Review

Potential Drug Herbal Interaction of the Commonly Used Medicinal Plants in the Management of Nephrolithiasis in Iraq: A Mini-Review

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Suhad Sami Humadi[1]

Abstract

Nephrolithiasis is a prevalent condition characterized by the formation of urinary tract stones, with a high incidence rate worldwide. The recurrent nature of this disease often directs the public to seek alternative therapies, including herbal medicine, due to a common perception of its safety. However, emerging evidence emphasizes the potential for herb–drug interactions, which may pose serious risks to patient health, particularly among elderly individuals and those with chronic diseases. In light of the increasing use of herbal remedies worldwide, this review aims to investigate the potential interactions between conventional drugs and commonly used anti-urolithiatic medicinal plants, based on findings from a recent ethnobotanical survey. Seven frequently used medicinal plants in Iraq were identified and reviewed, utilizing data published between 1900 and 2025, with a particular focus on pharmacokinetic and pharmacodynamic interaction mechanisms. This review intends to help healthcare professionals identify and manage potential herb–drug interactions, thereby enhancing patient safety and informed clinical decision-making in nephrolithiasis management.

Keywords

Nephrolithiasis, kidney stone, herbal medicine, herbal-drug interaction, Iraqi herbalists

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Introduction

Nephrolithiasis, also known as kidney stone disease, is a common condition worldwide characterized by the formation of crystalline stones of varying composition within the urinary tract.[1] It is associated with a high incidence and recurrence rate in various regions of the globe'[2] as well as in the Africo-Asian region known as the stone-forming belt.[3] Iraq, as geographically positioned in this area, demonstrates a significant proportion of kidney stone disease among all patients with urologic conditions.[4,5] The recurrent nature of kidney stone disease directs patients to explore alternative herbal therapies arising from their belief in the safety of these products.[6] However, accumulating evidence suggests that the concurrent use of herbal remedies and conventional medications may result in clinically significant herb–drug interactions, particularly in elderly patients and those exposed to polypharmacy, where the use of multiple drugs increases the risk of adverse interactions.[7,8] In Iraq, the use of medicinal plants for nephrolithiasis management remains common.[9] A recent Scopus-indexed cross-sectional survey conducted in 2024 among Iraqi herbalists identified seven widely used medicinal plants that are frequently administered alongside conventional pharmacotherapy.[10] Despite their extensive use, systematic evaluations of potential herb–drug interactions involving these plants remain limited.

Therefore, this study aims to address this gap by examining available pharmacological, phytochemical, and clinical evidence related to potential drug–herbal interactions, to support healthcare professionals in improving patient safety and preventing adverse outcomes in nephrolithiasis management.

Review Methodology

This mini-review was designed to examine the herbal-drug interactions of commonly used medicinal herbs in managing kidney stones in Iraq, using relevant scientific data extracted from various sources, including PubMed, Web of Science, HerbMed, NatMed Pro (formerly Natural Medicines), UpToDate Lexidrug, Medline, and Embase. Different articles and studies were reviewed for the last 20 years and extended later than 2000 in some cases to gather relevant data due to the minimal studies available in this area; the search involved using the scientific names of the selected herbs in addition to keywords such as "drug-herbal interaction,"

[1]Al-Zahrawi University, College of Pharmacy, Karbala, Iraq

Corresponding Author:
Suhad Sami Humadi, Al-Zahrawi University, College of Pharmacy, Karbala, Iraq.
Email: Suhadsami04@yahoo.com

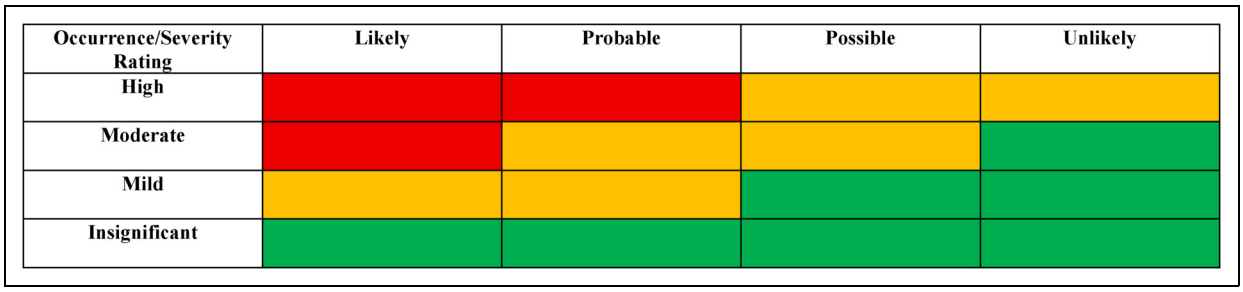

Figure 1. Stop light rating system adapted from the NatMed Pro database.
Interacting rate
MAJOR = Avoid use combination; contraindicated; strongly discourage patients from using this combination; a serious adverse outcome could occur.
MODERATE = Use with precaution or avoid use; warn patients that a significant interaction or adverse outcome could occur.
MINOR = Be aware that there is a chance of an interaction; advise patients to watch for warning signs of a potential interaction
Likelihood of Occurrence:
Likely = well-controlled human studies have demonstrated the existence of this interaction.
Probable = interaction has not been documented in well-controlled studies; however, interaction has been demonstrated in human studies or in controlled animal studies plus multiple case reports.
Possible = interaction has been documented in animal or in vitro research, or interaction has been documented in humans but is limited to case reports or conflicting clinical research.
Unlikely = interaction has been demonstrated in animal or in vitro research, but has been shown not to occur in humans.
SEVERITY:
High = life-threatening or requires medical intervention to prevent a serious adverse event.
Moderate = worsened clinical status and/or requires medication adjustment.
Mild = may cause minor clinical side effects. unlikely to require medication adjustment.
Insignificant = drug or supplement levels may be affected but will not cause clinical effects.

"adverse effects," "safety," "toxicity," "pharmacokinetic, pharmacodynamic interactions". The inclusion criteria were all studies and reviews, including in vivo and in vitro studies, as well as case reports. only English-based articles were included. Studies were selected based on their most recent publication and screened for their titles, abstracts, and full texts to obtain the necessary data. The tables demonstrating interactions were arranged and designed according to the NatMed Pro database stop light rating system, which is explained in Figures 1 and Table 1. This shows the occurrence/severity rating and explanations, in addition to the level of evidence used, respectively.

