

Review Article

The role of capsaicin and transient receptor potential vanilloid 1 gene activation in preventing kidney stone: A comprehensive review

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Abstract

Capsaicin is the primary alkaloid from capsicum plant (red chili pepper) and is approved by the Food and Drug Administration (FDA) for treating multiple ailments. It activates the transient receptor potential vanilloid 1 (TRPV1) gene, leading to sodium and calcium influx into cells. This triggers the depolarization of nociceptive neurons, causing spiciness perception. Recent studies underscore the health benefits of red chili pepper extract. This investigation aims to understand capsaicin's potential in treating and preventing kidney stones. The potential link between capsaicin and decreased kidney stone risk was also determined. Recently published articles on capsaicin's medical properties and the underlying potential mechanisms were searched out. Relevant references were obtained by searching PubMed electronic databases from April 2020 to September 2020. The impact of parameters such as calcium and oxalate levels were evaluated as common components of kidney stones. Capsaicin may have an impact on body weight, which may have an indirect effect on the risk of kidney stones. Several theories centered around the regular consumption of capsaicin, including the role of TRPV1 gene stimulation have been presented in this study. Stimulation of the TRPV1 gene by capsaicin may protect against kidney stone development. Individuals with a history of kidney stones who incorporate capsaicin into their diet may experience a significantly reduced risk of recurring kidney stone disease. This review elucidates theories supporting this protective effect. The consistent daily intake of red chili pepper (capsaicin) has been associated with a diminished incidence of stone formation. Further research is essential to establish the efficacy and safety of capsaicin.

Keywords: Transient receptor potential vanilloid 1 gene, Kidney stone disease, Capsaicin, Food and Drug Administration

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INTRODUCTION

Traditional medicine boasts of a diverse array of flavouring agents, including various spices. Herbal experts have long valued chili, the fiery red-hot chili pepper, which has been utilized in

the cultures of both Americans and Asians. Peppers contain capsaicin which is the chemical ingredient that gives chili peppers their heat, irritating nature, and serves as the pepper plant's defense against herbivores. Capsaicin attaches to nerve cell receptors when it comes in contact

with them, especially those that are linked to the sense of pain. Specifically, lips, skin, or eyes (after handling peppers) burn as a result [1]. They are recognized for their numerous beneficial effects, including anti-inflammatory and antiseptic properties [1]. Capsaicin has been locally used to treat skin allergies and neural disorders [2]. Transient receptor potential vanilloid 1 (TRPV1) is a non-selective cation channel, and it is essential to the sense of touch. Temperatures cause TRPV1 to become active, acting as a protein heat sensor. This activation adds to the searing feeling from scalding hot water or spicy peppers (Capsaicin). TRPV1 also contributes to pain signals triggered by inflammation, tissue damage, or exposure to irritants such as capsaicin. Acidic environments also activate TRPV1, which adds to the burning sensation of eating acidic meals or experiencing acid reflux in the stomach. TRPV1 functions as a cellular alarm system, picking up on cues such as heat, acidity, and certain chemicals and subsequently inducing responses like vasodilation, discomfort, or inflammation. It plays an essential role in regulating the function of the cardiovascular system and controlling blood pressure [3]. TRPV1 protein activation by capsaicin protects the heart from ischemia and injury via the production of substance P [4].

Frequent stimulation of TRPV1 protein by capsaicin vasodilates the vessels, induces endothelium vaso-relaxation and reduces hypertension [5]. Capsaicin possesses remarkable antioxidant properties, establishing itself as a natural antioxidant. Naturally occurring antioxidants, like capsaicin, are favoured over synthetic alternatives due to concerns about the carcinogenic nature of the latter. The antioxidants found in capsicum plants serve a protective role in the human body, guarding against oxidative processes primarily induced by free radicals and reactive oxygen production [6-9].

