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HISTORY

Contribution to the history of urological pharmacotherapy

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Abstract
Introduction: The aim of this work is to present a historical review of urological pharmacotherapy. The containers used to preserve and store medicines are an important source of information in historical research.
Material and methods: I studied written sources such as treatises of Medical and Therapeutic Materials, as well as material sources available at the Real Cartuja de Valldemossa Pharmacy Museum in Mallorca. I examined the old medicine containers and the labelling on ceramic recipients, glass jars and wooden boxes and other medicines found inside them.
Results: Different medicines, the most used over the centuries to treat diseases of the urinary system are described, including both simple (of plant, mineral or animal origin) and compound medicines: drumstick tree, agaricus, mechoacan, lupine, fennel, acacia gum, myrtle, Armenian bole, oleum scorpionum, hartshorn plantain, cantharides. I present evidence of knowledge available for each of these remedies in the main bibliographic sources, as well as proof that they were used in Valldemossa.
Conclusions: The basis of general and urological pharmacotherapy was concentrated on nature. Medicines of plant origin were the most used. The therapeutic inventory that mankind has accumulated throughout history is the result of a lengthy process of combining practices and knowledge of different cultures and societies.

PALABRAS CLAVE
Historia de la Medicina;
Prescripciones;
Materia Médica;
Farmacognosia;
Plantas medicinales;

Aportación a la historia de la farmacoterapia urológica

Resumen
Introducción: El objetivo de este trabajo es la revisión histórica de la farmacoterapia urológica. Los contenedores utilizados para la conservación y almacenamiento de los medicamentos son una importantísima fuente de información en la investigación histórica.

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Cartelas identificadoras de medicamentos

Material y método: Se ha acudido al estudio de fuentes escritas como son tratados de Materia Médica y Terapéutica y a fuentes materiales existentes en el Museo-Farmacia de la Farmacia Monástica de la Real Cartuja de Valldemossa, en Mallorca. Se revisan los antiguos contenedores de medicamentos y sus cartelas identificadoras en botes cerámicos, frascos de vidrio y cajas de madera y restos medicamentosos hallados en su interior.

Resultados: Se describen diferentes medicamentos, tanto simples (de origen vegetal, mineral o animal) como compuestos más usados a lo largo de los siglos para tratar las enfermedades del aparato urinario: cañafístula, agárico, mechoacán, altramuz, hinojo, goma arábiga, arrayán, bol armeno, *Oleum scorpionum*, cuerno de ciervo, cantáridas. Se presenta la evidencia de conocimiento disponible para cada uno de estos remedios en las principales fuentes bibliográficas y la prueba de que fueron empleados en Valldemossa.

Conclusiones: La base de la farmacoterapia general y urológica se centraba en la naturaleza. Los medicamentos de origen vegetal eran los más utilizados. El arsenal terapéutico que a lo largo de la historia ha reunido la humanidad es el resultado de un largo proceso de mestizaje de prácticas y conocimientos de distintas culturas y sociedades.

Introduction

As to be expected, the history of Urology has focused on the study of the surgical aspect of the specialization. The pharmacotherapeutic aspect has therefore been omitted, which also was of vital importance throughout of the centuries, given that many medicines were used to treat renal diseases, especially kidney stones. In fact, Kidney Stone disease was very frequent among nobility due to their eating habits, which were based on game. In his treatise, "Lilio de la Medicina", Bernardo de Gordonio declared: "*As the noble and rich often suffer from kidney pain, I will treat it in a special way*".[1]

The study that this work was aimed at is focused on the detailed analysis of some important medicines used throughout history by different renowned authors. To appropriately illustrate the work, I have presented images of different medicinal remains, as well as recipients with their labels found at the Real Cartuja de Valldemossa Pharmacy Museum (Mallorca), which was open from 1722 until 1929 (fig. 1). Throughout this period, which includes the Enlightment, Romanticism and Positivism eras, the bases of current Pharmacology were established.

