until the *Ephedra* species and varieties shall have been definitely identified and classified with proper botanical nomenclature applied to each distinct species and variety, and then assayed for alkaloidal content. The probabilities are that the Chinese species are botanically and chemically different from the European ones. In the literature, we find mention of the following Chinese *Ephedras*.

1. *Ephedra intermedia*, Schrenk and C. A. Meyer, var. *Tibetica*, Stapf. (Northwest China) same as

*Ephedra vulgaris*, Rich. var. *helvetica*, Hook. and Thomson. Referred to by Chen as Ma-Huang. Reported by various investigators to contain ephedrine and pseudo-ephedrine.

2. *Ephedra equisetina*, Bunge (North China). Sold as Ma-Huang; used for the extraction of ephedrine.

3. *Ephedra monosperma*, C. A. Meyer (Northwest China). Does not yield the same alkaloid as Ma-Huang.

4. *Ephedra monostachya*. Does not contain the same alkaloid as Ma-Huang. From this variety Spehr (10) isolated a basic principle which he termed "Ephedrine," but this is different from the ephedrine isolated from Ma-Huang by Nagai, Chen and others.

5. *Ephedra Gerardiana*, Wall (West China and Sikkim). We have found no definite information as to its alkaloidal content.

The general appearance and histology of the Chinese *Ephedra* used by Chen has been described by him. The drug Ma-Huang as obtained on the market varies somewhat in appearance. Mostly, it consists of the upper part of the plant with part of the root attached. The base of the plant generally is a single stem and root, but at times it may consist of a gnarled mass of reddish brown stems from which the thinner roots and stems of the same color branch out. These stems carry a large number of green or yellowish green, stiff, straight, thin, brittle, many-jointed branches, apparently without leaves since these are very small triangular sheaths located at the joints and rudimentary in character. The drug is obtainable also without roots and brown stems, consisting then of the greenish sticks alone, broken into smaller pieces. The taste is aromatic, bitter and astringent.

The alkaloidal content in Ma-Huang varies. We have analyzed a number of samples and shipments and found anywhere from 0.2% to 0.9% of total alkaloid. The highest content was found in a batch consisting almost entirely of green sticks, the lowest in a shipment in which more than half by weight consisted of reddish brown roots, trunks and stems. We, therefore, separated these from the green sticks and assayed them. They contained no alkaloid. The same result was obtained with another batch. It appears, therefore, that the alkaloids are contained in the green branches only. We have not analyzed the flowers and fruits. One batch purchased in a Chinese store in Chicago and consisting of green sticks only had a penetrating aromatic odor, which remained during the entire process of extraction and became very pronounced in the isolated alkaloid.

*European Ephedra Species*.—According to Holmes (8), *Ephedra vulgaris*, Rich. is identical to *Ephedra distachya*, Linn. and is a distinct species different from *Ephedra helvetica*, C. A. Meyer. We have been informed of the presence of the following varieties in Europe:

1. *Ephedra distachya*, Linn., same as  
*Ephedra vulgaris*, Rich. (East Tyrol), supposed to contain pseudo-ephedrine but not ephedrine.
2. *Ephedra helvetica*, C. A. Meyer (Switzerland, Italy, France), supposed to contain pseudo-ephedrine but not ephedrine.
3. *Ephedra Villarsii* (Italy).
4. *Ephedra fragilis* Desf. (Eastern Mediterranean).
5. *Ephedra altissima* (Switzerland).
6. *Ephedra Andina* (Switzerland).

In connection with these species, the information given to us by Mr. H. Correvon, founder of the Society for the Protection of Alpine Flora and Native Plants in Switzerland in answer to our inquiry regarding the plant we then called "*Ephedra vulgaris* var. *helvetica*" is of interest. He writes "It is found only in Canton Valais (around Sion) and is a rare plant; it is the Swiss form of *Ephedra distachya*, which in the environment of Suza, Italy is *E. Villarsii* and in East Tyrol

*E. distachya* (genuina). All three forms have the same aspect and differ only by botanic characters." In the U. S. Dispensatory 20th Edition, mention is made of *E. distachya*, L., stating that the branches and roots are used in Siberia as a remedy in gout and syphilis; also that the alkaloid of the species has been isolated and is different from ephedrine.

We are indebted to Dr. Albert Schneider of the North Pacific College of Oregon, Mr. Frank A. Thackery, U. S. Dept. of Agri., Mr. C. R. Orcutt, Mr. A. M. Woodbury, U. S. Dept. of the Interior, Dr. Ralph E. Terry, Oregon State Agri. College and Mr. W. H. Foster, Colton, California, for collecting the native *Ephedras* and furnishing much valuable information and to Prof. Bernard E. Read, Peking Union Medical College, Associate Curators, J. N. Rose and Paul C. Standley of the Smithsonian Inst., Prof. F. J. Smiley, Occidental College, California, Dr. Frank T. Greene, Dean of Cal. Univ. of San Francisco; Prof. P. J. Hanzlik, Stanford University, H. Correvon, Geneva, Switzerland, Prof. Alfonso Herrera, Mexico, Prof. H. M. Hall, University of California, Berkeley; H. P. Barss, Oregon State Agric. Col. and John A. Stevenson, U. S. Dept. of Agric. for their generous response to our inquiries on this subject.

#### REFERENCES.

- (1) "Pharmaceutical Plants of California," edition now exhausted.
- (2) PROCEEDINGS OF THE A. PH. A., Vol. 27, p. 285 (1879).
- (3) "Wheeler's Report," Vol. 3, 611 and 612, also Vol. 6, 50.
- (4) Ralph E. Terry, Thesis in May JOUR. A. PH. A.
- (5) K. K. Chen, "A Pharmacognostic and Chemical Study of Ma Huang," JOUR. A. PH. A., Vol. 14, No. 3, p. 189 (March 1925).
- (6) K. K. Chen and C. H. Kao, "Ephedrine and Pseudo-Ephedrine, Their Isolation, etc.," with a bibliography, JOUR. A. PH. A., Vol. 15, No. 8, p. 625 (1926).
- (7) *Jour. A. M. A.*, Vol. 87, No. 11, p. 849 (Sept. 11, 1926).
- (8) E. M. Holmes, "Botanical Source of Ephedrine and Pseudo-Ephedrine," *Pharm. Jour. and Pharm.*, p. 643 (Nov. 27, 1926).
- (9) Merck's *Berichte*, 13 (1893).
- (10) Spehr, "Pharmacogn. Chem. Untersuch. der Ephedra Monostachia," *Pharm. Zeitsch. Russ.*, 31 (1892).
- (11) E. M. Holmes, "Ephedra Equisetina," *Pharm. Jour. and Pharm.*, p. 44 (Jan. 8, 1927).

PHARMACEUTICAL DEPARTMENT,  
ABBOTT LABORATORIES,  
NORTH CHICAGO, ILL.

## EPHEDRINE: ITS ISOLATION AND DETECTION FROM THE TOXICOLOGICAL STANDPOINT.\*

BY KUEN TSIANG AND E. D. BROWN.

Ephedrine, an alkaloid obtained from an old Chinese drug, Ma Huang (*Ephedra vulgaris*) has been recently introduced as a new therapeutic agent and gives promise of possessing considerable merit. In 1924, Chen and Schmidt published a report on "The Action of Ephedrine" pointing out especially its effect

\* From the Department of Pharmacology, University of Minnesota.