Phytotherapy in urology. Current scientific evidence of its application in urolithiasis, chronic pelvic pain, erectile dysfunction and urinary tract infections

E. Morán*, A. Budia, E. Broseta, F. Boronat

Servicio de Urología, Hospital Universitario y Politécnico La Fe, Valencia, Spain

Received 4 April 2012; accepted 28 July 2012
Available online 9 July 2013

KEYWORDS
Phytotherapy; Urolithiasis; Chronic prostatitis; Erectile dysfunction; Urinary infection

Abstract
Objective: To assess the usefulness of phytotherapy in urolithiasis, urinary tract infections, erectile dysfunction (DE) and chronic prostatitis/chronic pelvic pain (PC/DPC).

Acquisition of the evidence: Systematic review of the evidence published until January 2011 using the following scientific terms: phytotherapy, urinary lithiasis, Chronic prostatitis, chronic pelvic pain, erectile dysfunction, urinary tract infection, cystitis and the scientific names of compounds following the rules of the International Code of Botanical Nomenclature. The databases used were MEDLINE and The Cochrane Library. We included articles published until January 2011 written in English and Spanish. We included studies in vitro/in vivo on animal models or human beings. Exclusion criteria were literature not in English and Spanish or articles with serious methodological flaws.

Synthesis of the evidence: We included 86 articles selecting 40 that met the inclusion criteria. In urolithiasis there are few works in humans. The phytae has its main use as prevention and in reducing the growth of residual fragments after ESWL. In PC/DPC the only compound that has shown effectiveness was the extract of pollen in a field of multimodal treatment. In DE there is no evidence for the use of herbal medicine. Most of the works have limitations in the design or low sample size. In urinary tract infections most of the products are diuretics. There is only evidence for the cranberry as prevention in young or pregnant women. It must not be used as a treatment for urinary tract infections.

Conclusions: Phytotherapy is useful in repeat urinary tract infections and CP/CPP. It plays a role in the urolithiasis and lacks usefulness in the ED.

© 2012 AEU. Published by Elsevier España, S.L. All rights reserved.
PALABRAS CLAVE
Fitoterapia; Urolitiasis; Prostatitis crónica; Disfunción eréctil; Infección urinaria

Fitoterapia en Urología. Evidencia científica actual de su aplicación en urolitiasis, dolor pélvico crónico, disfunción eréctil e infecciones urinarias

Resumen
Objetivo: Evaluar la utilidad de la fitoterapia en urolitiasis, infecciones urinarias, disfunción eréctil(DE) y prostatitis crónica/dolor pélvico crónico(PC/DPC).
Síntesis de la evidencia: Se incluyeron 86 artículos seleccionando 40 que cumplieron los criterios de inclusión. En Urolitiasis hay pocos trabajos en humanos. El fitato tiene su principal utilidad como prevención y en la disminución del crecimiento de fragmentos residuales tras ESWL. En PC/DPC el único compuesto que ha demostrado eficacia fue el extracto de polen en un ámbito de tratamiento multimodal. En DE no hay evidencia a favor del uso de la fitoterapia. La mayoría de los trabajos presentan limitaciones en el diseño o escaso tamaño muestral. En Infecciones urinarias la mayoría de los productos son diuréticos. Sólo existe evidencia para el arándano rojo como prevención en mujeres jóvenes o embarazadas. No debe emplearse como tratamiento de las infecciones urinarias.
Conclusiones: La fitoterapia muestra utilidad en las infecciones urinarias de repetición y en la PC/DPC. Tiene cierto papel en la urolitiasis y carece de utilidad en la DE.
© 2012 AEU. Publicado por Elsevier España, S.L. Todos los derechos reservados.

Introduction
The use of phytotherapy is widespread. There are hundreds of compounds that are used in clinical practice despite the lack of scientific evidence. These products combine different active ingredients, which makes the comparison difficult to reach a high level of evidence in the different published studies. Therefore, urologists are skeptical about the usefulness of these compounds, given the inconsistency in the literature.

The aim of this review is to evaluate the usefulness of phytotherapeutic compounds in various urological conditions, including urolithiasis, urinary tract infections, erectile dysfunction (ED), and chronic prostatitis/chronic pelvic pain.

Material and method
There has been a systematic review of the evidence in the literature published from January 1985 to January 2011. In order to carry out the review, a search of the scientific terms: phytotherapy, urolithiasis, urinary lithiasis, chronic prostatitis, chronic pelvic pain syndrome, ED, urinary tract infection, cystitis, lower urinary tract symptoms was introduced. They were searched in PubMed and The Cochrane Library. For the search of the phytotherapeutic compounds, the scientific names were used following the rules of the International Code of Botanical Nomenclature.