Materials and method

The definition that of medication given by the *Diccionario de autoridades* (D.A.) is clear and concise: "Any internal or external remedy that is applied to the patient to make him recover his health".[2] Medication was and is the link that Gordiano uses to connect the patient with the physician and the pharmacist. How it was prepared and dispensed were fundamental stages in medical function. To study it, we can refer to the medical literature of the time, which includes pharmacopoeia, prescriptions, antidotaries, treatises on Medical Materials and notarial inventory items, or to labelled containers and to the remains found inside them.

Towards the years 77-78, Pedanio Dioscórides (c.40 - c.90) de Anazarba (Cilicia, Armenia, in modern Turkey) wrote the work *Perí hyles iatrikês* ("*Regarding Medical Materials*"). Travelling as a physician of Nero's army, he collected many observations and new that were written in the treatise on Pharmacology that has remained throughout the centuries. It can be said that his influence lasted until the 18th Century. It contains five parts or "books", the first of which begins with a preface in which he expounds his plan and dedicates it to his master. Throughout the five parts, he describes the different herbal, animal and mineral remedies of the period.

In his *Methodus medendi,* Galeno used the work of Dioscórides as his basis. Medieval Arab medicine translated this work, which was the foundation on which its Pharmacology was developed. Urological pharmacotherapy is present in it. A noted authority on it is the Persian physician, Avicenna (980-1037) and, his work *Liber Canonis Medicinae* was the basis of western medicine until the Enlightment. He especially influenced all the Works of the Middle Ages, such as Bernardo de Gordonio's *Lilio de medicina*, written between1303 and 1305, or the work of d'Abû-l-Salt (1068-1134) *Kitâb al-aiddwiya al-mufrada* ("*Libro de los medicamentos simples*"), translated into Spanish by Arnau de Vilanova (ca. 1210-1311).

15th to 18th Century pharmacology is absolutely traditional, given that Dioscórides and Galeno continued to be effective until well into the 18th Century. However, during the Renaissance, an important contribution of simple news from America and Asia was seen, as well as commented editions of from Anazarbus. Pietro Mattioli (1500-1577) and the Spaniard, Andrés Laguna (ca.1510-1559) are their authors. In his masterpiece published in 1588, "*Tratado de todas las enfermedades de los riñones, vexiga y carnosidades de la verga, y urina*", Francisco Díaz (Alcalá de Henares ca. 1530- Madrid 1590) dedicated a significant part of it to pharmacotherapy. In general, during this period (15th to 18th Century), nature was still considered to be a source of remedies and it is faithful to

Figure 1 Shelf with different medicine containers at the Real Cartuja de Valldemossa Museum-Pharmacy.

the principle of therapeutic allopathy (*contraria contrariis curantur*), although there are authors like Hahnemann, who invoke homeopathy (*similia similibus curantur*).[3] The Encyclopaedic Book of Formulas by Mariano Pérez Mínguez edited between 1891 and 1904, includes the numerous formulas of the different pharmacopoeia of the time and established the guidelines of the different therapeutic pharmacological options of our ancestors, and which are repeated to a large extent and coincide with those of Dioscórides. The Treatise on Therapeutics by Armand Trousseau and Hermann Pidoux, translated into Spanish by Matías Nieto, was the most used in the second half of the 19th Century. The Encyclopaedic Book of Formulas makes reference to it on many occasions.

Based on these treatises, several of the most important drugs are described, which were used throughout the centuries to treat diseases of the urinary system: Drumstick Tree, Agaricus, Mechoacan, Lupine, Fennel, Acacia Gum, Myrtle, Armenian Bole, Oleum Scorpionum, Hartshorn Plantain, Cantharides. Proof of the knowledge available for each one of these remedies is presented in the main bibliographic sources and the evidence that they were

Figure 2 Ceramic container from the first half of the 18th Century and glass recipient with oleaginous content.

employed, such as the containers and labels of the Real Cartuja de Valldemossa Monastery Pharmacy (figs. 2 and 3).

Results

Drumstick Tree (Cassia fistula L.)