Evidence Synthesis

This study gathered data on the general information of the seven selected herbs, focusing on their potential drug-herbal interactions through a thorough review of a large number of articles across various resources. Results are represented in detail in Tables 1 to 7.

Adiantum capillus-veneris

The first plant in this review is *Adiantum capillus-veneris (A. capillus-veneris*) of the Adiantiaceae, commonly named Maidenhair fern. This herb is traditionally used in the management of respiratory disorders such as cold, asthma, cough, and pneumonia,[11,12] Several studies examined its pharmacological effects as an antioxidant, anti-inflammatory, antidiabetic, antibacterial anti cancer, antidiarrheal, and antispasmodic[13–16]; in addition to its role in hypothyroidism, and activity against testosterone-induced alopecia.[17,18] It acts as a lithiasis agent in the treatment of kidney stones, as demonstrated by several studies, and inhibits crystal aggregation, particularly of calcium crystals.[19–21] The phytochemical constituents responsible for the medicinal use of this plant appear to be more than 130 chemicals related to different chemical classes, namely triterpenoids, phyto steroids, flavonoids (quercetin, kaempferol, rutin and gallic acid), phenyl propanoids, and other phenolic compounds, such as

Table 1. Level of Evidence and Definitions Adapted from the NatMed Pro Database.

Level Letter	Definition
Level A	• High-quality randomized controlled trial (RCT) • High-quality meta-analysis (quantitative systematic review)
Level B	• Nonrandomized clinical trial • Nonquantitative systematic review • Lower quality RCT • Clinical cohort study • Case-control study • Historical control • Epidemiologic study
Level C	• Consensus • Expert opinion
Level D	• Anecdotal evidence • In vitro or animal study • Theoretical, based on pharmacology

Table 2. The Theoretical Drug-Herbal Interactions of *Adiantum capillus-veneris*.

Conventional Medications	Interaction mechanism	Outcome	Interact rating	Occurrence	Severity	Level of evidence	Ref.
Antihyperlipidemic medication	Decrease LDL, VLDL, TC Pharmacological modulation of pancreatic triacylglycerol lipase (PL) and α-amylase/ α-glucosidase (Pharmaco-dynamic interaction)	Potentiation of combined drug effect	Moderate	Possible	Moderate	D (In vitro or animal study)	[11,15,16]
Antidiabetic Medication	Decrease fasting blood glucose Possible through the presence of insulin-like substances in plants (flavonoids), which stimulate Beta-cells to produce more insulin (Pharmaco-dynamic interaction	Potentiation of combined drug effect (Hypo-glycemia)	Moderate	Possible	Moderate	D (In vitro or animal study)	[11,16,23]
Levothyroxine	Increase the level of T3 and T4, possibly through an increase in the level of Thyroid peroxidase (TPO), which catalyses the biosynthesis of thyroid hormone (Pharmaco-dynamic interaction	Potentiation of levothyroxine activity	Moderate	Possible (limited studies)	Moderate (limited studies)	D (In vitro or animal study)	[12,13,17]

coumarins, carotenoids, in addition to fatty acids, mucilage, and minerals.[11,17]

Regarding the plant's safety, limited studies have been conducted on the adverse effects and toxicity. In the evaluation of the acute toxicity in animals, mice administered *A. capillus-veneris* extract at doses up to 2 g/kg body weight exhibited no signs of mortality or apparent behavioral abnormalities, even at this elevated dose[17]; however, this plant is contraindicated in pregnancy due to its anti- implantation property[22]; and additional toxicological studies are still needed to certain their safety in humans.[17,22]

Drug-herbal interactions for this plant have not been investigated; despite extensive searching of all databases, the author reported theoretical interactions based on the plant's pharmacological activities derived from some studies, which are presented in "Table 2"; with monitoring tips presented in Figure 2.

Ammi visnaga

Ammi visnaga L. is a short biennial plant native to the Mediterranean area, commonly known as khella.[24] The oral decoction of khella has been utilized in both modern and traditional medicine for the treatment of various diseases and conditions, including cardiovascular disorders, respiratory conditions, kidney stones, and abdominal cramps, as well as antibacterial, antiviral, and antifungal activities.[25–27] Several studies have investigated the phytochemicals responsible for the pharmacological activity of the plant, including γ-pyrones such as visnadin, visnagin, and khellin, which exhibit vasodilating and bronchodilating effects, as well as coumarins, flavonoids, and essential oils, which demonstrate antibacterial and antioxidant properties.[25,28,29] The antilithiogenic activity of *Ammi visnaga* is primarily attributed to visnagin and khellin, which act through their vasodilating effect and interference with citrate metabolism, thereby inhibiting calcium oxalate crystallization.[27,30,31]

The oral dose of khella extract is standardized to 12% khellin. An average dose of *Ammi visnaga* is stated to be 20 mg of the khellin component per day.[27] Regarding plant safety, Studies are conflicting. Some studies have reported hepatotoxicity at high, prolonged doses, as well as an increase in liver enzymes.[27,32,33] Another study showed no effect on the liver in a 28-day trial on rats[34]; thus, it is essential to avoid using this herb in patients with liver function conditions and to monitor liver enzymes during use. Reports also stated its contraindication for use in pregnancy due to the uterine stimulant activity of khellin.[27,35] It was reported that the median lethal dose (LD50) was 3.6 g/kg for intraperitoneal administration and 10.1 g/kg for oral administration in rats.[36]

Drug-herbal interactions for khella have not been extensively investigated; some of the listed interactions are based on studies proving its pharmacological activity, while other interactions are based on the actual references as presented in "Table 3"; and monitoring tips in Figure 3.

