



## Knowledge, Attitude, and Practice (KAP) of Pharmacists about Natural Products Used for Urolithiasis in Shiraz, Iran

Kowsar Danesh<sup>1</sup> , Saeid Daneshamouz<sup>2</sup>, Iman Karimzadeh<sup>3</sup>, Abdolali Mohagheghzadeh<sup>1,4\*</sup> 

<sup>1</sup>Department of Traditional Pharmacy, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.

<sup>2</sup>Department of Pharmaceutics, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.

<sup>3</sup>Department of Clinical Pharmacy, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.

<sup>4</sup>Pharmaceutical Sciences Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.

### Abstract

**Background and objectives:** We wanted to figure out how pharmacists make their judgments about the efficacy of natural products in urolithiasis and how they make suggestions about these products.

**Methods:** A self-made descriptive questionnaire was designed, evaluated, and performed to assess pharmacists' knowledge, attitude, and practice (KAP) about natural products in urolithiasis in 46 young pharmacists and final year pharmacy students in Shiraz. **Results:** In all of the KAP sections, Rowatinex®, Cystone®, and Sankol® were the most known, believed to be effective, and preferred pharmacist products. Respondents had received different education hours. About 54% of them believed their education was averagely adequate. Brochures (63.0%), web-search (60.9%), and applications (45.7%) were the primary resources used by pharmacists, mainly to check the instruction of use. About 80% of pharmacists were unaware of the mechanism of action of at least 5 of 14 products. Generally, respondents had a positive view of natural products. In addition, they thought price and advertisements were effective in patients' and physicians' choice of products. More than half of pharmacists preferred to use clinical trials (52.2%) rather than systematic reviews (19.6%).

**Conclusion:** Providing a vast amount of information in the education process is not the best solution for preparing pharmacists for their role in community pharmacies. Besides the need for increasing clinical trials about complementary and alternative medicines and developing evidence-based databases, we need to train pharmacy students in professional ways to gain knowledge about complementary and alternative medicines.

**Keywords:** complementary therapies; evidence-based pharmacy practice; kidney calculi; pharmacy education; questionnaire

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### Introduction

In 2007, the urolithiasis prevalence was about 5.7 %, and its incidence was 241 per 100,000 in Iran [1]. Various natural products or herbs are used in urolithiasis for stone expulsion or prevention of stone re-formation. Not all of these products are significantly effective. However,

promising effects have been seen in in-vitro, in-vivo, and clinical studies [2]. Different natural products in urolithiasis are available in Iran. Some of the most prominent natural products available in the Iranian pharmaceutical market are Rowatinex®, Cystone®, Sankol®, Lithorex-B®,

\* Corresponding author: mohaghegh@sums.ac.ir

Urtica<sup>®</sup>, and Canephron<sup>®</sup>.

There is an increasing interest in natural products in society. On the other hand, discussions about natural products' efficacy, even among professionals like pharmacists, are not as detailed and specific as they talk about common medications. Knowledge, attitude, and practice (KAP) studies can be used as a situation analysis tool [3]. These studies use questionnaires to gain information about three parts: knowledge, attitude, and practice.

To obtain a perspective on how pharmacists get their knowledge of urolithiasis-related natural supplements, how they evaluate these products' use, and how they play their role in pharmacies, we designed and performed a KAP study. We also asked about the prevalence of natural supplement use in the community and physicians' practice from pharmacists' point of view to see how prevalent these products are and how important this topic can be for pharmacists.

## Material and Methods

### Ethical considerations

The study was approved and registered at Shiraz University of Medical Science with the ethical code: IR.SUMS.REC.1399.1139. The questionnaires were anonymous. Study objectives were described at the beginning of the questionnaire. Participants willingly started to answer the questionnaire.

### Questionnaire design

The primary questionnaire was developed based on study objectives, Food and Agriculture Organization (FAO) guidelines for nutrition-related KAP studies [3], and some articles from primary searches [4-9].

### Selection of natural products

Iran's natural products list provided by Iran Food and Drug Administration [10] published on 19/1/2020 was screened for urolithiasis-related products. If a product brochure/ manufacturer website claimed its efficacy for urolithiasis, it was selected to be included in the study.