Figure 1 Flow of inclusion of works in the review.

Inclusion criteria: articles published until January 2011 written in Spanish and English were included. We included in vitro/in vivo studies, both in animal models and humans. Exclusion criteria: The not Spanish/English literature or articles with serious methodological flaws (Fig. 1) were excluded.

Phytotherapy in urolithiasis
Lithiasic disease affects approximately 10–12% of the population in developed countries. There are over 70 species of plants that, traditionally, have been used in its treatment. Gürocakl and Küpeli conducted a review of all existing items in connection with the use of phytotherapy in lithiasic disease. The studies analyzed were, mostly, performed on animal models with only 5 studies in humans. In them, cranberry juice, grapefruit juice, lemon juice, Salvia...
*miltiorrhiza,* also used in chronic prostatitis, and cowpea, gahat or wild pea (*Vigna unguiculata*) were evaluated. Cranberry juice, in healthy patents, is able to modify the urinary composition in such a way that less lithogenic conditions are reached, as citrate increases and oxalate and phosphate removal decreases. However, concerning grapefruit juice, although it produces an increase in citrate, magnesium, and calcium, its high sugar content does not make it advisable. Koff et al. evaluated, in a prospective, well-designed study from the methodological point of view, if lemon juice brought benefits in terms of the urinary pH and citraturia compared to standard treatment with potassium citrate. To do this, they evaluated 21 renal stone former patients and concluded that lemon juice did not provide benefits compared to the usual treatment. *Vigna unguiculata,* in a prospective study on 8 healthy patients, increased the urine volume and magnesium, which could be a protection against lithiasis, although the mechanisms of this effect have not been demonstrated.

*Chancapiedra* or *Phyllanthus niruri* (Uriston®) was also evaluated in a prospective study on 150 patients, with random distribution and follow-up at 6 months as adjuvant treatment to extracorporeal shock wave lithotripsy (ESWL). This compound increased the rates of stone free patients only for those lithiases located in the lower calyx. In this study, we compared Uriston® to other treatments, so that the benefit against current medical therapies was not evaluated. Its mechanism of action is under consideration, although it might act by inhibiting the glass-glass or glass-matrix interactions. The growth of the lithiasis was prospectively evaluated in a paper, in rats, which observed how chronic treatment with *Phyllanthus niruri* inhibited the growth of the lithiasis thanks to the addition of glycosaminoglycans to the stone.

The mechanism of action by which these substances influence the incidence of lithiasis decreasing the formation of lithiases with such a different composition is not clarified. We have studied a component which is common to many of these plants, saponins. Among them, escin and glycyrrinic acid stand out as potential crystallization inhibitors.

One of the most studied compounds is phytates. This element appears in cereals, nuts, and beans. It is especially useful in stones containing calcium oxalate monohydrate. Furthermore, phytates demonstrated to in vitro inhibit the growth of extracorporeal postlithotripsy stone fragments. In this case, the effect was not limited to calcium oxalate monohydrate, but it was also useful in those lithiases of uric acid, calcium oxalate dehydrate, and hydroxyapatite. Considering that after ESWL, 10−26% of the residual fragments will undergo growth, this may be an interesting application. It has been recently studied that phytates would also participate in the inhibition of the calcification of other soft tissues, presenting a promising role in cardiovascular disease and Alzheimer.

However, these products are not exempt from side effects. There have been reports of severe dystonias cases with the intake of Salvia miltiorrhiza because it contains coumarin, a potent neurotoxin. With all these data, we could conclude that the studies on the role of phytotherapeutic products in lithiasis are abundant in the literature. However, they are mostly on animal models, with short follow-ups and with a limited treatment length, making it difficult to draw clear conclusions about them. The most studied has been the phytate, so its mechanism of action is well known. Its use includes, in addition to prevention, a complement to therapy with ESWL. Moreover, it can have beneficial effects in other conditions related to calcium deposits.

**Phytotherapy in prostatitis/chronic pelvic pain**

Type III chronic prostatitis/chronic pelvic pain of the NIH has a still unknown etiology, although since its description in 1968 by Meares and Stamey, there have been many advances in its study and treatment. Therapy includes antimicrobials, alpha-blockers, anti-inflammatory, or even hormonal manipulations or minimally invasive therapies.

