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A history of the therapeutic use of liquorice in Europe

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Abstract

Liquorice root has been used in Europe since prehistoric times, and is well documented in written form starting with the ancient Greeks. In this review we compare the independent development of medical uses of this botanical drug in several ancient cultures, attempting to show the rationality of specific indications across different ethnic groups with different cultural backgrounds. Identical specific indications in different cultures highlight universally reproducible therapeutic effects that are beyond those of a mere placebo.

In the first part of the review, historical sources dealing with liquorice (Scythian, Greek, Roman, and from the Middle Ages in Germany, Italy, Spain, England) have been considered. In the second part, the historical records of diseases treated with liquorice have been presented. Finally, a comparison between traditional use in and outside Europe, with the most important recent scientific studies concerning its use, is presented.

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Keywords: Liquorice; History; Traditional therapy; Diseases; Clinical effects; Therapeutic use

Contents

1. The historical sources about liquorice ................................................................. 318
2. Diseases treated by liquorice ................................................................. 319
   2.1. Disease of the respiratory system ......................................................... 320
   2.2. Diseases of the gastrointestinal system .............................................. 320
   2.3. Diseases of the cardiovascular system .............................................. 321
   2.4. Diseases of the urogenital system ...................................................... 321
   2.5. Skin diseases .............................................................................. 321
   2.6. Eye diseases ....................................................................................... 321
   2.7. Other applications ........................................................................ 321
3. Discussion of the historical data ................................................................. 322
4. Comparison with traditions of liquorice use outside Europe ................. 322
5. Results of bioscientific research referring to the historical indications of liquorice ......................................................... 322
6. Conclusions ......................................................................................... 323

References ..................................................................................................... 323

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I. The historical sources about liquorice

Since the beginning of recorded history humans have made use of liquorice (the species Glycyrrhiza glabra L., Leguminosae) as a remedy. Traditions from different geographical regions and different time periods have documented its extensive use (Armanini et al., 2002). The first documented medicinal use of liquorice can be traced back to ancient Assyrian, Egyptian, Chinese and Indian cultures (Thompson, 1930; Chopra et al., 1958).

Greek sources provide the first use of liquorice as a drug in Europe (see Table 1). The name of the plant itself is derived from two Greek terms, γλυκύς “sweet,” and ριζη “root”. According to Theophrastus (IV–III century B.C.), the great botanist, pharmacologist and disciple of Plato and Aristotle, the Greeks probably learnt about the pharmacological uses of liquorice from the Scythians, an ethnic group who lived to the north and east of Greece in the area of the Ukraine between the Black and Caspian Seas. Theophrastus, among the first to study medicinal herbs with exemplary scientific accuracy, named the plant “the Scythian root” (Hott, 1961).

In the first century A.D., Pedanius Dioscorides (ca. 40–90 A.D.), placed liquorice among the 650 medicinal substances of plant origin listed in his De Materia Medica (Dioscorides, edition 1958). In contrast to Theophrastus, who was a pure botanist, Dioscorides was a pharmacognosist. Everything he wrote about plants was dominated by an examination of their therapeutic effects. In his treatise Dioscorides therefore classified plants according to their nutritional and medicinal properties and not based on their morphology.

In Rome, in Dioscorides’ time Greek science was studied comprehensively. This included the medicinal properties of certain plants. Further additions were made to this body of learning. At the beginning of the Imperial Age (I–V century A.D.), the monumental work Naturalis Historia of Plinius the Elder (23–79 A.D.) gave a detailed description of the liquorice plant (Plinius, editions 1875, 1897). The list of properties that Plinius attributed to liquorice is highly significant. For example, he suggested liquorice as a remedy for asthma, maladies of the throat, ulcerations of the mouth, and even advised its use to combat sterility. This last effect has been confirmed by the most recent observations regarding the estrogenic effects of certain compounds present in the drug (Armanini et al., 2002).

Liquorice was a very well-known remedy during ancient Roman times, as documented by the quotations of its beneficial effects reported by several other Roman authors (Table 1), including Aulus Cornelius Celsus (ca. 25 B.C.—ca. 50 A.D.) and Scribonius Largus (2–52 A.D.), Claudius Galen (Galen, 129–211 A.D.), Marcellus Empiricus (IV/V century A.D.) and Cassius Felix (V century A.D.) (Celsus, edition 1859; Cassius, edition 1879; Scribonius, edition 1893; Marcellus, edition 1889).