### Validity

The questions were discussed with team members and four graduated pharmacists/last-year pharmacy students. Based on these discussions, multiple revisions were applied. Then, validity was evaluated using content

validity index (CVI) [11]. We asked six pharmacy professors as the expert panel to assess questions using Google forms. Four of them answered the questions.

The form consisted of questionnaire questions and four Likert scale-like options. The panel of experts was asked to determine the level of relevancy for each of the questions, based on the goals of each section, choosing one of these choices: "totally relevant", "quite relevant", "somewhat relevant", and "irrelevant". One point was considered for the answer "Totally relevant" or "quite relevant" and 0 if the answer was "somewhat relevant" or "irrelevant". For each question, the average score was calculated by summing up each expert score and dividing the score by the total number of experts. This was how we calculated item-level content validity index (I-CVI).

Based on Lynn 1985 [12] and with some modifications, questions with I-CVI=1 were included in the questionnaire, questions with I-CVI=0.75 were modified, and questions with I-CVI less than 0.5 were omitted. The modifications and deletions were recorded.

Scale-level content validity index (S-CVI) for each question was calculated by summing up each question I-CVI and dividing it by the number of questions. (S-CVI/Ave). We calculated S-CVI/Ave for each KAP section. S-SVI/Ave is acceptable when it is more than 0.8, but it is better to be higher than 0.9 [11].

### Reliability

Because of the broadness of the questions, we could not use Cronbach's alpha. Therefore, based on Collins 2003 [13], we used cognitive interview to evaluate the reliability of the questionnaire by asking respondents to describe why they had chosen a specific answer and explaining their thinking patterns. Four people, consisting of two last-year pharmacy students, one newly graduated pharmacist, and one pharmacy professor, were asked to answer the questionnaire. Then, we arranged an interview time with each respondent. As it was not possible to do this process for all questions, questions that seemed to be misinterpreted by most of the respondents were chosen to be asked in the interview. Other highlighted misinterpreted questions in the previous validity check by pharmacist/pharmacy students and our own judgment of those questions susceptible to

misinterpretation were also included. Based on each person's response, they were also asked to describe their answers to some other questions. If respondents mentioned a point frequently, it was considered in re-evaluating and correcting the questions.

### Data collection

The study was performed using an online questionnaire service in April 2021. The questionnaire was distributed through social media in pharmacy-related groups. As our population target was Shiraz pharmacists and pharmacy students, we tried to send the link in public groups and avoid private messages to reduce the risk of having a selected population bias. Fifty-nine pharmacists/pharmacy students responded to the questionnaire. Forty-six of these responses were eligible to be analyzed.

### Data analysis

Respondents' answers were gathered through excel spreadsheets (Microsoft excel 2019) and sorted using pivot tables. As our questionnaire had a qualitative format and was intended to evaluate the population situation on the topic, categorical variables and qualitative data were reported as percentages. These variables were judged by the mode of data, variable/variables chosen by most respondents. Items with the

frequency of more than 50% or 1<sup>st</sup>-3<sup>rd</sup> most frequent items of each question were reported and discussed. In open questions, we labeled answers with the same meaning or theme like any word that meant "web search" in the same categories and then reported their frequency. We specified points from 1-5 for each option for Likert-scale questions, while 1 and 5 corresponded to complete disagreement and complete agreement, respectively. Then the average score for each question was reported. The normal distribution of continuous variables was determined by the Kolmogorov-Smirnov test via the SPSS software (Version 16.0. SPSS, USA). Normally and non-normally distributed continuous data were expressed as the mean  $\pm$  standard deviation (SD) and median (interquartile range), respectively.

### Results and Discussion

After screening and evaluating Iran's list of natural products, 14 products were selected. Products and their active pharmaceutical ingredients (API) are described in Table 1. The questionnaire form is presented in the supplementary material (S1).

Five questions out of 46 had an I-CVI  $\leq$  0.5 and were omitted. Twelve questions had an I-CVI=0.75 and were modified. Other questions I-CVI was equal to 1.

