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Review Article

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CYP3A4–associated food drug interactions: The impact of combined intake of alprazolam with cranberry and pomegranate juice treating anxiety caused by kidney stones

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ABSTRACT

Nephrolithiasis is a common disease and incurs a significant burden on the health care system globally. Patients with kidney stones can be treated with natural remedy such as cranberry, pomegranate, and grape juice. Patients with kidney stone experience anxiety and insomnia as a result of the pain caused by the stones. As a result, physicians may prescribe anxiolytics to treat anxiety, among which alprazolam is a commonly prescribed medication. Meanwhile, cranberry and pomegranate juice are prescribed by many herbal specialists for the treatment of renal calculi. The enzyme CYP3A4 primarily metabolizes alprazolam, while fruit juices such as cranberry and pomegranate juices are potent inhibitors of CYP3A4. Therefore, there could be a drug-food interaction between alprazolam and cranberry and pomegranate juices when consumed concomitantly. A detailed pharmacodynamic and pharmacokinetic investigation is required to ascertain the food-drug interaction between alprazolam, cranberry, and pomegranate juice to avoid the possible toxicity of alprazolam. This review article provides insights about the possible CYP3A4-associated drug interactions between alprazolam and juices of cranberry and pomegranate, for the safe and effective usage of alprazolam in treating anxiety disorders caused by kidney stones.

KEYWORDS: Alprazolam; Cranberry juice; Kidney stones; Anxiety; Pomegranate juice

1. Introduction

In clinical practice, drug-food interactions are a serious problem. By interfering with pharmacokinetic processes including absorption and excretion, foods can impact the drug efficacy. Pharmacologic and pharmacodynamic pathways influence drug-food interactions by modifying drug effects. Similarly, several medicines can influence food intake, absorption, metabolism, and utilization. A variety of medications, including anti-neoplastic medicines, have been reported to suppress appetite, resulting in decreased food intake and nutritional deficit. To prevent substantial drug-food interactions, healthcare practitioners such as physicians, chemists, and dieticians must recognize and collaborate in identifying and reporting such interactions. By optimizing treatment effects and preserving optimal nutritional status, minimizing unfavorable drug-food interactions would improve patient care[1].

2. Curative effect of cranberry and pomegranate juices on kidney stones

Cranberry juice possesses antilithogenic characteristics and should be considered as a conservative therapy approach for controlling calcium oxalate urolithiasis[2]. Moreover, a study have demonstrated that pomegranate juice possesses antioxidant characteristics that can potentially mitigate the development of kidney stones by diminishing oxidative stress inside the kidneys. Research suggests that the presence of citric acid in cranberry may have the ability to dissolve specific forms of kidney stones[3].

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The presence of citric acid can elevate urinary citrate levels, hence impeding the development of calcium oxalate stones and potentially aiding in the dissolution of pre-existing stones. The antibacterial properties of cranberry juice are widely recognized for their effectiveness in preventing urinary tract infections (UTIs). UTIs can potentially contribute to the development of some types of kidney stones. Consuming cranberry juice may indirectly lower the risk of stone formation by preventing UTIs. Maintaining proper hydration is essential in the prevention of kidney stones, since adequate fluid consumption can aid in the elimination of compounds that contribute to the development of stones. Consuming cranberry and pomegranate drinks may increase fluid intake, therefore facilitating hydration and potentially diminishing the likelihood of developing kidney stones. Both cranberry and pomegranate juices include compounds, such as anthocyanins and flavonoids, that have anti-inflammatory properties. Consuming these liquids may help mitigate chronic inflammation in the kidneys, hence reducing the likelihood of kidney stone formation. Cranberry juice contains a high concentration of proanthocyanidins, which have demonstrated the ability to inhibit bacterial attachment to the urinary tract walls. Proanthocyanidins indirectly mitigate the risk of specific forms of kidney stones by decreasing the possibility of UTIs. Cranberry juice contains quinic acid, which has been demonstrated to prevent the development of calcium oxalate crystals, a prevalent constituent of kidney stones.