At the beginning of the Middle Ages (VI–XV century), Saint Isidor, bishop of Seville (560–636), included the etymology of Glycyrrhiza in his Etymologiae sive Originum, his renowned encyclopedia, in which he examined the names of objects as a way to understanding their nature (Isidorus Hispalensis, edition 1911).

The School of Salerno (VIII–IX century A.D.) was the center of fusion of Greco–Roman and Arabic cultures in the field of medical studies. In Salerno the work Regimen sanitatis carefully examined liquorice and its pharmacological properties (Tacuinum Sanitatis, XIV century, edition 1986) acquiring the knowledge derived from outstanding Arabic medical scientists like Mohammed Ibn Zakaria Abu Bekr Alrazi (“Rhazes”, 850–925 A.D.) and Ibn Sina (“Avicenna”, 980–1037 A.D.). The Canone of Avicenna entered the European tradition, and was considered an important recapitulation of the medical knowledge of Hippocrates and Galen (Avicenna, 1562).

During the Middle Ages the knowledge of phytotherapy was passed on in monasteries where works of importance were copied. Hildegard von Bingen (1098–1179), prioress

| Period | Location | Author |
|--------|----------|--------|
| IV–III century A.D. | Greece | Theophrastus |
| I century A.D. | Rome, Italy | Dioscorides, Plinius the Elder, Aulus Cornelius |
| II century A.D. | Rome, Italy | Claudius Galen |
| V century A.D. | Rome, Italy | Marcellus Empiricus, Cassius Felix |
| VI–VII century A.D. | Seville, Spain | Saint Isidor |
| VIII–IX century A.D. | Salerno, Italy | School of Salerno |
| IX–XI century A.D. | Bagdad, Iraq | Rhazes |
| XII century A.D. | Rupertsberg, Germany | Hildegard von Bingen |
| XIII century A.D. | Damascus, Syria | Ibn Al Barthu |
| XIV century A.D. | Palnza, Italy | Jacobus Philippus |
| XV–XVI century A.D. | Tubingen, Germany | Leonard Fuchs |
| XVI century A.D. | Rome, Italy | Castore Durante |
| XVII century A.D. | London, England | Nicholas Culpeper |
| XVIII century A.D. | Neapel, Italy | Giuseppe Doncelli |
| XVIII century A.D. | Upsala, Sweden | Carl von Linne |
of the convent of Rupertsberg near Bingen wrote a treatise on medicines inspired in its structure by authors of antiquity, but integrated with knowledge which was the fruit of popular experience with herbs, including liquorice (Hildegard von Bingen, edition 1903).

After her treatise, the most comprehensive collection and critical analysis of the entire phytotherapeutic knowledge of the Mediterranean area, including North Africa and Asia minor, was put together by Abu Mohammed Abdallah Ben Ahmed Dhiyleddin Ibn Albanitar (ca. 1197–1248) from Malaga in Spain. He was the greatest botanist of his time and his manuscript was based on the works of more than 150 physicians and botanists from Theophrustus to Ibn Sina. He was the head of pharmacists in Egypt and served at the court of king Elkamel in Damascus in Syria. In his work, the “Great Compendium of the power of known simple therapeutics and nutrients”, he covered more than 1400 substances of plant, mineral or animal origin (Von Sontheimer, 1842).

In the XIV century the use of liquorice was again documented in the work of Jacobus Philippus (1390–1400), Paduan friar and author of El libro agregà de Serapion, a translation into Paduan dialect of the work by the Cordovan Arab Serapion the Younger (Jacobus Philippus, edition 1962).

Between the end of the XV century and the beginning of the XVI, Botany as a science was born and liquorice was categorized according to taxonomic classifications that the scholars of the time were rapidly developing. The first attempt at creating a botanical nomenclature came from Leonhard Fuchs (1501–1566) who, concerning liquorice, accurately describes and characterizes the plant (Fuchs, 1545), and reports its scientific name to be the German term Süssholz (“sweet root”), which is still in use today. Works of eminent Arabic scientists like Al Razi continued to be translated into Latin. One example is Gerardo Toletano of Cremona’s translation (1544) of the books that Al Razi wrote for the calif Al Mansur (“Liber Almansoris”), which he dedicated to Andreas Vesalius (1514-64) the famous Belgian anatomist, who studied at Padua University, and whose dissections and descriptions of the human body helped to correct misconceptions which had prevailed since ancient times (Gerrardum Toletanum, 1544).