**Table 1.** Natural products in urolithiasis available in Iran market

	Name	Ingredients	Dosage form	Manufacturer
1	Rowatinex®	Alpha & beta pinene, camphene, fenchone, borneol, anethol, and cineol	Softgel	Rowa pharmaceuticals
2	Lithorex-B®	<i>Cucurbita pepo</i> , <i>Populous nigra</i> , and <i>Solidago canadensis</i>	Tablet	Barijessence
3	Diurin®	<i>Equisetum arvense</i>	Drop	IranDarouk
4	Rudioretic®	<i>Equisetum arvense</i>	Capsule	GhaemDaroo
5	Moderic®	<i>Equisetum arvense</i>	Coated tablet	GolDarou
6	Sankol®	<i>Foeniculum vulgare</i> , <i>Laurus nobilis</i> , <i>Tribulus terrestris</i> , <i>Cuminum cyminum</i> , <i>Cucumis melo</i> , <i>Zea mays</i> , and <i>Cerasus avium</i>	Drop	GolDarou
7	Diuretic®	No information	Teabag	Armaghan Tabiat
8	Zol Urosept®	<i>Arctostaphylos uva-ursi</i>	Coated tablet	Zolang Respina
9	Cystone®	<i>Didymocarpus pedicellata</i> , <i>Saxifraga ligulata</i> , <i>Rubia cordifolia</i> , <i>Cyperus scariosus</i> , <i>Achyranthes aspera</i> , <i>Onosma bracteatum</i> , <i>Vernonia cinerea</i> , Shilajeet, and "Hajrul yahood bhasma"	Tablet	Himalaya
10	Tropin®	<i>Tribulus terrestris</i> , <i>Prunus avium</i> , <i>Zea mays</i> , <i>Foeniculum vulgare</i>	Tablet	Hakim Momen Tabrizi
11	Renamix®	<i>Equisetum arvense</i> , <i>Phaseolus vulgaris</i> , <i>Arctostaphylos uva-ursi</i> , <i>Betula pendula</i> , <i>Orthosiphon aristatus</i> , <i>Glycyrrhiza glabra</i> , <i>Ononis spinosa</i> , <i>Mentha piperita</i>	Drop	Matin Asa Pharmed
12	Canephron®	<i>Centaurium erythraea</i> , <i>Levisticum officinale</i> , and <i>Rosmarinus officinalis</i>	Coated tablet	Bionorica
13	Urtica®	<i>Urtica dioica</i>	Syrup	Zardband
14	Sandkim®	<i>Cucumis melo</i> , <i>Cucumis sativus</i> , <i>Citrus medica</i> , <i>Vigna unguiculata</i> , <i>Tribulus terrestris</i> , <i>Foeniculum vulgare</i> , <i>Prunus domestica</i> , <i>Adiantum capillus-veneris</i> , <i>Capparis spinosa</i> , <i>Apium graveolens</i> , <i>Raphanus sativus</i> , <i>Carum carvi</i> , <i>Cyperus esculentus</i>	Syrup	Kimiagar Tous

The primary S-CVI/Ave for general questions, knowledge, attitude and practice questions were 0.75, 0.89, 0.93, and 0.93, respectively. After omitting questions with I-CVI  $\leq$  0.5, the S-CVI/Ave were 0.87, 0.92, 0.97, and 0.91. All the participants stated that the questions were fluent; however, some description was added to the questions that seemed frequently misinterpreted by the respondents, such as questions 7, 14-18, 30, and 37.

In the case of question 37, all participants chose clinical trials rather than review articles, while we expected vice versa. By asking further questions, it seemed that all the participants unconsciously considered clinical trials more valuable. Therefore, we changed the option from "review articles" to "systematic reviews". But this trend in selecting clinical trials continued.

In question 30, regarding factors important for pharmacists to present drug information to patients, we changed the question to be about a specific product (Sankol®) that was assumed to be known by most of the pharmacist to avoid general answers.

In total, 203 persons checked the questionnaire, 109 began to answer, and 59 fully responded to the questionnaire. The response rate was 54%. On average, it took respondents 23.3 minutes to answer the questionnaire. After omitting respondents that were out of the targeted population, 46 responses remained for further analysis.

More than half (67.39%) of the study population were female. The Mean  $\pm$  SD age of participants was 28.26  $\pm$  5.587 years. The age distribution of the participants was not normal ( $p < 0.001$ ), most of the participants were in their 20s. All of the participants were living in Shiraz. Most of them had spent or were spending their Pharm. D. education at Shiraz School of Pharmacy except four respondents. Respondents who were categorized as Pharm. D. students are those in their last year of pharmacy education and were spending their internship program at educational pharmacies of Shiraz University of Medical Science (Table 2).