Petroselinum sativum

Petroselinum sativum Hoffm. (synonyms of *Petroselinum crispum*), commonly known as parsley and belonging to the family Apiaceae, is a fragrant herb with a rich cultural history of use in traditional medicinal practices.[38] Parsley has its origins in the Mediterranean area but is now grown worldwide.[39] Traditionally, parsley has been used to manage various ailments,

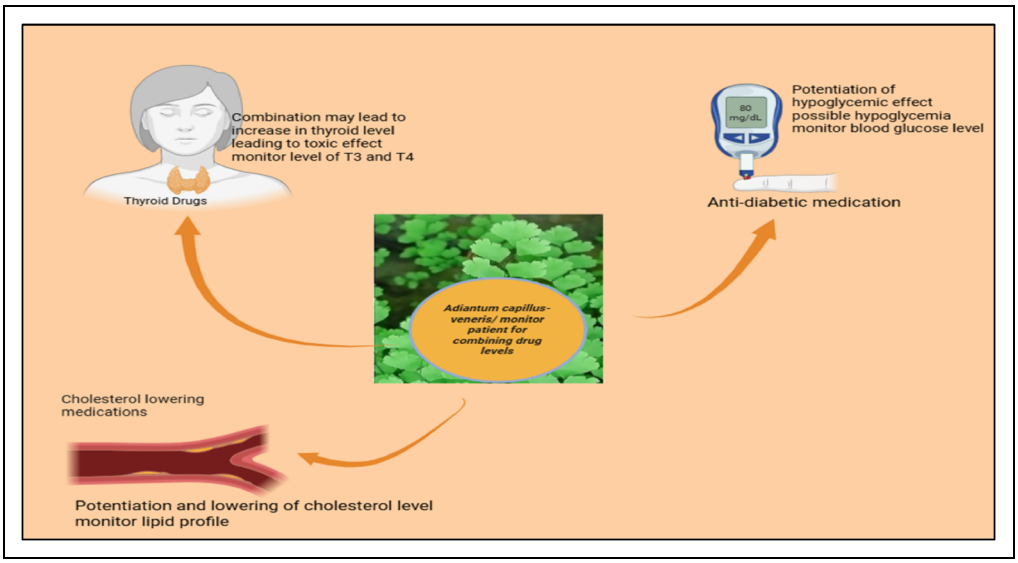

Figure 2. Drug-herbal interaction of *Adiantum capillus-vene* and monitoring tips (created using BioRender).

Table 3. The Drug-Herbal Interactions of *Ammi visnaga*.

Conventional Medications	Interaction mechanism	Outcome	Interact rating	Occurrence	Severity	Level of evidence	Ref.
Antihypertensive medication	Vasodilation, possibly through calcium channel blocking activity (Pharmacodynamic interaction)	Theoretically Potentiation of effect hypotension	Moderate	Possible	Moderate	D (In vitro or animal study)	[25,26]
Photosensitizing drugs (quinolone, sulfa, amitriptyline)	Khellin and the furocoumarin constituent are structurally similar to psoralen, thus increasing photosensitization (Pharmacodynamic interaction)	Increase skin sensitivity to sunlight	Moderate	Possible	Moderate	D (Anecdotal evidence)	[27]
Hepatotoxic drugs (Paracetamol, amiodarone, INH, carbamazepine, etc)	Increase liver transaminases enzymes (Pharmacodynamic interaction)	Potentiation of the hepatotoxic effect of combining drugs	Moderate	Possible	High	B (Nonrandomized clinical trial)	[32]
Digoxin	Visnadin has negative inotropic effects that might counter the effects of cardiac glycosides (Pharmacodynamic interaction)	Decrease the effectiveness of digoxin	Moderate	Possible	High	D (In vitro or animal study)	[35,37]

including diabetes, hyperlipidemia, hyperuricemia, renal disease, cardiovascular disease, and hypertension.[40] Several studies have reported the pharmacological activity of this herb, including antimicrobial, estrogenic activity, antioxidant, antiplatelet, antilithiatic, and diuretic properties.[41] The phytochemical constituents of parsley include flavonoids, furanocoumarins, carotenoids, essential oils (phenylpropane and terpene compounds as major constituents), phytoestrogens, and minerals.[40] The role of *Petroselinum sativum* as an antilithic agent is thought to be through reducing urinary calcium excretion and alkalinizing the urine, thereby decreasing the formation of stones.[42,43]

Regarding the safety of this herb, clinical data are lacking to provide dosing recommendations. In general, *Petroselinum sativum* is considered safe for use as a food, based on the U.S. Food and

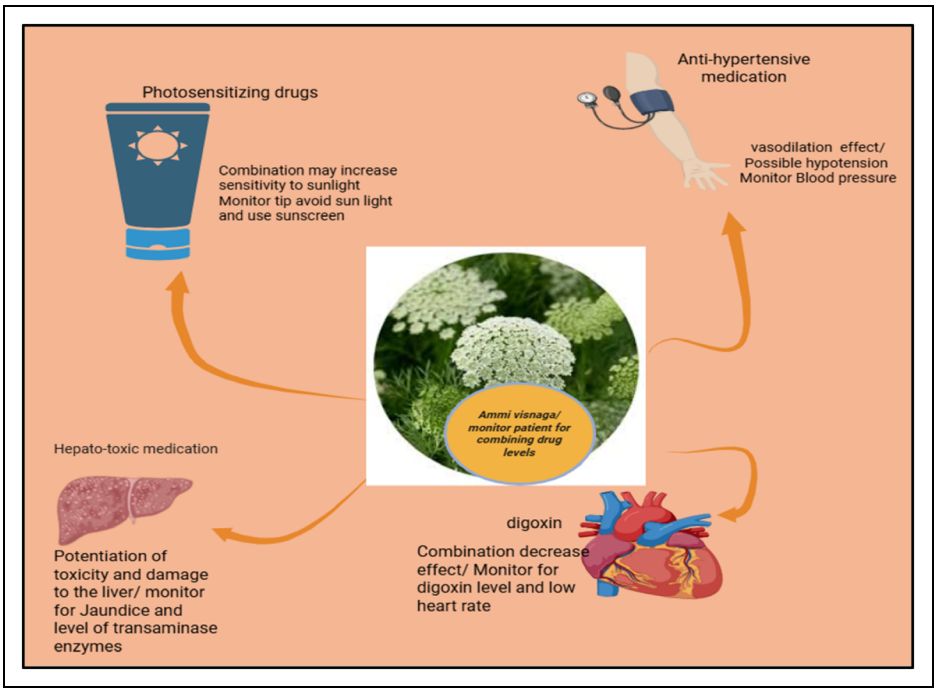

Figure 3. Drug/ herbal interaction of *Ammi visnaga* monitoring tips (created using BioRender).