Next came Castore Durante (1529–1590), physician to the Popes Gregory XIII and Sixtus V and an important name among botanists, who also mentioned liquorice, referring to it here by its modern name, explaining its etymology as “sweet root” and citing several areas of Germany where it was cultivated (Donzelli, 1737). The Swedish naturalist Carl von Linné (1707–1778) proceeded to subdivide plants into genus and species, adopting a nomenclature with two names. Within the genus Glycyrrhiza that he coined, he identified three different species: Glycyrrhiza glabra, Glycyrrhiza echinata and Glycyrrhiza hirsuta (Linné, 1764, 1774).

At the threshold to the Industrial Age liquorice can be found again in a new formulation in the Pharmaceutical Code established by the Republic of Venice, only a few years prior to its decline (1790). In this Code, liquorice is described as being among the various ingredients used to make “teriaca”, an ancient remedy considered a panacea for any pathology (Codice Farmaceutico, 1790).

2. Diseases treated by liquorice

In this section the various historical uses of liquorice are summarized (Table 2) and a comparison with modern indications and uses is also included.
Table 2

Comparison of liquorice uses in the antiquity and today

| Apparatus          | Uses in the past                                                                 | Recently proposed uses                                                                 |
|--------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Respiratory system | Asthma, diseases affecting voice, lung diseases, cough (Theophrastus, Dioscorides, Scribonius Largus, Marcellus Empiricus, Cassius Felix, Avicenna, Jacobus Philippus and Nicholas Culpeper) | For dissolving and facilitating the discharge of mucus in cataracts and for upper respiratory tract (Commission E Monograph, Blumenthal et al., 2000) |
| Gastrointestinal system | Burning sensation of stomach, diseases of liver, mouth ulcers (Dioscorides, Plinius the Elder, Marcellus Empiricus, Avicenna and Nicholas Culpeper) | Gastric and duodenal ulcers (Blumenthal et al., 2000), adjuvant in treating spasmodic pains of chronic gastritis (Bradley, 1992; Weicht and Bosket, 1994) |
| Cardiovascular system | Artery diseases, heart palpitations, angina (Scribonius Largus, Avicenna and Hildegard von Bingen) | Antioxidant, hypolipidemic (Fuhrman et al., 1997; Fuhrman et al., 2002) |
| Genital-urinary system | Bladder and kidney pain, kidney stones, diuretic (Plinius the Elder, Dioscorides, Aulus Cornelius Celsus, Claudius Galen, Marcellus Empiricus, Avicenna, Jacobus Philippus, Castore Durante, Nicholas Culpeper and Giuseppe Donzelli) | No described rational uses, but a diuretic effect only in association with other herbs (Ross, 2001) |
| Skin                | Skin lesions, ulcers, condyloma, genital ulcers (Dioscorides and Nicholas Culpeper) | For the treatment of atopic dermatitis (Saeedi et al., 2003), antiinflammatory against U.V., edema and erythema (Fujiya et al., 1994; Huhler and Richards, 2004) |
| Eye                 | Pterygium (Dioscorides, Plinius the Elder, Nicholas Culpeper)                     | No described rational uses                                                                 |
| Other               | Against thirst, fever and neuralgia (Theophrastus, Dioscorides and Marcellus Empiricus) | No described rational uses                                                                 |

2.1 Disease of the respiratory system

Theophrastus prescribed the root for respiratory problems associated with non-productive cough and asthma (Hort, 1961). Uses reported by Plinius are evident from the following quote from his main work (Plinius, Naturalis Historia, XXII, edition 1897): He considered it indicated “... to combat maladies of the throat; moreover, for the voice it is very good to use the juice once it has condensed, simply placing it under the tongue; this is also used for the chest...”

According to Ibn Al Baithar, Dioscorides recommended it for hoarseness of the voice and chest pain. Ibn Al Baithar also cited the “Book of Experiences” (a source now lost), which also recommended its use for hoarseness of the voice and cough (Von Sontheimer, 1842).

Scribonius Largus, a Roman doctor of the first century A.D., indicated that liquorice was a valid remedy for problems of the voice (Scribonius, edition 1983). Among the authors of the late Roman period, Marcellus Empiricus (V century a.d.) suggested the use of liquorice to treat disturbances or pathologies of the lung (Marcellus, edition 1889). Cassius Felix was active at the same time as Marcellus Empiricus. He prescribed liquorice (which he referred to as glicurita) for dry cough: as long as the herb is mixed with oregano, thyme and hyssop (Cassius, edition 1879).