The only compound that has proven effective is pollen extract (Cernilton®). In 2006, a double-blind study with random distribution versus placebo where superiority of pollen extract was evident versus placebo in terms of improvement in pain score, filling and emptying symptoms from the start to the end of the treatment after 6 months of therapy was carried out. Wagenlehner et al. showed that pollen extract improved symptoms, pain, and quality of life after 12 weeks of treatment in patients with this condition, there being differences in favor of this at 6 weeks of treatment compared to placebo, and well tolerated.

Other compounds that have not shown efficacy were green tea or *Serenoa repens.* The latter, in a prospective and randomized trial on 64 patients with a follow-up of one year, which compared *Serenoa repens* to finasteride, demonstrated no equality or superiority to treatment with inhibitors of 5α reductase. Other studies supporting their use do not show in their results validated questionnaires or the dosage at which the study was conducted. Thus, Morgia et al., compared *Serenoa repens* associated to selenium and lycopene versus *Serenoa repens* alone, not comparing it therefore to other medical treatments with more proven efficacy. In addition, the follow-up time was short (8 weeks).

Quercetin belongs to the group of isoflavonoids and it can be found in onions, grapes, and green tea. Its effectiveness was demonstrated in a well-designed, randomized, double-blind clinical trial, where we observed, compared to placebo, a significant improvement in the scores of validated questionnaires.

In a relatively recent literature review by Capodice et al. it becomes evident that of the 19 articles analyzed, in 8, data on the posology or dosage of the compounds are missing. These works mainly evaluated quercetin, pollen extract, and *Serenoa repens.* In light of these studies, it seems that phytotherapy is a pharmacological group of help in these patients but as part of a multimodal approach in which phytotherapy cannot be considered as the cornerstone of the treatment.
Phytotherapy in erectile dysfunction

The main agents used in the therapy of this condition have been yohimbine, ginseng, and Ginkgo biloba. Although in animal studies yohimbine was able to increase libido, in human studies, it seems to have some improvement in symptoms but without being able to reach valid conclusions. Moreover, it is not to prevent interaction with nitrates (when combined with L-arginine), unlike treatment with inhibitors of 5-phosphodiesterase (5-PDE). The second compound studied is ginseng. Several mechanisms of action such as a hormonal effect similar to that of testosterone (although no differences have been shown in the serum levels of this hormone in patients treated with ginseng) are postulated, or the induction of smooth muscle relaxation of cavernous bodies by the NO pathway through the ginsenosides. Ginseng was compared, in older studies, to placebo and trazodone, showing better results in terms of early loss of tumescence, rigidity, and libido in patients taking Ginseng. Recently, only a small, randomized, well-designed study on 45 patients showed that Korean red ginseng might be effective in treating ED but without being able to draw consistent enough conclusions to recommend its use. In this study, no comparison was made to the 5-PDE inhibitors. With a dose of 1g/3 times a day, Andrade et al. studied on 60 patients, in a double-blind paper and with placebo group, the efficacy of ginseng. Using the validated questionnaire International Index of Erectile Function (IIEF-5), we observed superiority of the treatment versus placebo.

In 2008, a systematic review including 7 randomized trials comparing placebo to ginseng in the management of ED was done. We found a significant benefit of ginseng versus placebo, although the quality of the studies is low and the conclusions reached in this study are insufficient to recommend this product as a treatment for ED.

The third most traded product is Ginkgo biloba. This has been studied primarily in ED induced by antidepressant drugs, and, although good results were obtained in the first instance, those papers did not include placebo group and the ginkgo biloba doses were highly variable, which makes drawing conclusions difficult. However, in more recent and methodologically more comprehensive studies, there were no statistically significant differences.

Recently, Andean maca (Lepidium meyenii) has become very popular. On it, randomized, double-blind studies have been carried out, all with a small number of patients, which showed a subjective improvement in patients with ED, objectified by means of IIEF-5 or SAT-P questionnaires. Regarding the IIEF-5 score, the placebo group showed improvement as well, but less significant. Only in the SAT-P satisfaction questionnaires, the maca proved superior to placebo.

The major compounds studied are summarized in Table 1. Therefore, the current clinical evidence does not recommend the use of phytotherapy in the treatment of ED. Some studies even warn that some of these compounds may contain 5-PDE in their composition.

Phytotherapy in urinary infections

The whole plant extracts used to prevent urinary tract infections is very broad and does not present a clear pathophysiological basis on which its mechanism of action is based. The main products and their properties are shown in Table 2.