Despite the widespread belief that cranberries improve urinary tract health by making urine more acidic, research shows that they have an anti-adhesion mechanism against certain urinary pathogens[4]. Cranberry juice is widely used as a natural remedy for preventing renal calculi, which are common among women and the elderly. Furthermore, cranberry juice has been proven effective in lowering bladder infection in women with repeated incidents and bacteriuria in the elderly. Clinical advantages are linked with long-term use and frequent ingestion[5]. Acidifying urine is necessary to avoid the formation of calcium phosphate and struvite stones. Cranberry juice has the ability to lower urine pH levels without causing any adverse consequences that may result from consuming acidic substances. Pomegranate aids in maintaining urinary health by regulating the concentrations of calcium, phosphates, and oxalates in the blood, which are known to contribute to the formation of kidney stones. The use of cranberry juice resulted in a 50% statistically significant reduction in urine ionized calcium levels in patients with renal stones[6]. Furthermore, research conducted on individuals aged 18-70 years old with kidney stones who were administered a 100 mg dosage of pomegranate extract for a period of 90 d demonstrated the body's capacity to inhibit the development of stones[7].

The arils of the fruit of pomegranates are abundant in organic acids, sugars, minerals, vitamins, and polyphenols, which exhibit antioxidant properties. Furthermore, flavonoids are the primary polyphenols found in fruits, including condensed tannins and hydrolysable tannins. Pomegranates contain hydrolyzable tannins, specifically ellagitannins and gallotannins. The main hydrolyzable tannin found in pomegranates is punicalagin. The substantial antioxidant capabilities of cranberries can be attributed mostly to their abundant phytochemical composition, which encompasses three categories of flavonoids (flavonols, anthocyanins, and proanthocyanidins)[8], catechins, hydroxycinnamic and other phenolic acids, as well as triterpenoids. The fruits contain high levels of antioxidants such as anthocyanins and proanthocyanins, along with salicylic acid and vitamin C.

3. Anxiety caused by kidney stones and its treatment

Kidney stones in themselves cannot directly induce anxiety, but the pain and discomfort linked to kidney stones can contribute to the experience of stress and anxiety. Kidney stones can cause significant symptoms such as excruciating pain, nausea, vomiting, and hematuria. The presence of these symptoms, along with the unpredictability of the stone's passage and the possibility of it happening again, can have a profound psychological impact on individuals. The anxiety could be associated with the apprehension of encountering another distressing incident, apprehensions about the efficacy of the treatment, or worry about potential problems. Moreover, the uncertainty around the timing of kidney stone passage and the lack of control over the situation might lead to increased levels of anxiety.

According to Barlow, anxiety is a future-oriented mental state related to preparing for possible imminent unfavorable occurrences[9]. Anxiety disorders are a group of extremely common mental health conditions that can impair daily functioning and well-being[10]. They can occur in conjunction with other mental health disorders, such as depression[11]. The most prevalent mental health condition in the world is anxiety[12]. According to epidemiological research, 50% of anxious people have sleep problems, including insomnia, which can worsen anxiety[13]. Social anxiety disorder, a common anxiety disorder, generally develops early and causes depression and drug abuse[14]. In human and animal models, age, genetics, and environment affect gender differences in anxiety and depression. A frequent illness, generalised anxiety disorder, causes anxiety and worry over unrelated events, which might exacerbate in particular situations. This illness affects twice as many women as men. Generalized anxiety disorder symptoms include threat, restlessness, irritability, tension, sleep problems, palpitations, dry mouth, and perspiration[15]. Anxiety, sadness, addiction, and personality disorders often co-occur[16].

3.1. Treatment for anxiety

In clinical practice, It is becoming increasingly typical to overuse benzodiazepines to treat anxiety, mood, and sleep issues. GABAergic medications, in particular benzodiazepine drugs, have consequences, interaction with other medicinal products, and the chances to cause addiction. GABA-boosting dietary supplements

pose similar and distinct risks. There are safe recommendations for patients for natural, non-chemical anxiety remedies[17]. Alprazolam is a triazolobenzodiazepine with a high potency that has been approved by the US Food and Drug Administration in order to cure panic and anxiety disorders. Alprazolam is transformed in the liver by a process called hepatic microsomal oxidation, resulting in the formation of two main metabolites: 4 and alpha-hydroxy alprazolam. The principal enzyme responsible for metabolizing alprazolam is cytochrome P450 (CYP) 3A4[18]. Managing the symptoms and indications of anxiety poses a persistent challenge in clinical practice. When choosing between treatment options, it is important to consider anxiety in relation to its environmental, psychological, and biological factors[19]. Alprazolam exhibits antidepressant properties, making it a potentially beneficial option for individuals with anxiety associated with depression[20]. The majority of near-fatal alprazolam instances are the result of polydrug use. Drugs that inhibit or increase CYP3A4 have an effect on alprazolam. Potent CYP3A inhibitors may raise alprazolam plasma concentrations, increasing adverse effects[21]. The adverse effects of benzodiazepines are extensively documented and include both subjective sedation and objective cognitive impairment. This results in tangible issues, such as a greater vulnerability to accidents. Tolerance develops for most of these side-effects, except for memory impairments. These dangers are directly proportional to the dose. Paradoxical reactions characterized by increased anxiety and anger are infrequent and unpredictable. Drug interactions primarily pertain to other sedative substances, particularly alcohol. The safety of benzodiazepines in cases of overdose has been subject to investigation[22].