All of the respondents were familiar with Sankol®, Cystone®, and Rowatinex® and 89.1% with Lithorex-B®. Therefore, we expected more accurate answers about these products.

Most pharmacists (91.3%) believed that Cystone® and Sankol® were the most prescribed natural products in urolithiasis (NPIUs).

Rowatinex® and Lithorex-B® were in second and third places (60.9% and 39.1%, respectively). Although most of the pharmacists were asked about a natural product in urolithiasis (NPIU) as an over-the-counter product (OTC), it seems that NPIUs are not among the recurrent subjects that pharmacists are asked about. However, pharmacists reported that when they were asked, patients primarily expected NPIUs to alleviate their pain (37.1%). In the second place, they needed a medication that could expel their stone (20.0%). They also wanted to know how to use the products (17.1%).

**Table 2.** General characteristics of the study population

<b>Age and gender</b>	
Mean age $\pm$ SD (age range), years	28.26 $\pm$ 5.59 (23-56)
Gender (male: female)	15:31
<b>Education, number of people (percentage)</b>	
Pharm. D. or Pharmacy student	36 (78.3%)
Ph.D. or Ph.D. student	10 (21.7%)
<b>Work experience, number of people (percentage)</b>	
Less than 1 year	12 (26.1%)
More than 1 year	34 (73.9%)
<b>Current working status, number of people (percentage)</b>	
Currently active	33 (71.7%)
Currently inactive	13 (28.2%)

Knowledge: Most respondents (89.1%) had gained relevant education in courses like medicinal herbs, pharmacognosy, pharmacotherapy, and community pharmacy internship during their Pharm. D program. About half of the study population (53.7%) believed their education was averagely adequate. However, more than one-third (39.1%) of the cohort said their education adequacy was low or very low. "Brochures and manufacturer website" were the most used resource by respondents (63.0%) for patient counseling. "Web search" and "drug information applications" were in second and third places (60.9% and 45.7%, respectively). When we asked respondents to write titles of their resources, answers differed in their orders. "Darooyab", a drug information application, was reported by 30.4% of respondents as the first source of information. Most respondents (71.7%) used these resources to obtain "instruction of use" of herbal medicines.

Most of the respondents (60.8%) could find some of the information they needed and counsel patients with some satisfaction. They had average satisfaction from their resources.

Most respondents (65.2%) said they knew the

instruction of the use of at least five NPIUs; however, a considerable portion of the respondents were unaware of NPIUs mechanism of action (80.4%).

Sankol® was chosen by most of the respondents as a stone expulsive agent (65.2%) and a product that can prevent stone re-formation (23.9%). Cystone® was also believed by most respondents (34.8%) to cause stone dissolution. Alternatively, concerning questions about stone dissolution and stone prevention, the number of the respondents who declared they were not sure about the answer was more than those who chose one of the products (39.1% and 45.7% for stone dissolution and stone prevention, respectively)

**Attitude:** In general, respondents had a positive view of natural product use (4.1 points out of 5), and most of them believed that natural products were somehow effective in the treatment of urolithiasis (3.8 points).

Respondents considered all three secondary factors mentioned in the questionnaire (cost, preference toward foreign products, pharmaceutical companies advertising) affecting NPIU choice and prescription. Still, they valued the price of products and advertisements (4.1 points) more than the preference toward foreign products (3.9 points).

Most respondents (52.2%) believed that NPIUs efficacy was in line with their brochures, while 37.0% had no opinion about this question. The average point for this question was 3.4 out of 5. Most respondents had average to low preparation for counseling (2.6 points). However, this feeling of low preparation may be influenced by previously asked questions in the knowledge section.

The average score on attitude questions was more than half (>2.5 points). The largest belonged to the effectiveness of herbal products in general, the impact of price, and the impact of advertisement (4.1 points), and preparation for patients' counseling had the lowest score (2.6 points). Cystone® (65.2%), Rowatinex® (63.0%), and Sankol® (58.7%) were chosen as the most effective products. They were also the most known products by the respondents.