In the Canone of Ibn Sina (also known as Avicenna), liquorice is also cited as a remedy for diseases of the respiratory tract (Avicenna, 1462). According to Ibn Al Baithar, Ibn Sina (X century a.d.) stated that it makes the voice clear and reduces hoarseness of the voice (Von Sontheimer, 1842). Al Razi (IX and X century a.d.) mentioned liquorice as an ingredient in mixtures for various kinds of cough in chapter 52 of his work “Liber Almanorsis” where he described cough as a symptom of several lung diseases but particularly those following a coryzal illness, and he listed liquorice in the latter as part of a second line treatment for dry and moist cough types. Notably liquorice is not mentioned among treatments for what was most likely tuberculosis (“De ptisi”) or for chest diseases associated with blood stained sputum (Gerardum Toletanum, 1544).

In Tacuinum sanitatis in medicina, from the XIV century, the plant liquoritia (as it had become known by that time) was described (av. 76), and various uses are suggested even though it was mostly recommended to combat ailments of the respiratory tract and hoarseness (confert raucedini vocis et asperiini gaturtsi) (Tacuinum Sanitatis, edition 1886).

Jacobus Philippus (1390–1400), in his translation of the work by the Cordovan Arab Serapion the Younger, after a description of the plant according to Dioscorides, stated that the main property (“virtue”) of liquorice is “fredda de puocha frigidit`e e humida temperamentre” (cool and moist in temperament), confirmed the indications in cases of respiratory diseases (Jacobus Philippus, edition 1962).

Nicholas Culpeper (1616–1654), in his work the Complete Herbal (1653) finally stated that “it is hot and moist in temperament, helps the roughness of the windpipe, hoarseness, . . . its concoct helps difficulty of breathing” (Culpeper, edition 1995).

2.2 Diseases of the gastrointestinal system

According to Ibn Al Baithar, Dioscorides found liquorice beneficial for a burning sensation in the stomach and diseases of the liver (Von Sontheimer, 1842). This, he states, was also recorded in the “book of experiences” where benefit for all
Among the authors of the late Roman period, Marcellus Empiricus (V century) stated that it is beneficial in cases of palpitations (Von Sontheimer, 1842). Among the authors of the late Roman period, Marcellus Empiricus (V century a.d.) suggested the use of liquorice to treat many disturbances or pathologies of the stomach, intestine and indigestion (Marcellus, edition 1889). Ibn Sina in his Canone (980–1037 a.d.) also cited liquorice as a remedy for the stomach (Avicenna, 1562). After this there is a lack of mention of gastrointestinal applications for centuries.

Only Nicholas Culpeper (1616–1654), in his work the “Complete Herbal” (1653), has reiterated this traditional use by stating that “...it concocts raw humors in the stomach” (Culpeper, edition 1995).

2.5. Skin diseases

Theophrastus is the first source of information about the use of liquorice to combat skin lesions: “It is useful ... administered in honey, for wounds” (Theophrastus, in Hort, edition 1861). Plinius added further indications: “It also cures ... condyloma, and genital ulcers.” (Plinius, Naturalis Historia, XXII, edition 1897). Dioscorides mentioned in the same century, according to Ibn Al Baithar, its use to treat granulomas at the base of (finger or toe) nails and ulcers in this region (Von Sontheimer, 1942). Ibn Sina in his Canone considered it to be a remedy for wounds and ulcers (Avicenna, 1562).

2.6. Eye diseases

According to Ibn Al Baithar, Dioscorides mentioned it as a remedy for pterygium which is a disease characterized by a fibrotic web of connective tissue growing into the cornea from the conjunctiva eventually leading to blindness (Von Sontheimer, 1842). Plinius mentions the use of liquorice powder in the same condition. He wrote: “... often applied in the form of powder, it can cure pterygium” (Plinius, Naturalis Historia, XXII, edition 1897). This may indicate that both, who were contemporaries drew this very specific indication from a common older source.

Much later Nicholas Culpeper (1616–1654), wrote in 1653: “... beaten into powder, and the powder put into the eye, is a special remedy for a pin and web” (Culpeper, edition 1995).
2.7. Other applications

In particular, from what Theophrastus stated in his treatise of botanical pharmacology, *Enquiry into plants*, it would seem that the Scythians were able to survive in the desert for many days without water thanks to the liquorice root: "... also it has the property of quenching thirst, if one holds it in the mouth; wherefore they say that the Scythians, with the help of this and maes milk cheese can go even eleven or twelve days without drinking" (Theophrastus, in Hort, edition 1961). The thirst-quenching ability is, according to Ibn Al Baithar, mentioned in the third book of Dioscorides, Galen’s sixth book and the “Book of experiences”. Marcellus Empiricus (V century a.d.) mentioned it as a remedy for fever (Marcellus, edition 1889). According to Ibn Al Baithar, Rhazes reported furthermore that Elbur (a source of unknown origin) mentions that liquorice can reduce tumors of the limbs and indurations (Von Sontheimer, 1842).