Given the widespread need for natural supplements that alleviate daily stress, there is a diverse array of items readily accessible in the market. The customer is advised to differentiate between the sedative properties of sleep aids and the anxiety-reducing benefits of anxiolytics. Furthermore, even if the anxiolytic properties of GABA can be consistently proven, the precise mechanism by which these supplements exert their effects remains uncertain. However they may cause risk of sedation and motor in-coordination as that of Benzodiazepines[23].

4. CYP3A4 enzyme

Patients diagnosed with kidney stone illness experienced increased stress levels when they passed two or more stones per year and exhibited symptoms. Sex, age, and unemployment among females may also be factors contributing to a state of stress in this group of people[24]. Because the CYP3A4 enzyme metabolizes the bulk of clinically used medications (60%), it is frequently implicated in herb-drug interactions through changes in enzyme activity and/or expression[25]. A large number of essential medications have been recognized as CYP3A4 substrates, inducers, or inhibitors. The potential impact on drug disposition, effectiveness, or toxicity resulting from the concurrent administration of these compounds with a recognized CYP3A4 substrate is contingent upon the drugs' capacity to function as CYP3A4 inducers, inhibitors, or substrates[26]. Among benzodiazepines, CYP3A4 mostly metabolises alprazolam, triazolam, brotizolam, and midazolam, while quazepam, diazepam, and flunitrazepam are partially metabolized. Drugs that inhibit/induce the metabolism of benzodiazepines by acting on CYP3A4 cause side effects or diminish the therapeutic efficacy of BZD's. As a result, combining the two classes of medicines should be avoided, and benzodiazepines dose should be adjusted if it is inevitable[27]. The role of CYP3A4 in clinical practice was highlighted by reports of cardiac arrhythmia from combining nonsedating antihistamine terfenadine with antifungal agents like ketoconazole or antibiotic erythromycin. This potentially lethal cardiac arrhythmia, "torsades de pointes," is a supraventricular tachycardia characterized by recurrent twisting of QRS complexes and rates of 200-250 beats/min. It can lead to ventricular fibrillation. Terfenadine and astemizole (prodrugs) nonsedating antihistamines, can produce cardiotoxicity if metabolism is blocked. CYP3A4 converts them into less cardiotoxic, powerful antihistamines. Both ketoconazole and erythromycin serve as selective CYP3A4 inhibitors. Ketoconazole is a strong inhibitor.

4.1. Inhibitors of CYP3A4

Inhibitors of CYP3A4 activity almost invariably raise plasma concentrations of CYP3A4 substrate drugs. Some drugs, such as itraconazole, ketoconazole, and clarithromycin, are very powerful CYP3A4 inhibitors that may significantly reduce CYP3A4 activity.

4.2. Inducers of the CYP3A4 enzyme

Drugs that boost CYP3A4 activity are known as CYP3A4 inducers. It should be noted that the CYP3A4 enzyme is extremely sensitive to enzyme inducers and that there may be considerable decrease in the plasma concentrations of the CYP3A4 substrate. For instance, rifampin, a potent CYP3A4 inducer, may cause a 90% decrease in the serum levels of CYP3A4 substrates including buspirone, triazolam, and verapamil in a patient [28].