**Practice:** While suggesting a product to a physician, most responses focused on the purpose of treatment (69.6 %) and stone composition (60.9%). Among non-scientific determinants, plenty of respondents (82.6%) valued patients' feedback as a pivotal factor in their judgment. Moreover, half of the respondents said the

frequency of product prescription by physicians is important in their decisions.

Sankol®, Cystone®, and Rowatinex® were the most suggested products by respondents. When respondents were asked to describe their choice when directly facing a patient, a low portion of them made their suggestions based on patients' feedback. They preferred to refer the patient to the physician (45.7%) or get a history and then make a decision (45.7%).

For a quick review, most respondents preferred clinical studies (52.2%), followed by textbooks (26.1%). Systematic reviews were in third place, chosen by 19.6 % of respondents. However, more than half of the respondents (58.7%) had not searched for references and articles about product efficacy. Cystone was searched more than other words. More than half (63.2%) of respondents described search results as averagely adequate.

We asked the study population to identify three products they would order for their own pharmacy. A slight decrease was seen in the popularity of Cystone®, while the interest in Lithorex-B® decreased considerably. However, the general trend was like other questions, and they preferred to order Sankol® (84.8%), Rowatinex® (84.8%), and Cystone® (76.1%) more than other products.

Detailed answers to questions of each section are available in the supplementary material.

People worldwide tend to use complementary and alternative medicine (CAM) as they think they are safe and beneficial, also because of a lack of trust in the efficacy of conventional medicines. This desire to use CAM is more prevalent among patients with diseases that are less likely to be cured, like cancer [14]. This massive interest among people has led to the appearance of invalid information that makes it hard for people and health care providers to decide appropriately. Urolithiasis is no exception to this rule. In addition, as pharmacists are accessible to patients, they can provide patients with evidence-based information and prohibit the circle of misleading information. They are also one of the healthcare providers in Iran with more advanced knowledge about natural products, so that can provide other healthcare providers with high quality information. Hence, pharmacists must have the proper knowledge, know how to get reliable information, and how apply them in practice. Therefore, we evaluated pharmacists' KAP about NPIUs in this study.

Some studies have shown that physicians and health care providers feel it challenging to provide patients with a dietary recommendation due to a lack of confidence or lack of enough information while they believe it can be helpful. They may also be wrong about the information they have [15,16]. In addition, based on a systematic review of KAPs in 2006 in Canada and US, pharmacists had some concerns about the adequacy of available information about supplements and their safety. Considerable percentages of pharmacists were not satisfied with existing information about dietary supplements. Pharmacists felt more comfortable advising supplements if there was better regulation. They had a low desire to ask about patients' current use of supplements. On the other hand, they did not think they had enough information about dietary supplements, and their level of knowledge varied about different herbs [9].

From a national perspective, Mehralian et al. performed a KAP study in 2014 in Tehran, Iran, about the same subject. The study shows that more knowledge of dietary supplements leads to better practice. Also, pharmacists with more experience and those who owned the pharmacy had more knowledge about supplements. The latter may be due to financial interests [5].

Some studies have evaluated NPIU's efficacy on different scales, from animal studies to randomized clinical trials. A summary of some of the available information has been provided here: Rowatinex®: There are some randomized clinical trials about Rowatinex® efficacy. It can be more effective than a placebo in stone expulsion, and its combination with tamsulosin has shown better efficacy than tamsulosin alone [17,18].

Cystone®: Some studies have shown Cystone® to reduce the stone size and increase stone expulsion compared to placebo. According to a meta-analysis of 2 randomized controlled trials [19], Cystone® showed more efficacy in the treatment of urinary tract stones (including stone size reduction and expulsion) than placebo. However, two crossover studies discussed in the same article [20] failed to demonstrate that Cystone® could prevent stone formation in patients who did not respond to other treatments. The low quality of available studies and small sample size are among the limitations mentioned by the authors [19].

Sankol®: There are some studies evaluating some of Sankol® APIs separately, but few studies have considered Sankol® as a whole product. A study on rats receiving Sankol® 888 mg/kg/day shows that Sankol® was successful in stone prevention by reducing serum urea, uric acid, calcium, and phosphorous. It also prevented stone crystallization in the kidney. However, there were some concerns regarding Sankol® safety due to some tissue damage in rats [21,22].