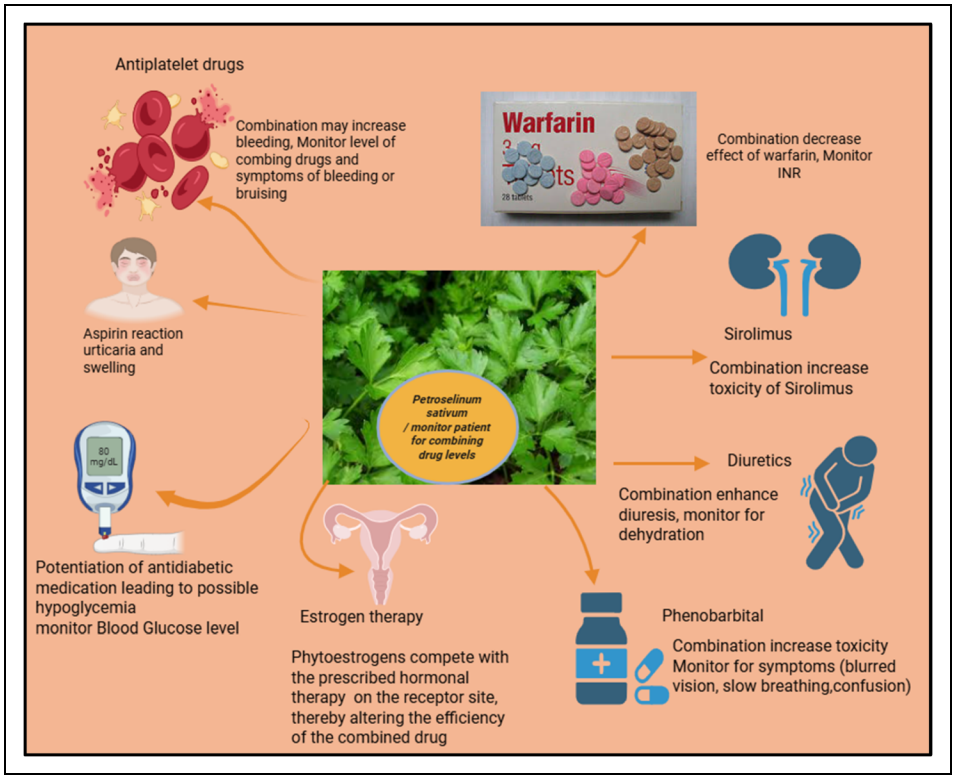

Figure 4. Drug/herbal interaction of *Petroselinum sativum* and risk management (created using BioRender).

Table 4. The Drug-Herbal Interactions of *Petroselinum sativum*.

Conventional Medications	Interaction mechanism	Outcome	Interact rating	Occurrence	Severity	Level of evidence	Ref.
Antiplatelets	Inhibition of platelet aggregation and an increase in bleeding time (Pharmacodynamic Interaction)	Risk of bleeding	Moderate	Possible	High	D (In vitro or animal study)	[49,50]
Warfarin	Parsley contains vit K (Pharmacodynamic Interaction)	Theoretically, high amounts of parsley leaf and root might decrease the effects of warfarin.	Moderate	Possible	High	D (Theoretical, based on pharmacology)	[35]
Estrogen	Parsley contains significant phytoestrogens that exhibit estrogen-like activity (Pharmacodynamic Interaction)	Theoretical possibility of modulating estrogen receptors	Moderate	Possible	Moderate	D (In vitro or animal study)	[48]
Sirolimus	Inhibit cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) enzymes involved in the metabolism and transport of sirolimus (Pharmacokinetic Interaction)	Increase level of sirolimus	Moderate	Possible	Moderate	D (Anecdotal evidence)	[51]
Substrate for cytochrome P450 1A2 (CYP1A2**)**	Inhibition of CYP1A2 Pharmacokinetic Interaction	Increase the level of substrate in the body	Moderate	Possible	Moderate	D (Theoretical based on pharmacology)	[52]
Aspirin	Aspirin might increase the severity of allergic reactions to parsley	Urticaria and swelling	Minore	unlikely	Moderate	D (Anecdotal evidence)	[53]
Antidiabetic medication	Lower glucose level: Inhibition of gluconeogenesis and direct stimulation of glycolysis may be involved in the mechanism of action of this plant (Pharmacodynamic Interaction)	Potentiation of antidiabetic effect (hypoglycemia)	Moderate	Possible	Moderate	D (In vitro or animal study)	[54,55]
Diuretics	Inhibiting the Na^+/K^+ pump decreases the reabsorption of sodium and potassium, resulting in an osmotic movement of water into the tubular lumen and promoting diuresis. (Pharmacodynamic interaction)	Parsley might enhance or interfere with the effects of diuretic drugs	Moderate	Possible	Moderate	D (Theoretical, based on pharmacology)	[56]
Phenobarbital	Inhibition of cytochrome P450 Pharmacokinetic Interaction)	Increase the duration of pentobarbital effects	Moderate	Possible	High	D (In vitro or animal study)	[57]
Methoxsalen	additive phototoxicity through parsley coumarins Pharmacodynamic Interaction)	Parsley may increase the photosensitizing effects of Methoxsalen	Moderate	Possible	Moderate	D (Theoretical, based on pharmacology)	[58]

Table 5. The Drug-Herbal Interactions of Arabic Gum (AG).

Conventional Medications	Interaction mechanism	Outcome	Interact rating	Occurrence	Severity	Level of evidence	Ref.
Amoxicillin	AG decreases the absorption of amoxicillin when taken concurrently (Pharmacokinetic Interaction)	Decrease the effect of amoxicillin	Moderate	Probable	Moderate	B (Lower quality RCT)	[68]
Naproxen	Fibers in AG increase the absorption of water-insoluble medications as naproxen (Pharmacokinetic Interaction)	Increase naproxen bioavailability	Moderate	Possible	Moderate	B (Lower quality RCT)	[68]

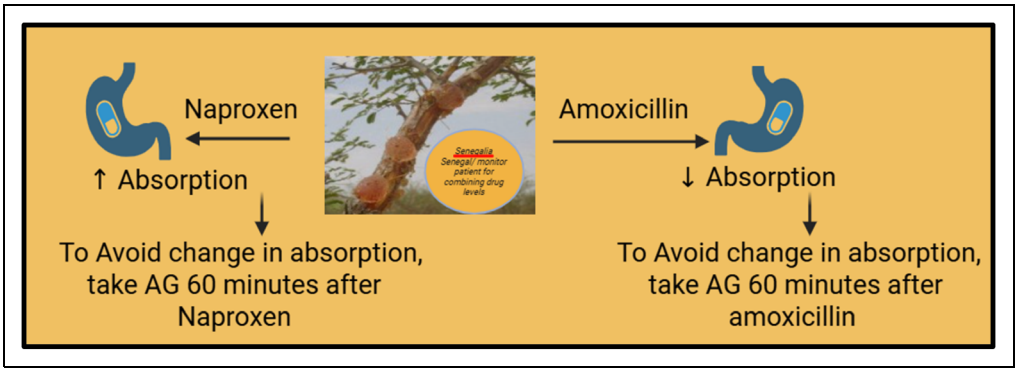

Figure 5. The drug-herbal interactions of Arabic Gum and monitoring tips (created using BioRender).