It is a simple medicine of plant origin that belongs to the *Caesalpiniaceae* family. The pulp of its fruit was used and which was obtained from a tree from tropical African and Asian countries. Used in classic Indian medicine, it spread to Europe during the High Middle Ages.[4] Dioscórides said that it purges choleric humour, which mitigates urinary burning and clarifies the blood.[5] It is said that the Egyptians used it to treat kidney and bladder diseases.[6] Bernardo de Gordonio recommended it in the form of an enema for kidney pain and kidney and bladder apostemes (abscesses). Francisco Díaz used it as a compound (sucker) with tementine to facilitate the expulsion of ureteral calculi.[7]

Figure 3 Wooden box containing staghorn remains.

Agaricus (Polyporus officinalis Fries)

It is a fungus of the *Poliporaceae* (Basidiomycete) family. It grows on the trunk of certain trees, such as the Alpine larch and the Moroccan cedar. It is a simple medicine of plant origin and is practically the only fungus used as a medicine. Dioscórides gave it numerous virtues. He assured that it "it is useful to those with kidney pain or who cannot urinate". Laguna adds in his notes that is "produces micturition". It principal medicinal virtue was purging and it was in the form of trochisci, which was a pharmaceutical form similar to today's pills, although larger. It was also used in powder form, a pharmaceutical operation that consisted of pulverizing it. Gordonio also recommended it in the form of a purgative for treating kidney pain caused by obstruction. Its active principle is agaricin or agaric acid. In small doses, it paralyzes the nerve endings of the sweat glands. Díaz used it as part of a magistral formula used as a purgative in the treatment of nephritic colic. In 1767, Haen

discovered its antisudoral property, hence thereafter, it was administered in consumptives to reduce night sweat,[8] although occasionally it was still used at the beginning of the 20th Century as a purgative in doses of more than 3 grammes.[9]

Mechoacan (Pulvis Mechoacanae, Convolvulus mechoacanna Vandelli)

It is a plant of the *Convolvulaceae* family, brought to Spain from Mexico by conquerors in the 16th Century (originally from the province of Mechoacan). The dried root was used in the form of flower. Its most known medicinal virtue was that of being a mild purgative. In his treatise, *Historia medicinal de las cosas que se traen de nuestras Indias Occidentales (1565-1574)*, Nicolás Monardes (1493-1588) dedicated detailed pharmacognosic and therapeutic studies to it, comparing it to *Exogonium purga* Bent, also denominated convulvulus mechoacan, which was a more intense purgative. Francisco Díaz published his treatise in 1588, years after the publication of Monardes, thus giving the idea of how well informed he was. Numerous purgative formulas existed with mechoacan in the form of boluses, wines, electuaries, syrups, pills or potions. Cruveilhier's powders were also recommended to treat albuminous nephritis.[8]

Lupine (Lupinos albus L) and Fenugreek (Trigonella Foenumgroecum L)

The seeds of these plants were used, but their leaves were also used as dressing for swelling and the cooked seed caused vomiting.[5] It is cultivated on the Iberian Peninsula. Bernardo de Gordonio did not cite lupine, but he did mention fenugreek flour to which he also attributed emollient virtues. Its medicinal properties include emmenagogue, aperient and emollient (substance that when applied externally, relaxes and softens the inflamed areas). Díaz recommended both in the form of an ointment, as an anodyne in nephritic colic.

Fennel (Anethum foeniculum L)

It is one of the five major root aperients and is quite common throughout Europe in steep banks and wasteland. It was already used by the ancient Egyptians, who said *"it helps to ease kidney pain and to stimulate urination"*.[5] Bernardo de Gordonio recommended it to alleviate kidney pain in the form of an enema in a decoction which among others, included mallows, violets, chards, mercurials, anise, cumin, rue seeds, rape oil and honey. He added that if the pained was not cured with this enema, "*rapidly move the patient in a circle or on a trotting jumping horse*"[1]). Díaz recommended it in cases of "kidney stones" or as a renal confomative and describes several forms among which "aperient spices" stand out as diuretic, made with the roots of celery, parsley, fennel and asparagus. There is no doubt that it also has antioxidant properties. In fact, fennel seeds contain selenium and scientific evidence exists on the role of this mineral in the prevention of prostate cancer and as an antioxidant. However, the excessive consumption of selenium, 4 to 5 times more than the normal dose may be toxic, which is manifested by gastrointestinal and neuromuscular symptoms, thyroid malfunction and reduction of sperm motility.