5. Possibility of drug interactions between alprazolam with cranberry and pomegranate

Alprazolam, a widely used anxiolytic and hypnotic drug for several cases of generalized and specific anxieties is mainly metabolized by the CYP3A4 enzyme. Renal calculi often lead to severe pain and nocturnal sleep disturbances that may lead to insomnia and anxiety. Traditionally cranberry and pomegranate juices are widely used to cure kidney stones. As anxiety may be associated with kidney

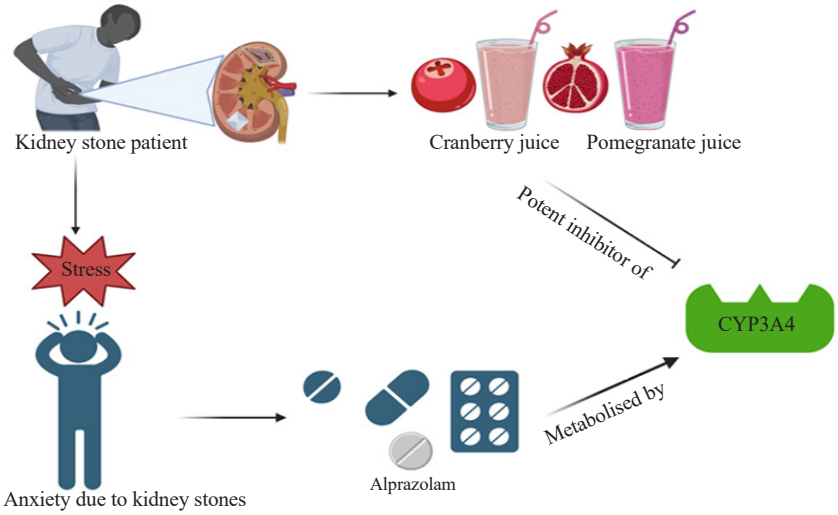


Figure 1. Food-drug interaction between alprazolam and juice of cranberry and pomegranate.

stones patients may also use alprazolam. However, if alprazolam is used concomitantly with cranberry and pomegranate juices (inhibitors of CYP3A4), it may lead to inhibition of CYP3A4 and enhanced levels of alprazolam (alprazolam toxicity). This drug interaction must be explored scientifically using pharmacodynamic and pharmacokinetic models.

Cranberry juice includes furanocoumarins, which have the ability to suppress the activity of CYP3A4 enzymes. This inhibition has the potential to elevate the concentration of alprazolam in the body, resulting in intensified sedative effects and an elevated risk of adverse effects such as sleepiness, dizziness, and poor coordination. Nevertheless, the clinical importance of this interaction is not firmly established and can differ based on individual characteristics such as the quantity of cranberry juice ingested and the patient's overall health condition.

Furthermore, pomegranate juice consists of polyphenols, which have demonstrated the ability to inhibit the activity of CYP3A4[29]. Consuming pomegranate juice with alprazolam may raise the blood levels of alprazolam, resulting in stronger sedative effects and a greater possibility of undesirable reactions.

The process of this drug-food interaction is illustrated by Figure 1.

6. Conclusions

In conclusion, the potential interaction between alprazolam, a commonly prescribed medication for anxiety disorders, and kidney stone treatments such as cranberry and pomegranate juices requires careful consideration. While there is no substantial evidence to suggest direct harmful interactions between alprazolam and these juices in the context of kidney stone treatment, it is essential to approach this combination with caution. Cranberry and pomegranate juices are often utilized for their potential health benefits, including assisting in kidney stone prevention and management. The extent of the interaction between alprazolam and cranberry or pomegranate juice is influenced by several factors, including as the quantity and frequency of juice consumption, individual variations in drug metabolism, and overall health condition. Although the combination may not be highly risky for everyone, those who are taking alprazolam should exercise caution when ingesting cranberry or pomegranate juice and should see their healthcare professional about any potential issues. Healthcare providers may suggest modifying the dosage of alprazolam, abstaining from consuming cranberry or pomegranate products while taking alprazolam, or closely monitoring for indications of medication interactions or negative effects. It is imperative for patients to consistently disclose to their healthcare professionals all drugs, supplements, and dietary habits in order to minimise the likelihood of interactions and guarantee a safe and efficient course of treatment. In addition, healthcare providers have a vital responsibility in informing patients about possible interactions and advocating for the safe use of medication in combination with dietary decisions.

Conflict of interest statement

The authors claim there is no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding author upon request.

Authors' contributions

Narasappa KK involved in the design, data collection, analysis and interpretation, manuscript drafting, revision, and approval

for publication. Kadiri SK carried out conception, design, data interpretation, manuscript drafting, revision and approval. Tiwari P and Bindigi R oversaw the data interpretation and revision. Kumar MV involved in manuscript drafting and revision.

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