Potential evidence has shown a strong correlation between kidney stones and coronary heart disease, especially in female patients in 3 extensive cohort studies [10,11]. Based on this protective mechanism, the protective role of capsaicin over kidney tissues and, hence, its preventive effect on kidney stone incidence is hypothesized. Thermogenesis, weight loss, and cholesterol/triglyceride lowering abilities are proven favourable actions resulting from capsaicin consumption. These actions may be the ways by which capsaicin prevents kidney stones, as these manifestations are the leading cause of kidney stones.

Kidney stones are a worldwide medical problem that affects all cultural and ethnic groups [12]. The underlying causes of kidney stones are not fully elucidated. Unfortunately, recurrence is as high as 50 %, which makes treatment expensive, especially for frequent stone formers [13].

Many risk factors, such as obesity, lifestyle and daily food habits, are associated with kidney stone occurrence and recurrence [14]. These risk factors are considered changeable with a drastic shift in therapeutic lifestyle changes (TLC). Besides, herbal and naturally occurring substances could possess preventive health capabilities. This review investigates red pepper's potential for preventing kidney stones as a result of its component (capsaicin). Here, it is evidenced that if used regularly, capsaicin, the active ingredient of chili peppers, could improve kidney function and hopefully reduce the incidence of nephrolithiasis for stone formers and people with predisposing factors.

Search procedure

Capsaicin physiologically is an agonist and activator of the TRPV1 receptor [15]. In this review, recently published articles on capsaicin's medical properties and the underlying potential mechanisms have been compiled and relevant references have been obtained by searching PubMed electronic databases from April 2020 to September 2020. Keywords were "capsaicin", "antioxidant", "medical uses", "kidney", and "TRPV1". Capsaicin's antioxidant and cell protective (especially in the heart and kidney) capabilities were another motive for developing the study hypothesis. Capsaicin is effective against the production of lipid hydro-peroxides, which are potent free radicals that consequently result in cell damage [16]. Dyslipidemia has already been found to be associated with kidney stones [17]. So capsaicin, an antioxidant [9] and lipid-lowering agent [18,19] indirectly lowers the incidence/recurrence of kidney stones, especially in frequent formers. These observations will provide robust proof of the theory among stone formers.

Old uses of capsaicin versus new emerging applications

The health benefits of capsaicin have been explored for several decades by herbalists in traditional medicine in many areas worldwide. However, the current use of capsaicin has not been fully elucidated. Pain-relieving features of capsaicin and other medical uses will need to be tested and validated. Some clinical conditions in

which capsaicin has been proven to be effective are summarised in Table 1.

There is emerging evidence of evolutionary beneficial effect of capsaicin. Recent reports showed that capsaicin is used for the treatment of superficial punctate keratopathy [42], Asthma [43], labor and delivery pain [44], Alzheimer's disease [45], Fibromyalgia [46] and episodic Cluster headaches [47].

Following the model of this study, rats that ingested cholesterol had more frequent manifestations of hypercalciuria and hyperoxaluria and consequently, a high risk for developing kidney stones [48]. The potential mechanism of how capsaicin might have a direct/indirect protective effect on the kidney during or before kidney stone incidence has been presented in Figure 1 along with relevant information to support these results. TRPV1, a capsaicin receptor, has been proven to regulate blood pressure [3]. In addition, TRPV1 stimulation by capsaicin protects the heart from ischemia and injury by producing substance P [4]. Another report showed that TRPV1 stimulation via capsaicin reduced hypertension [5]. These reports substantiate the results because these actions indirectly protect kidneys as well. A significant role of vitamin E, a component of capsaicin and other endogenous antioxidants in peppers, is its potent antioxidant ability that reduces free radicals and reactive

oxygen in the body [6-9]. These factors all contribute to the prevention of kidney stones.

Other reports have shown an association between kidney stones and obesity [51,52]. Capsaicin's thermogenic and anti-obesity properties could indirectly contribute to its preventive effect against kidney stones. Deregulated blood fat (i.e. cholesterol, low-density lipoprotein (LDL) and triglycerides) has an evident association with kidney stone formation [17]. Hence, capsaicin's dual positive action as an antioxidant [9] and lipid-lowering agent [18,19] could indirectly lower the incidence/recurrence of potential kidney stones, especially in frequent formers (Figure 1).