Acacia gum

It is the gummatous exudation (gum-resin) produced when the bark of the acacia (*Acacia vera* Willd.), a tree of the mimosaceae family, is cut. It thus forms a mixture of gum and resin, originally from Africa, from Arabia to Senegal. The ancient Egyptians knew it from more than four thousand years ago. In relation to this compound, Dioscórides said: "*They say that if applied with an egg in the form of dressing for burns, it prevents the formation blisters*"). For this reason, acacia gum had multiple uses, of which the following are worth mention: basis for cough drops, diascordio, theriaca, midritato, topical emollient for inflamed mucosa, chest and sweetener dissolved in the mouth and irritation of the urinary tracts. Bernardo de Gordonio recommended it for kidney ulcers in the form of trochisci prepared with numerous simple drugs, of which it is worth mentioning the four cold seeds, white poppy seeds, myrtle, acacia gum and Armenian bole, as well as for kidney ulcers when taken orally and for bladder ulcers in instillations dissolved in milk. Francisco Díaz cites Avicenna and recommends a remedy that he used, which he knows to break stones. An emollient tisane made with acacia gum was used basically as an antiphlogistic or emollient for irritation of the urinary organs until the end of the 19th Century.

Myrtle (Myrtus communis L.)

It is the flower of the myrtle. The name *arrayán* in Spanish come from the Arabic Ar-Rayhan or Rihan (meaning "aromatic"), a plant of the mirtaceae family. Dioscórides attributed many virtues to the myrtle. He used to say that *"it has styptical properties; it dries up those that spit blood and those with a smarting bladder."* The importance that of this plant confirms the fact that it was mentioned practically in all the medical treatises of all the periods (Theophrastus of Eresus, Abu-s-Salt, the Circa Instans by Mateo Plateario or the Antidotarium de Arnau de Vilanova). Bernardo de Gordonio also mentioned it, recommending it to increase kidney heat in the form of an ointment in the case of pain. Díaz recommended it in different forms such as the decoction of myrtle to treat bladder ulcers. It is also said to have diuretic properties and its distillation, myrtol, was considered to as an antiseptic and renal disinfectant as it was eliminated through urine.

Haematite

Today, two varieties of iron minerals bear this name, red haematite, which is one of the most important iron minerals, and brown or limonite haematite, which is ferric hydroxide. Dioscórides said it had properties to treat urinary retention, although its fundamental virtue, given its wine red colour based on "*signatura rerum*" (the signature of all things), which was oriented depending on

the morphology and colour of the natural product towards its possible therapeutic uses, were haemorrhages. Díaz recommended it for "*the flow of blood through the penis*" in the form of syrup. In the 19th Century, different iron salts were used as reconstituants (martial preparations), especially in the so-called chlorosis. It was also used for blennorraghia and to combat) albuminuria.[10]

Armenian bole

This medicine's colour is due to the ferric oxide and silicate that it contains. It was sold in the form of discs with a seal (*terra sigillata rubra*) and in ancient times came from Armenia. The translation by Arnau de Vilanova (ca. 1210-1311) between 1282 and 1293 of the work of d'Abû-l-Salt (1068-1134) *Kitâb al-adwiya al-mufrada* (The Book of Simple Medicines), which he called *Translatio albuzale de simplicibus*, already mentioned it as an astringent (haemostatic) in bladder diseases. Bernardo de Gordonio recommended it for haematuria, as did Francisco Díaz, who recommended it for inflammation of the kidneys and haematuria. Already in 1984, it was mentioned in the Encyclopaedic Book of Formulas as a haemostatic.