Drug Administration (FDA), and is likely safe when used in an appropriate amount for the short term with no toxicity reported.[44–47] A study performed in rats suggested a dose of 200–600 mg/kg body weight for the treatment of kidney stones.[42] However, High doses of parsley extract, as 1 g/kg body weight, may lead to substantial increases in liver enzymes, indicating hepatotoxicity. In addition, the increase in blood urea nitrogen and creatinine levels suggests kidney toxicity.[48] Data also confirmed the unsafe use in pregnancy and possible congenital malformation.[49]

Several drug-herbal interactions have been reported; detailed information is presented in "Table 4 and Figure 4".

Senegalia Senegal *(Acacia senegal)*

Senegalia Senegal, also known as acacia gum or Arabic gum (AG), is an edible constituent widely used as an excipient in both the food and industrial sectors. AG is a gummy exudate derived from the air-dried sap exuded from the branches and trunk of *Senegalia Senegal* of the family Leguminosae.[59] Plant species of this genus are naturally found in tropical and subtropical regions worldwide, including Africa, Australia, Central America, the Middle East, and South Asia.[60] A literature review revealed the traditional use of this plant in managing gastrointestinal tract conditions, promoting oral hygiene, and addressing disorders such as obesity and diabetes. Reports also suggest its role in hyperlipidemia, gingival inflammation, and antibacterial activities, as well as its therapeutic role in managing chronic kidney conditions.[59–62] Its role in urolithiasis is not directly related to its effect on kidney stones, but it is prebiotic, anti-inflammatory, and antioxidant, which plays an essential role in preventing kidney damage.[61,63] GA reduced plasma urea and creatinine levels, improved creatinine clearance, and significantly altered electrolyte excretion, resulting in improved overall water and electrolyte balance in healthy mice.[61] GA is a complex combination of polysaccharides and glycoproteins, which accounts for its water solubility and low viscosity. The main components are the arabinogalactan protein complex. This compound consists of several minerals, such as magnesium, calcium, and potassium salts of arabic acid.[62]

Regarding safety, AG is widely identified as safe for human utilization and has been classified as "Generally Recognized As Safe" (GRAS) by the FDA in the United States. It is also considered safe for use as a food additive by the European Food Safety Authority.[61,64,65] According to references, it is considered safe to be taken orally in a dose of up to 30 grams of powdered gum daily for 3 months[66,67]; however, reliable information on its use during pregnancy and lactation is not available.[65] Research is limited for typical dosing information.

The drug herbal interactions of AG are related to the suspending osmotic property in drug preparations. AG may enhance the bioavailability of water-insoluble drugs, such as naproxen, but reduce the absorption of polar drugs, like amoxicillin.[68] To avoid changes in absorption, it is advisable to take gum arabic 30–60 min after oral medications. These interactions are represented in "Table 5 and Figure 5."

Tribulus terrestris

Tribulus terrestris (TT), commonly known as "Al-Gutub" in Iraq, manuscriptto the family Zygophyllaceae. TT is a small

Table 6. The Drug-Herbal Interactions of Tribulus terrestris.

Conventional Medications	Interaction Mechanism	Outcome	Interact rating	Occurrence	Severity	level of evidence	Ref.
Antidiabetic medication	Inhibit the gluconeogenesis, influence glucose metabolism in normal mice, and cause a significant decrease in the blood glucose level of diabetic mice delay the absorption of glucose by inhibiting β-glucosidase in the small intestine and lowering the postprandial glucose levels (Pharmacodynamic Interaction)	Increase the risk of hypoglycemia.	Moderate	possible	Moderate	D (In vitro or animal study)	86,87
Metformin	Saponin content enhances the absorption of metformin from the intestine (Pharmacokinetic Interaction)	Increase the bioavailability of metformin	Moderate	Possible	Moderate	D (In vitro or animal study)	88
Antihypertensive medication	Inhibiting angiotensin-converting enzyme (ACE) (Pharmacodynamic Interaction)	Might increase the risk of hypotension.	Moderate	Possible	Moderate	D (In vitro or animal study)	89–92
Lithium	Reduce renal excretion of lithium (Pharmacokinetic Interaction)	Might increase the lithium	Moderate	Possible	Moderate	D (Theoretical, based on pharmacology)	93
Statins	Moderate inhibitor of cytochrome P450 3A4 (Pharmacokinetic Interaction)	Increase risk of Rhabdomyolysis	Moderate	Possible	Sever	D (In vitro or animal study)	94

annual plant that grows in Mediterranean, subtropical, and desert climate regions worldwide, including India, China, the southern United States, Mexico, Spain, and Bulgaria.[69,70] Traditionally used as an aphrodisiac, in addition to other folk uses, including the management of kidney disorders, antioxidant, anti-inflammatory, respiratory, and skin conditions[71,72]; it has also shown effectiveness as an antibacterial, antidiabetic, and cardioprotective agent.[71,73–75] Its role as an antilithiatic was documented by the fact that TT extract suppresses the formation and growth of calcium oxalate crystals, as well as having a protective effect at the cellular level.[69,76] A wide range of bioactive and chemically diverse phytoconstituents has been associated with the various uses of TT. These include steroidal saponins, flavonoids, tannins, terpenoids, glycosides, amide derivatives, amino acids, protein, polyphenol carboxylic acids, and alkaloids.[69,72]

For the safety of TT extract, studies have shown that oral doses of 750–1500 mg per day are apparently safe for up to 90 days of use, as well as the powdered TT fruits in an oral dose of 6 g per day for 2 months; however, there is no documentation for its safety beyond three months of treatments.[77–80] Studies have found that chronic use of large doses can adversely affect liver and kidney function.[81] While there are no available studies on the use during lactation, its use in pregnancy is not recommended due to its effect on fetal development.[82]

Literature reveals that TT has a hormonal effect and is therefore used as an aphrodisiac, although drug interactions with hormones have not been investigated. Studies suggest its careful use due to its potential to disrupt the endocrine system.[83–85] Other studied interactions are illustrated in "Table 6 and Figure 6".