Lithorex-B®: One randomized controlled trial compares the efficacy of treatment with tamsulosin alone or in combination with Lithorex-B® after extracorporeal shock wave lithotripsy (ESWL) for two weeks in kidney and upper ureteral calculi. The study demonstrated that Lithorex-B® resulted in no significant difference in the treatment. The expulsion rate for tamsulosin alone was also lower than in other studies [23].

Urtica®: A study in rats has shown some promising effects of *Urtica dioica* in stone dissolution and preventing stone formation [24].

*Equisetum arvense* products: In animal studies, *Equisetum arvense* or horsetail has shown mild diuretic effects and anti-spasmodic properties. It is also believed to be effective in urinary tract infections (UTI) [25]. We could not find a clinical study about its efficacy in urolithiasis. Diurin®, Rudioritic®, and Moderic® are available natural products in Iran that contain *E. arvense*.

Canephron®: It is famous mainly for the treatment of UTI. However, it is used in urolithiasis, too. One randomized controlled trial has shown the efficacy of Canephron® in faster stone expulsion in stones about 1mm after ESWL. Some other published clinical studies in German and Russian languages [26].

Our study showed that Rowatinex®, Cystone®, and Sankol® are the most known NPIUs and are believed to be effective by most pharmacists. These three products, especially Rowatinex® and Cystone®, also have more scientific evidence than other NPIUs. Their reputation, more available studies, and frequency in usage might show that these three products are more effective than other NPIUs; however, this is only a hypothesis, and there is not enough data to scientifically conclude the most effective product or to decide which one can be more effective in stone dissolution, expulsion, or prevention.

About the source of knowledge for patients counseling, 'Darooyab', web search, handouts,

and brochures were among the most used resources for counseling patients at pharmacy. Although respondents considered scientific references (45.7%) and professionals (34.8%) more than other options like brochures (23.9%) as a convenient way of gaining knowledge, article, and textbooks gained less attention. The resources were looked at mainly to check the instruction of use.

“Darooyab” is a prominent and national online database and application that provides information about medications’ available dosage forms, manufacturer, therapeutic category, generic and brand name, and a brief description of the direction of use, warnings, and contraindications. However, its focus is on common medications rather than CAMs. For natural supplements, information is mainly limited to APIs, manufacturers, and dosage forms. Therefore, we did not expect it to provide a detailed description of the direction of use, the most reported reason for use by our respondents. “Darooyab” and other mostly chosen resources like web search are not expected to provide advanced information for counseling about CAMs. They are not the exact sources we expect to be checked by a professional. However, this feedback by respondents showed the importance of information being readily accessible. Other ways are not as convenient as these. To our knowledge, up to now, there is no available UpToDate-like application to find the answer to natural product questions, an application that answers clinical questions simply and efficiently, optimized for use in practice. Other relevant references, such as PDR for herbal medicines (4<sup>th</sup> Edition) and Lexi-Natural Products, are not much updated or widely available in Iran, respectively. They are not also fully optimized for clinical use. Enough information for providing such databases may not even exist, and we suffer from a lack of high quality randomized controlled trials data about CAMs.

Patients’ feedback was the most non-scientific important factor for pharmacists when recommending a product. We cannot deny that experience is an essential factor, but it is susceptible to bias and misjudgment. It can also make a loop of famous products becoming more famous without supporting information. However, gathering patients’ feedback about NPIUs, evaluating possible biases, and combining results with clinical studies can be recommended to assess product efficacy.

Pharmacists preferred to use clinical trials rather than systematic reviews. It seemed that they were not familiar enough with systematic reviews and their level in the hierarchy of evidence, or they saw clinical studies as more reliable for some reasons. When performed correctly, systematic reviews gather information with less bias than narrative reviews and are highly important in evidence-based medicine. Therefore, healthcare providers must understand their value.

Most pharmacists believed they were not adequately prepared for patient counseling. More than half of the population were aware of at least five NPIUs directions of use. Nearly half of them claimed to be aware of their APIs. Only 19.6% knew the product’s mechanism of action. While being aware of products’ mechanism of action can help them to explain NPIUs effect and to see if it matches patients’ expectations. The questionnaire itself may have caused pharmacists to feel less confident; however, we need to evaluate what factors make pharmacists feel unprepared. Our questionnaire has shown some problems in pharmacists’ way of getting information, but it is hard to conclude whether lack of proper information is the main reason for this lack of confidence or not.