Red cranberry (Vaccinium macrocarpon) is undoubtedly the most studied phytotherapeutic product in this field, able to reduce the recurrence of urinary tract infections in selected groups up to 30%, being necessary to treat 6.4 patients (NNT) to prevent a UTI in a follow-up period of 6 months. In 2008, a review was published with 10 studies evaluating the effectiveness of phytotherapy in the UTIs. Of them, only 2, methodologically correct, showed that red cranberry can reduce the number of recurrent UTIs.

The mechanism of action is well known and it is based on the inhibition of bacterial adherence (mainly from 1 and P fimbriae of Escherichia coli) thanks to 2 compounds, proanthocyanidins (P fimbriae) and fructose (1 fimbriae). Several studies have been conducted on sexually active women and showed a significant decrease in the incidence of UTI in patients taking cranberry prophylactically, this being a cost-effective measure and without differences between the different routes of administration. However, these findings are applicable only to a particular group of patients, young women, while in older women or men, similar efficacy has not yet been demonstrated. There is a high dropout rate due to side effects, so this substance is probably not well tolerated in long-term prophylactic regimens. However, in a recent, methodologically well-designed paper, it was demonstrated that in a population of young women (319) who had had a UTI, red cranberry
administration did not decrease the incidence of UTI within 6 months.\textsuperscript{31}

We also assessed its effectiveness in the population of pregnant women. In 2008, Wing et al.\textsuperscript{33} published a study concluding that there is a protective effect of red cranberry in these patients when administered 3 times a day compared to a single dose versus placebo, both in asymptomatic bacteriuria and in symptomatic UTI. However, there was a 30\% dropout rate because of poor tolerance of the product. In terms of safety, Dugoua et al.\textsuperscript{34} conducted a systematic review of the literature to assess the safety of this product during pregnancy and breastfeeding, finding no adverse effects for the fetus or neonate.

Other subpopulations studied have been, for example, old women,\textsuperscript{35} where a prospective, randomized, double-blind study showed a reduction in the incidence of bacteriuria and pyuria. However, in this study, they did not refer to clinical infections but to asymptomatic bacteriuria, so the primary objective of this work is not comparable to that of other studies. No benefit has been shown in another group of patients with recurrent abundant infections either, as it is the case of patients with neurogenic bladder, although some articles report decreased UTIs in the presence of biofilm around the catheter in spinal cord injured patients. Most show that, in this group, red cranberry does not decrease the number of infections.\textsuperscript{36}

There is unanimity in the literature that its role is purely preventive; however, most agree that it is not an indication of urinary tract infection treatment.

The main side effect or interaction described (12 cases) has been warfarin interaction in a way that the INR of these patients increased, as well as their risk of bleeding.\textsuperscript{37} This could be explained by an inhibition of cytochrome p450. Moreover, as other side effects, we could highlight the gastrointestinal ones or weight gain. Berberine is an alkaloid plant of the isoquinoline alkaloid group. It is found in plants such as Berberis, goldenseal (Hydrastis Canadensis), and Coptis chinensis\textsuperscript{38} and it has demonstrated, in in vitro models, a reduction in bacterial adherence. In this case, it is formally contraindicated in pregnancy because it increases uterine contractions.

\textit{Lactobacillus} orally has not proven effective. One study,\textsuperscript{39} initially well designed, where urinary tract infections are prevented in 3 arms, one with placebo, one with red cranberries, and one with \textit{Lactobacillus}, had several weaknesses. One of them is the lack of double-blind control, and the other one, the low number of patients recruited. On the other hand, topical vaginal application, in the absence of more complete studies, appears to improve the incidence of recurrent urinary infections.\textsuperscript{40}

Therefore, it seems that red cranberry may be effective in preventing recurrent urinary tract infections in the population subgroup representing young and pregnant women, so the guidelines of the European Association of Urology give it a grade of recommendation C with 11a level of evidence. In the rest of the population, there are no properly designed studies to support this indication.

However, from the pharmacoeconomic point of view, cost-effectiveness studies are required, as it seems that night antimicrobial prophylaxis gets better results with better tolerance and lower price.

\textbf{Conclusions}

As general limitations, there was a large discrepancy between the results of studies with similar designs, mainly because of the lack of homogeneity in the doses and treatment regimens of many of the compounds. Phytotherapy shows greater utility in recurrent urinary tract infections (only red cranberry in the population of young and pregnant women) and in chronic prostatitis or chronic pelvic pain (as part of a multimodal treatment, not as monotherapy), so it is collected in the clinical guidelines with grade of recommendation/level of evidence C/IIa and B/IIb-III, respectively. It plays a role in urolithiasis (mainly in the prevention) and lacks utility in the ED.

\textbf{Conflict of interest}

The authors declare that they have no conflict of interest.

\textbf{References}