Trigonella foenum-graecum

Trigonella foenum-graecum, commonly known as "halba" or "fenugreek," is an annual plant of the family Leguminosae. It is grown in the Mediterranean region, Western Asia, and Southern Europe, and is a well-known spice in human food, as well as one of the oldest botanical herbs used in ancient history.[95,96] Traditionally, fenugreek has been used to treat different conditions, including digestive disorders, skin inflammation, as a demulcent, a lactation stimulant, and a laxative.[95,97] Several pharmacological properties have been documented for fenugreek, including antioxidant, anti-inflammatory, antihyperlipidemic, antidiabetic, antibacterial, and anticancer effects.[98,99] These medicinal properties are attributed to the bioactive compounds, including alkaloids (trigonelline, choline), steroidal sapogenins (yamogenin, diosgenin, smilagenin, sarsasapogenin), saponins, flavonoids (quercetin, rutin, vitexin), fiber, lipids, and amino acids.[100] Its role in kidney stone prevention is attributed to the ability of the seed extract to reduce and prevent the growth of calcium oxalate crystals, a mechanism thought to be mediated through diuretic and antioxidant activity, thereby lowering the risk of stone formation.[100,101]

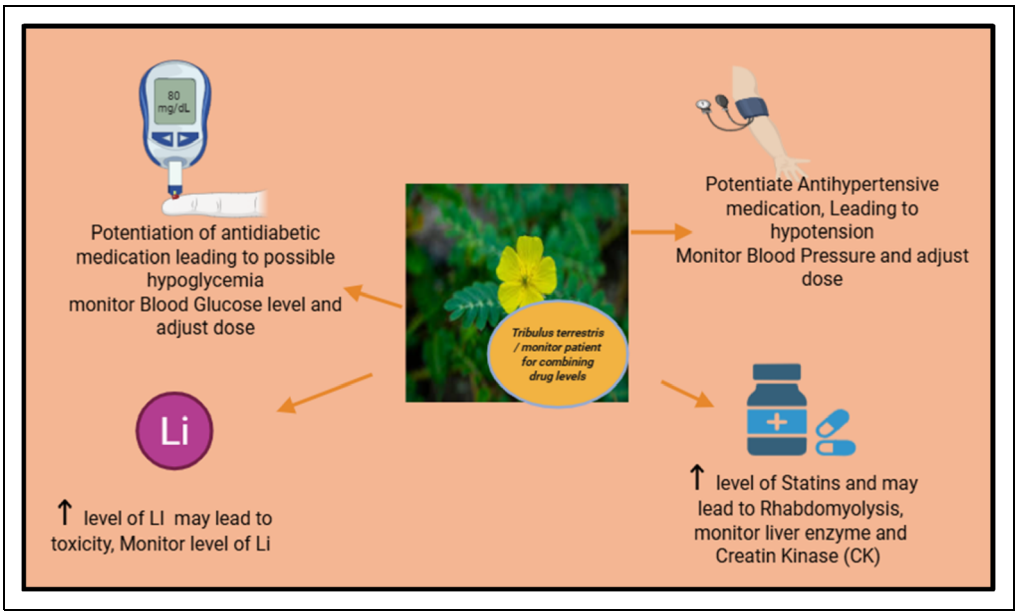

Figure 6. The drug-herbal interactions of *Tribulus terrestris* and monitoring tips (created using BioRender).

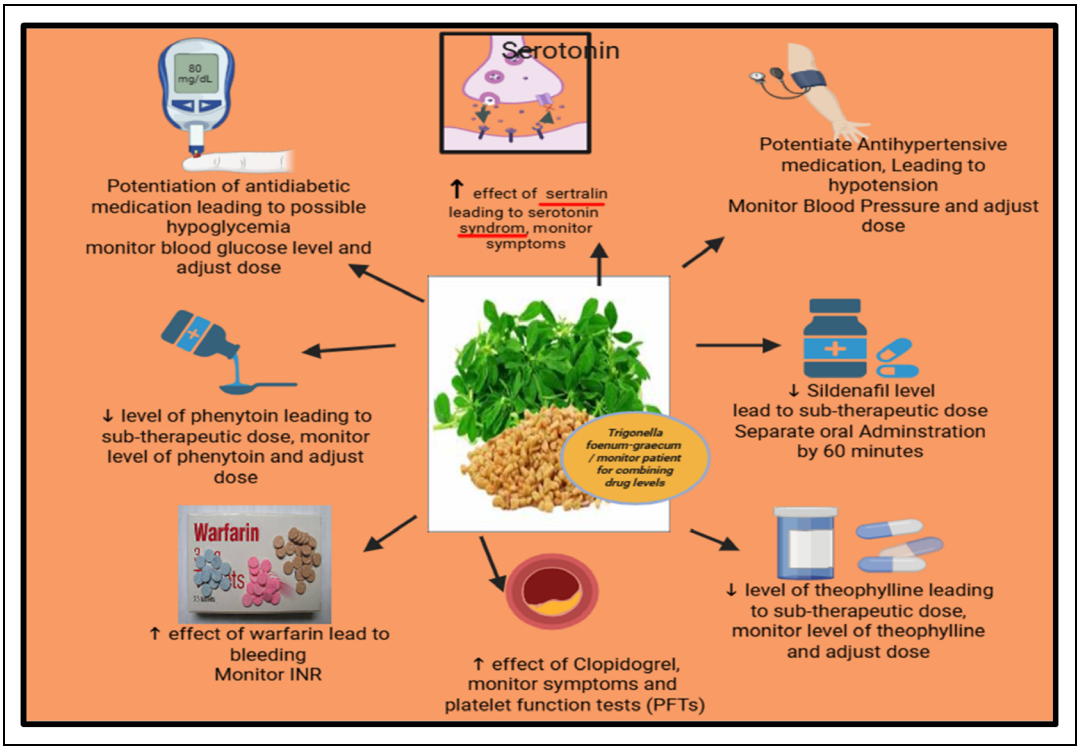

Figure 7. The drug-herbal interactions of *Trigonella foenum-graecum* and monitoring tips (created using BioRender).

In regard to the safety of this herb extract, references suggested its safety when used in an appropriate amount, which is represented by fenugreek seed powder in an oral dose of 5–10 grams daily for up to 3 years, and fenugreek seed extract in a dose of 1 gram daily for up to 3 months is considered safe.[102–106] A study based on an animal model suggested that oral doses for humans should not exceed 350 mg/kg (21 g per 60 kg) to prevent accidental overdose.[107]

The use of fenugreek during pregnancy in an amount greater than that found in food has potential oxytocic and uterine stimulant activity, and cases have been reported for congenital malformations.[107,108] The use during lactation is possibly safe if used

Table 7. The Drug-Herbal Interactions of Trigonella foenum-graecum.