Oleum scorpionum (Scorpio Europeus L)

Bernardo de Gordonio recommended scorpion oil for kidney pain, rubbing it on the aching area mixed with theriaca. Laguna said that there were two types, marine and land. "*Scorpion oil fortifies and protects against pestilence and against any other poison. Applied to the kidneys, it disintegrates stones*".[5] Compound scorpion oil contained the root of aristolochia, gentian and sedge root, as well as caper root bark. It was used for bites of poisonous animals and rubbed on the kidneys and pubis to facilitate the expulsion of urine and the stones. It was considered to be diuretic and lithontropic. Laguna also recommended it in urethral lavages to combat bladder stones. Of his many anodynes, Francisco Díaz also recommended scorpion oil for nephritic colic: "*an omelette made with scorpion oil is a very useful anodyne remedy*".[7] Morales Patiño mentions that at the beginning of the 20th Century, the chemists' shops in Havana sold a "scorpion oil" that was rubbed on to the lower abdomen to combat urinary retention, according to an anonymous document disseminated by the Pharmaceutical Museum of Matanzas.

Hartshorn plantain (Cervus elaphus L. hispanicus)

Aristotle, Pliny and Dioscórides had already written about the virtues of this organic medicine. Its medicinal properties were nutritional and bone-strengthening in cases of rickets; it was also used as an analeptic, emollient and absorbent. It was used in pieces or scraped (fig. 3). It ceased to be used during the 19th Century, although at the end of this century, the numerous compounds that it comprised were still mentioned, for example in the form of an anthelmintic oil used to treat diarrhoea. Staghorns, bones and the teeth of different animals such as the wild boar, were used to obtain calcium phosphate. Díaz mentions a remedy to "*break the stone*" based on crushed hartshorn plantain and also recommends it for haematuria mixed with watered wine. The Encyclopaedic Book of Formulas mentions a diuretic potion and some antigout powders made with this compound.

Cantharides (Lytta vesicatoria L.)

Also known as Spanish fly, it is poisonous cleopteron (fig. 4) whose use dates back to Hippocrates. Since then until today, it has been used as a drug for different purposes. In his work "*Natural History*" Pliny[11] mentions it on up to fourteen occasions: "*it has the property of burning the flesh... it also provokes urination; that is why Hippocrates gave it to hydropics*". Dioscórides said it had lithontriptic properties and also described its dangers, given that when taken orally, "*it caused blood in the urine and corroded the bladder and kidneys*". He also knew its effects on penile erection: "*it is so effective in producing lust in these creatures*". In the 1st Century A.D., Arataeus of Capadocia

Figure 4 Cantharides (Meloe Vesicatorius, L.).

invented the vesicatory dressing with cantharinidin. De Gordonio also recommended this dressing in combination with scorpion ash for kidney stones in the form of a decoction. Laguna does not mention them, which without doubt is not due to his ignorance, but to possible accidents that its application or consumption caused in his patients. In 1868, Armand Trousseau dedicated up to 10 pages to it, mentioning renal accidents with haematuria caused by the application of vesicatories, in addition to spontaneous erection, penile gangrene and metrorrhagia in women. He cited different authors that used them, from Hippocrates, Pliny, Werloff, Bartolino or Dupuytren, among others. In fact, it is still described in the 1930 Spanish pharmacopoeia. Dermatologists currently use it occasionally as an abrasive in the moluscum. It was mainly indicated for vesication, a technique that was part of therapies such as purging or bleeding. Its action is the result of cantharinidin ($C_{10}H_{12}O_4$), a pharmacore isolated by Robiquet (1780-1840) in 1810. In fact, two grammes of cantharide powder can kill an adult. Curiously, it was the first effective treatment used for erectile dysfunction. In France in the 18th Century, the "Richelieu pills" made with cantharide powder were known, and contemporary literature, through Gabriel García Márquez in his book "The General in His Labyrinth, offers us the last moments of Simón Bolívar as a result of applying a vesicatory dressing with cantharinidin. Haematuria is a consequence of the generalized necrosis of the urothelium that cantharinidin causes.