From pharmacists’ point of view, most of the patients expect NPIUs to relieve their pain and, secondly, to expel their stones. They also have questions about how to use the product; maybe these are questions that pharmacists should be more prepared to answer. Questions about NPIUs and OTC demands for these products were chosen by most respondents to be about 0-20%, so NPIUs may not be one of the primary subjects of which a pharmacist should be aware.

In most of the sections, there are no right and wrong answers; as for some of the questions, there is no definite answer yet. The primary purpose of this study was to understand the current situation in the use of NPIU from pharmacists’ point of view, their source of knowledge, their attitude, and how they finally perform based on this knowledge and background to find the gaps in the current education system and source of knowledge.

To our knowledge, it is the first KAP study on urolithiasis and related natural products specifically focused on pharmacists.

The questionnaire was designed to comprehensively evaluate pharmacists’ knowledge, attitude, and practice toward NPIUs.

Therefore, these questions can be used as a pre-structure for developing further and more specified and detailed questions about NPIUs or other disease-specific natural products. Also, the questions refer to different concerns of educators for preparing future pharmacists for their roles. However, our attempt to cover many objectives in one questionnaire may have made its result hard to evaluate. More specific questions covered in different studies could lead to better results.

The response rate was not as much as we expected, and the sample size was relatively small. Therefore, our results may not be generalizable. Due to the study being descriptive, a more advanced quantitative description of the results was not applicable.

The face-to-face questions that we performed for reliability check, had more depth and were more detailed than performing the questionnaire online. However, due to the COVID-19 pandemic, pharmacists seemed more interested in answering questions online.

We thought having knowledge questions at the beginning of the questionnaire could be misleading as it can make respondents aware of what kind of practice is considered reasonable by researchers leading to false-positive answers. However, we have obeyed the prevalent form of KAP studies, having knowledge questions at the beginning of the questionnaire.

### Conclusion

Collectively, the main factors considered as gaps in pharmacists' KAP about NPIUs in this study are as follows:

- Lack of appropriate resources about NPIUs efficacy and CAMs in general
- Not using professional resources
- The use of professional resources to be time-consuming or inconvenient for use in clinical practice
- Low knowledge of products efficacy
- Low awareness of the hierarchy of evidence
- Low preparation and self-confidence for counseling
- Too much attention to patients' feedback and common prescription

Natural product manufacturers can also use the results of this study as a kind of situation analysis tool; how is the current use of NPIUs, and which type of "research and development" measures are needed to support the use of these products scientifically.

There is a crucial need for evidence-based information about CAMs, as not all have proper randomized clinical trials. Up to now, we cannot provide clinical information about all CAMs. However, as our knowledge of CAMs is changing every day, a considerable amount of material for education would not necessarily prepare pharmacists for their future roles; we should emphasize how pharmacists search for existing information and make critical judgments. We also need to expand evidence-based practice for CAM and prepare pharmacists and other health care providers with the appropriate tool, methods, and judgment techniques for evaluating CAMs.

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### Author contributions

Kowsar Danesh, Saeid Daneshamouz, Iman Karimzadeh, and Abdolali Mohagheghzadeh developed the original idea of the paper; Kowsar Danesh, Iman Karimzadeh, and Abdolali Mohagheghzadeh designed the questionnaire; Kowsar Danesh, Saeid Daneshamouz, Iman Karimzadeh, and Abdolali Mohagheghzadeh gathered the data; Kowsar Danesh analyzed the manuscript in addition to using Saeid Daneshamouz, Iman Karimzadeh, and Abdolali Mohagheghzadeh comments and opinions; Kowsar Danesh made the first draft; Iman Karimzadeh revised the draft, and Abdolali Mohagheghzadeh finalized the draft; all authors approved the final manuscript.

### Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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### **Abbreviations**

KAP: knowledge, attitude, and practice; NPIUs: natural products in urolithiasis; OTC: over the counter; CVI: content validity index; I-CVI: item-level content validity index; S-CVI: scale-level content validity index; ESWL: extracorporeal shock wave lithotripsy; UTI: urinary tract infection; CAM: complementary and alternative medicines