3. Discussion of the historical data

We have described the development of the medical uses of liquorice in Europe which is mainly based on the knowledge accumulated by the ancient Greeks. A comparison with the independent developments of medical uses of this root in other cultures can show the validity of specific indications in different ethnic groups with different cultural backgrounds. Identical specific indications in different cultures also make it more likely that there is a universally reproducible therapeutic effect beyond that of a placebo.

It is often difficult to discern whether or not it was the main effective agent for treating specific ailments when used in mixtures of herbs. However, the presence of liquorice as a constant ingredient in various mixtures with differing components especially when used by different cultures for the same indication suggests that it is a key remedy for this disease.

All reported uses of liquorice, in the past and present, refer to the content of saponins and flavonoids found in liquorice root. The main chemical constituents are triterpene saponins, of which glycyrrhizin is the principal component. Glycyrrhizin is a glycoside occurring as a mixture of calcium, sodium and potassium salts of glycyrrhizinic acid (Fig. 2, also named glycyrrhetic acid). Following hydrolysis, it releases two molecules of α-glucuronic acid and the aglycone 18 β-glycyrrhetinic acid (Fig. 2, also called glycyrrhetic acid).

Several flavonoids are present in liquorice, both as glycosides and aglycones, and are also responsible for the described effects.

4. Comparison with traditions of liquorice use outside Europe

The major systems of phytotherapeutic knowledge outside Europe are found in the Ayurveda system in the Indian subcontinent and in China.

In China, liquorice is used in almost all herbal preparations. The use of liquorice (“ Gan Cao”) is documented in the oldest source on remedies in China, the *Shenong bencao* created 200 n.c. According to legend this work is based on sources dating back to the Emperor Shennong (ca. 2700 b.c.). The reported indications include some which were common in Europe like: pharyngitis, cough, palpitations, gastric pain, ulcers in the intestinal tract and sores. In addition to this, an area of application not found in Europe is intoxication by drugs and poisoned food (Leung, 1993). The latter indication of liquorice features also prominently in the Indian Ayurveda system. This is a system of medical knowledge including phytotherapy which started to be codified about 450 n.c. in India, while the oldest surviving Sanskrit text dates from about 500 a.d. (Wujastyk, 2003). The uses of *Glycyrrhiza glabra* (in Sanskrit: klitaka, madhuka, yasti or yastimadhu) reported here apart from its use in antidote mixtures for a variety of acute and chronic poisonings, include improvement of the voice, an indication mentioned in the context of viral respiratory tract infections, wound infections, operation wounds of the ear, excessively bleeding punctures from blood letting (Wujastyk, 2003) and acute and chronic liver diseases like hepatitis (Thyagarajan et al., 2002).

European, Indian and Chinese traditions all contain references to antiviral effects in the context of viral induced voice changes in laryngitis, pharyngitis, most likely viral induced cough, viral hepatitis and viral skin diseases like condyloma and ulcers. There is now good scientific data confirming these effects in vitro and in animal studies which we will summarize.

5. Results of bioscientific research referring to the historical indications of liquorice

Liquorice is largely used as a flavouring and sweetening agent, but has been proposed also for various clinical applications (Armanini et al., 2005). According to many Pharmacopias, liquorice presents demulcent and expectorant properties for dissolving and facilitating the discharge of mucus in catarhths and for upper respiratory tract diseases.
5. Pharmacological Effects

Liquorice has shown beneficial effects against various diseases. In vitro, it inhibits LDL oxidation, which is crucial in preventing arterial disease (Fuhrman et al., 2002; Cinatl et al., 2003; Lin, 2003). It also demonstrates antioxidant properties, protecting against the replication of SARS-associated coronavirus (Lancet 361, 2645–2646). Furthermore, recent studies suggest that liquorice may possess anti-inflammatory and mineralocorticoid properties, which could be useful in the treatment of atopic dermatitis (Saeedi et al., 2003), as well as beneficial effects on excessive tissue growth around nails, as reported in ancient manuscripts (Dioscorides, 1958; Avicenna, 1562).

In summary, the ancient knowledge regarding liquorice provides a valuable basis for modern research, suggesting that further investigation is warranted to exploit these potential therapeutic benefits.

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