Conventional Drug	Mechanism of interaction	Outcome	Interac rating	occurrence	Severity	level of evidence	Ref.
Anti diabetic Medication	Fenugreek seeds stimulate insulin release from beta cells and improve insulin signaling, glucagon suppression, and delay gastric emptying (Pharmaco-dynamic Interaction)	Increase the risk of hypoglycemia.	Moderate	Probable	Moderate	B (Nonrandomized clinical trial)	[95,112]
Antihypertensive medication (metoprolol, amlodipine, losartan)	Decrease systolic blood pressure (mechanism possibly through Inhibition of CYP3A4 and CYP2C9 pharmacokinetic interaction)	Theoretically, fenugreek seed might increase the hypotensive effects of combined drug	Moderate	Probable	Moderate	B (Nonrandomized clinical trial)	[113–116]
Sildenafil	Fenugreek has the potential to affect sildenafil absorption (Pharmacokinetic Interaction)	Theoretically, concurrent use of sildenafil and fenugreek might reduce the levels and therapeutic effects of sildenafil.	Moderate	Possible	Moderate	D (In vitro or animal study)	[117]
Theophylline	Modulating CYP1A2 (Pharmacokinetic Interaction)	Theoretically, fenugreek may reduce the levels and clinical effects of theophylline.	Moderate	Possible	Moderate	D (In vitro or animal study)	[118]
Phenytoin	Increased clearance of Phenytoin (Pharmacokinetic Interaction)	Theoretically, fenugreek might decrease plasma levels of phenytoin.	Moderate	Possible	Moderate	D (In vitro or animal study)	[119]
Clopidogrel	Theoretically, fenugreek may have antiplatelets activity due to the presence of coumarin -like phytochemicals (Pharmacodynamic Interaction) more over Fenugreek can alter theCYP450 thereby altering level of Clopidogrel (Pharmacokinetic interaction)	Alter the effect of Clopidogrel and prolonged bleeding time	Moderate	Possible	Moderate	D (In vitro or animal study)	[120]
Warfarin	Some fenugreek constituents have antiplatelet effects coumarin -like phytochemicals (Pharmacodynamic Interaction)	Theoretically, fenugreek may have additive effects with warfarin, potentially increasing the international normalized ratio (INR).	Moderate	Possible	High	D (Anecdotal evidence)	[121,122]
Sertraline	Fenugreek may potentiate the serotonergic effect of sertraline due to its phytoconstituent as 4-hydroxyisoleucine (Pharmacodynamic Interaction	Serotonin syndrome	Moderate	Possible	Moderate	D (In vitro or animal study)	[123]

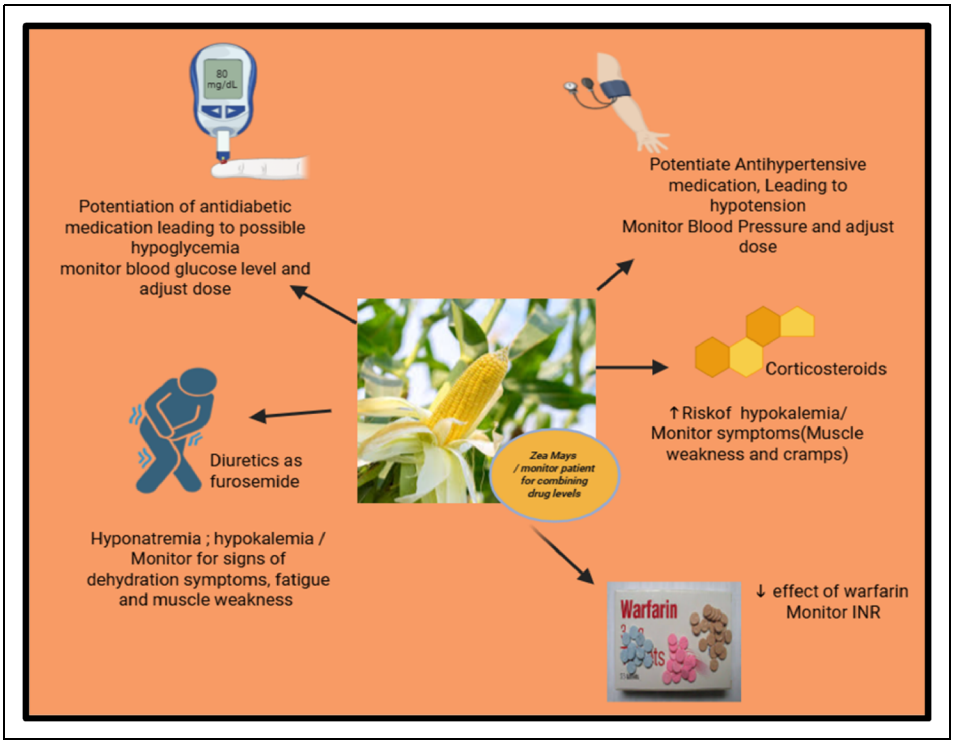

Figure 8. The drug-herbal interactions of *Zea mays* and monitoring tips (created using BioRender).

for a short term, although most available clinical data lack testing on lactating women or nursing infants.[109,110] Some studies suggest that a dose of 1725 mg, administered three times daily for three weeks, may be considered safe.[111]

The drug herbal interaction of fenugreek is represented in "Table 7 and Figure 7."

Zea mays *(Corn Silk)*

Corn silk (CS), the elongated stigma of the female flower of *Zea mays* (F. Poaceae), is considered the third most widely grown crop worldwide and a primary cereal in various countries and regions, including Southern and Eastern Africa, Central America, and Mexico.[124] It is a widely available agricultural byproduct often considered a waste product and traditionally used in the management of diabetes, obesity, prostate disorders, as a diuretic, and kidney disorders.[125] Recent research has documented the pharmacological activities of CS extract, including antioxidant, anti-inflammatory, anticancer, hypotensive, antidiabetic, hypolipidemic, antibacterial, antifatigue, antidepressant, and anticoagulant properties.[125–128] The bioactive components of CS are reported to include polyphenolic compounds, flavonoids, tannins, alkaloids, volatile oils, steroids (sitosterol and stigmasterol), saponins, proteins, various minerals, and vitamins.[128–130] Regarding the antiurolithiatic activity, a recent study reported that the mechanism involved both diuretic activity and alkalinization of urinary pH, thereby preventing the formation of calcium oxalate crystals. Moreover, CS antibacterial and antioxidant activity aid in kidney protection.[131]

Concerning the safe consumption of this herb, references suggest that corn silk and its extract, when used in amounts found in food, have a Generally Recognized as Safe (GRAS) status in the US.[44] Recent studies showed that an oral dose of CS extract at 500 mg/kg body weight is generally safe, but doses equal to or higher than 2000 mg/kg for longer durations is considered toxic and should be avoided; thus, the study recommended a safe dose of less than 1000 mg/kg body weight for the therapeutic purposes.[128,132] The use in pregnancy in larger amounts is considered unsafe due to the uterine stimulant effects of CS[133]; however, there is no available data on its use during lactation.