More health benefits of capsaicin in kidney stone prevention

Capsaicin is known to prevent coronary heart disease and other heart conditions via its antioxidant activity and other underlying mechanism such as thermogenesis and anti-ischemic abilities [6-9,35]. One important report showed that capsaicin patch application provided constant pain relief for up to 12 weeks [49]. These same patches prevent and cure kidney stone pain as they provide sustained release capsaicin. An indirect or direct prevention of kidney stones and a reduction in kidney stone pain are summarised in Figure 2.

Table 1: Current evidence for common pharmacological uses of capsaicin

Clinical condition	Possible mechanism	Reference
General pain relief	TRPV1 is among the transient release potential (TRP) ion channel family. The initial pain caused by capsaicin (due to intense TRPV1 activation) paradoxically leads to a decrease in pain sensitivity over time. This decrease is because the nerve cells become desensitized and have diminished stores of calcium and Substance P, making them less responsive to further pain stimuli.	[20-22]
Weight reduction	Thermogenesis and fat-burning	[23-27]
Anticancer	Mediated interaction with TRPV1 receptor, apoptosis induction, reducing cell viability by induction of cell arrest	[28-31]
Cardiovascular actions	Platelets aggregation inhibition, triglyceride and cholesterol-lowering ability	[32-35]
Gastrointestinal actions	It activates the cyclooxygenase 1 enzyme (COX1), which has gastro-protective actions, increased absorptive surface, and increased zinc absorption.	[36-38]
Urinary bladder action	Capsaicin application reduces the bladder volume. Capsaicin alleviates Painful bladder syndrome and hyperactive bladder.	[39]
Dermatological actions	Hypoxia-inducible factor-1 α (HIF-1 α), a psoriatic factor, is down-regulated by capsaicin, thus alleviating psoriasis. Capsaicin suppresses histamine and substance-mediated itching	[40,41]

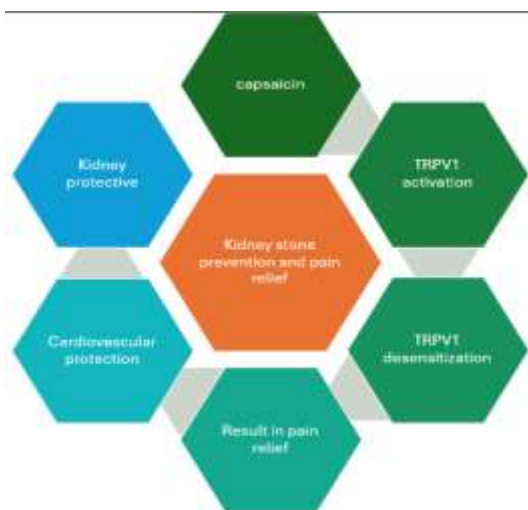


Figure 1: Proposed mechanism of how capsaicin might have direct/indirect protective effect on the kidney during or before kidney stone incidence

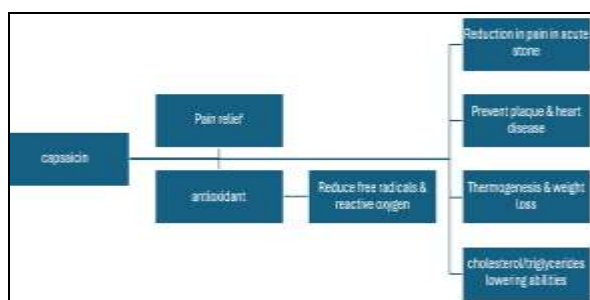


Figure 2: Capsaicin provides pain relief in acute stone attacks, prevents heart disease and contributes to weight loss, which are risk factors for kidney stone disease