Discussion

The armamentarium that mankind has gathered in the course of history is no more than the result of a long process of a mixture of processes and knowledge of different cultures and societies. From the Greek and Roman era with Dioscórides, medicinal remedies from the Mediterranean were used. Classic Greek medicine knew how to collect such elements from ancient Egypt. This armamentarium was augmented with products that the Arabs from Africa and the East introduced during the Middle Ages. During the 16th and 17th Centuries, pharmacotherapy was increased, thanks to the American medicines that the Spanish introduced and the Oriental medicines that the Portuguese introduced. Only some products were added after the chemical revolution of the Renaissance. At the end of the 18th Century, Bichat (1771-1802) said that the medicines used were the same, despite the fact that underlying therapeutic ideas were changing. This meant that their empiric use was the same; what changed was the theories on their effects. These theories swung from scepticism, nihilism and therapeutic eclecticism. Other theories such as vitalism or broussism were at least picturesque and helped little with the development of pharmacological therapies. Until well into the 19th Century, this did not change.

Medicines were divided into two large groups: simple and compound. This division was above all didactic, as on occasions, simple medicines were also sold separately. Simple medicines would be those that we could call the raw material, a nominalized adjective indicating a non-compound medicine that is administered as is from nature or with minor variations, or that is used to prepare compound medicines. They represent the basis of practical pharmacotherapy from ancient times until the 20th Century. All of them came from nature until chemical drugs began to be used, and they came from three kingdoms: plant, mineral and animal.

Plants became part of the majority of compounds and were used whole of in part (roots, leaves, flowers, fruit); some taxonomic families predominated. The *apiaceous* family was the most used. The study of its origin gives an idea of the importance of the trade routes begun by the Phoenicians twelve centuries before Christ. Tyro traders supplied Greece with incense, myrrh, ginger and cinnamon. During the era of Alexander, trading intensified with Persia, India and Arabia. The Romans took over from the Greeks and the route of the Alps favoured their spread by land. After the fall of the Roman Empire, Byzantium appropriated the routes between the East and West; Venice and Marseille were the two most important stops. The crusades propitiated the establishment of numerous traders, whose base was Venice, where traffic and trade were liberalized in 1082. Montpellier and Marseille also played an important role in the Middle Ages. However, the discovery of America and the opening of the Indian trade routes provided new simple medicines such as ipecac, sarsaparilla or quinine. The Spanish, Dutch, Portuguese and English fought to dominate these routes, which saw the thriving of prosperous trade routes. During the 18th Century, the monopoly of Chinese opium changed to the hands of the English. Thus, the origin of many simple medicines was the East, Africa and subsequently the New World, although botanical gardens were slowly created to cultivate them. Many monastery chemists had their own fields of simple medicinal plants. Pharmacies had to have sufficient supplies to prepare compound medicines.

During the 18th Century, substances introduced during bygone eras, such as guaiacum or quinine continued to be used, continuing the Hippocrates trend that finally resulted in therapeutic scepticism and confidence in the healing power of nature. The Enlightment inherited an aggressive polypharmacy that physicians began to look at with suspicion. During the 19th Century, the bases of modern pharmacology were established. Physical and chemical sciences were developed, which allowed the evolution of biological thought, doing away with old interpretative systems.

In short, the armamentarium that mankind has gathered over history is the result of a long process of mixed practices and knowledge of different cultures and societies. Curiously, pharmacological therapy did not change until well into the 19th Century, with the initiation of the isolation of alkaloids. The basis of ancient general and urological pharmacotherapy was nature. Medicines were divided into simple, from the plant (the most used), mineral or animal kingdom, and compound medicines, when the aforesaid were processed following the indications of physicians or the different pharmacopoeias. This work shows that to be able to study the history of Pharmacotherapy, it is necessary to refer to the treatises on Medicine and to the evidence that has endured in time, principally the recipients used

to preserve and store the medicines, whether made of ceramic, glass or wood.[12-14]

Conflict of interest

The authors declare not to have any conflict of interest.

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