The drug-herbal interaction reported in the literature is demonstrated in "Table 8 and Figure 8."

Clinical Implications of Herb–Drug Interactions

The prevalence of botanical use of herbs has increased significantly worldwide, with a public usage rate as high as 80%, according to the literature.[141] People culturally believe in the safety of these natural products, and this belief has extended from early civilizations to the present day.[142–144] Patients often do not disclose their use of supplements and herbal products to their healthcare providers due to this belief and a lack of awareness of potential interactions that could occur with their current disease state or conventional medications.[145,146] This practice exposes patients to unwanted side effects and reactions that put them at risk and hinder the management of their condition by primary care personnel. Several research studies have

Table 8. The Drug-Herbal Interactions of *Zea mays*.

Conventional Drug	Mechanism of interaction	Outcome	Interaction rating	Occurrence	Severity	level of evidence	Ref.
Hypoglycemic medication	CS inhibited JNK-IRS-GLUT4 signal transduction in skeletal muscle via antioxidative effects. Inhibition of the α-amylase activity and α-glucosidase activity, increases hepatic glycogen by inhibiting glucokinase Inhibiting gluconeogenesis (Pharmacodynamic Interaction)	Hypoglycemia	Moderate	Possible	Moderate	D (Theoretical based on pharmacology)	134–136
Antihypertensive medication	Potassium-induced natriuresis; also, via Angiotensin-converting enzyme (ACE) inhibitory phytopeptide in corn silk (Pharmacodynamic Interaction)	Potentiation of antihypertensive drugs leading to hypotension	Moderate	Possible	Moderate	D (Theoretical based on pharmacology)	137–139
Corticosteroids	Potassium-induced natriuresis and diuresis by corn silk extract will counteract the sodium-retaining effects of mineralocorticoids (Pharmacodynamic interaction)	Increase the risk of hypokalemia.	Moderate	Possible	High	D (Theoretical based on pharmacology)	137
Diuretics	Increases urine volume and promotes the urinary excretion of sodium and potassium (Pharmacodynamic interaction)	Hyponatremia ; hypokalemia and dehydration.	Moderate	Possible	High	D (Theoretical based on pharmacology)	137
Warfarin	Contain Vitamin K phytochemicals that antagonized the effect of warfarin (Pharmacodynamic interaction)	May reduce the anticoagulant effect of warfarin	Moderate	Likely	Mild	D (Theoretical based on pharmacology)	140

addressed this risk and discussed herbal drug interactions in general[147,148]; however, to the author's knowledge, there have been limited studies that specifically examined herbal interactions in the management of kidney stones. Thus, this review aimed to discuss the potential drug-herbal interactions for commonly used herbs in the management of urolithiasis in Iraq, as this condition is one of the major urological conditions in this region.[10] This review is crucial for clinicians and pharmacists to understand the potential interactions between patients' medications and herbal products, thereby preventing adverse effects on patient health and providing guidance on monitoring and managing these interactions. Seven medicinal herbs were selected for this review based on a previous survey on the most commonly used herbs in the management of kidney stones.[10] These herbs were selected based on the highest use value (UV) reported in the mentioned study. An extensive review of various data sources was then conducted, examining related studies in this context. Some of the interactions were based on the theoretical explanation of the pharmacological properties of the studied herbs, such as *A. capillus-veneris and Ammi visnaga*, as there were limited studies regarding the safety of consuming these products with other medications, as compared to the rest of the studied herbs, where more articles were documenting their interactions. The results showed that the most frequently interacting medications were related to cardiovascular disorders (anticoagulants and antihypertensive medications) and Diabetes (antidiabetic medications), which are the two most common disorders affecting patients worldwide,[149] with some drugs having low therapeutic indices (as warfarin and digoxin).[150] These interactions would affect patients of different age levels, particularly the elderly, due to their age-associated physiological alterations in organ systems, which in turn significantly modify drug pharmacokinetics and pharmacodynamics, thus imposing an even greater risk of harmful effects.[151]

The literature survey also explained the mechanism of drug-herb interactions as cited in the Tables (2-8), but the exact mechanisms behind many reported interactions between drugs and herbal medicines remain largely unclear.[152] This may be due to the fact that herbal products consist of different phytochemicals that exert varying effects, making it challenging to evaluate these interactions based on the percentage of these chemicals in the studied herb.[150,153] The chemical metabolite profiles are also influenced by plant species, chemotype, cultivation conditions, harvesting practices, extraction, and preparation methods.[152] The difficulty extends to the fact that most herbs are not used as a single entity but rather as mixtures of herbs in a single herbal product, thus predicting the exact influence on concurrent medication use is difficult. Some of the listed interactions in this review were related to the pharmacokinetic interactions, such as the modulation of drug absorption (as *Senegalia Senegal, Tribulus terrestris*, and *Trigonella foenum-graecum*) or metabolism through inhibiting CYP450 (*Petroselinum sativum, Tribulus terrestris, Trigonella foenum-graecum*) or alteration in drug excretion (*Tribulus terrestris, Trigonella foenum-graecum, and Zea mays*); other interactions are pharmacodynamic, which is

represented by the synergistic effect of the herbal products, thus potentiate the effect of the concurrent drug.

Conclusion

This review highlights potential drug-herbal interactions associated with the use of commonly used medical herbs in the management of kidney stones. It also emphasizes raising awareness among healthcare practitioners as well as the public regarding the possible potential risks of using herbs concurrently with conventional therapy and highlights the importance of reporting any interactions or adverse reactions that may result from this use.

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ORCID iD

Suhad Sami Humadi https://orcid.org/0000-0002-0073-5168

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