DISCUSSION

This study focused on the positive effects of capsaicin and its co-existing beneficial ingredients, such as capsaicinoids, tocopherol and ascorbic acid, that constitute chili pepper's healthy content. Based on validated capsaicin antioxidant natural abilities, it has protective effects over multiple body organs and oxidative processes produced predominantly by free radicals and reactive-oxygen production [6-9]. Potential evidence has shown a strong association between kidney stone formation and coronary heart disease, especially in female patients in 3 extensive cohort studies [10,11]. Capsaicin plays a protective role in kidney tissues and may ultimately be used as a preventive measure against the occurrence of kidney stones. The proven benefits of capsaicin consumption, such as thermogenesis, weight loss, and lowering cholesterol/triglycerides, support this hypothesis. Findings have demonstrated that chili pepper extract prevents kidney stones, given that these factors contribute

to kidney stone formation. Another potential theory suggests that members of the TRP family, including TRPV1, are considered calcium channel modulators [52]. One report showed that TRPV5 knockdown mice have evident hypercalciuria [53] which is the leading cause and risk factor for kidney stone formation [54]. This function is hypothetically related to TRPV1 as it has a high affinity for other TRP family channels. The TRPV1 is responsible for calcium influx to neurons in a cascade for pain perception [55]. Repeated capsaicin utilization was found to down-regulate the TRPV1 expression on pain receptors, thereby reducing pain. The first dose of capsaicin administration is usually painful until the under-expression of TRPV1 is achieved. It functions as an herbal medicine, which, when used for a long time, exerts a neuropeptide pain-relieving effect due to the stimulation of TRPV1 [56]. Many reports have also shown that administering TRPV1 blockers such as capsaicin reduces pain [57,58] and their cardioprotective properties via neurogenic activation [35].

In cancer treatment, regulating TRPV1 channels provides a favourable action; hence, capsaicin is a potential therapeutic option due to the mediated calcium influx processes, which may lead to apoptosis [31]. However, the specific role of this channel must be thoroughly investigated to find the best site of intervention due to the complexity of cancer initiation and progression.

CONCLUSION

Capsaicin from red chili peppers effectively prevents kidney stone formation by addressing significant factors contributing to the disease. Regular daily consumption of capsaicin, the active ingredient in red chili pepper, may be a preventive measure against kidney stones. Individuals who incorporate red chili pepper in their diet, especially those with a history of kidney stones, may experience a notably reduced risk of developing this condition. Beyond its well-established health benefits, consistent daily intake of red chili pepper has been associated with a decreased likelihood of stone formation. Further research is necessary to substantiate the efficacy and safety of capsaicin as a preventive measure for kidney stones.

Recommendations

The following approaches are recommended for a more in-depth investigation into the role of chili pepper extract in preventing kidney stones:

1. Research that implements a well-designed questionnaire, such as a Food Frequency

Questionnaire (FFQ), specifically tailored for individuals who regularly consume red pepper. This questionnaire should capture both personal and family histories of kidney stones, providing valuable insights to complement these results.

2. Conducting comprehensive blood tests, clinicopathological examinations, and biochemical monitoring for individuals with a history of frequent kidney stone formation. This targeted analysis will be instrumental in understanding the potential benefits of chili pepper extract in reducing the prevalence of kidney stones.

Undertaking a large prospective cohort study with a multicenter, randomized, and controlled design. This approach will contribute to establishing a detailed profile of capsaicin's efficacy and safety across diverse settings. Such a study design will provide robust evidence of the preventive potential of capsaicin in mitigating kidney stone formation.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities

pertaining to claims relating to the content of this article will be borne by the authors. Concept and design: Naeem Shalan and Anas Khaleel, Data acquisition: Naeem Shalan and Anas Khaleel, Data analysis and interpretation: Naeem Shalana and Anas Khaleel, Drafting manuscript: Ali Al-Samydai, Critical revision of the manuscript: Ali Al-Samydai.

Use of Artificial Intelligence/large language models

We declare that in this work, Artificial Intelligence/large language models were used for editorial work (writing, editing, and translation)

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