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The Effect of *Punica granatum* Leaf Tea on Potassium Oxonate Induced Gout in Male Wistar Rats

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Abstract

Gout is a prevalent and debilitating inflammatory condition caused by the deposition of monosodium urate crystals in the joints, leading to acute pain, swelling, and redness. This study aimed to evaluate the effect of *Punica granatum* leaf tea on potassium oxonate-induced gout in male Wistar rats. Thirty rats were allocated into six groups of five animals each, and gout was induced by intraperitoneal administration of potassium oxonate at 250 mg/kg body weight for 14 days. *P. granatum* leaf tea was administered at doses of 10, 20, and 30 mg/kg body weight. The findings showed that potassium oxonate significantly increased serum uric acid, creatinine, IL-1β, IL-6, TNF-α, and hepatic xanthine oxidase activity relative to the normal control. Among the tested doses, 30 mg/kg body weight produced a significant ($p < 0.05$) reduction in uric acid (4.80 ± 0.06 mg/dL vs. 7.37 ± 0.15 mg/dL), IL-1β (25.41 ± 0.79 pg/mL vs. 31.45 ± 2.71 pg/mL), and hepatic xanthine oxidase activity (5.93 ± 0.20 U/L vs. 11.89 ± 1.11 U/L), with effects comparable to the standard drug group. The same dose also showed a more pronounced effect than the standard drug in reducing TNF-α (7.44 ± 0.58 pg/mL vs. 10.95 ± 1.87 pg/mL) and ALP (63.16 ± 2.06 U/L vs. 68.00 ± 1.98 U/L). The study concludes that *Punica granatum* leaf tea exhibits anti-hyperuricemic,

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anti-inflammatory, and organ-protective effects in potassium oxonate-induced gout, highlighting its potential contribution as a natural therapeutic candidate for gout management.

Keywords: *Punica granatum*; Gout; Hyperuricemia; Xanthine Oxidase; Inflammatory Cytokines

INTRODUCTION

Gout is defined as a form of inflammatory arthritis characterised by sudden and severe pains, swelling, and redness in the joints, most commonly affecting the big toe. This condition arises from the accumulation of monosodium urate (MSU) crystals in the joints and surrounding tissues, which occurs due to elevated levels of uric acid in the blood, a condition known as hyperuricemia (Fenando *et al.*, 2023). Hyperuricemia is defined by a serum urate concentration above the saturation point (≥0·41 mmol/L [≥6·8 mg/dL]) as a result of reduced renal excretion of uric acid (Dalbeth *et al.*, 2021).

Gout arises from a complex interplay of dietary and genetic factors that elevate serum uric acid levels, leading to hyperuricemia and subsequent deposition of urate crystals in joints. Diets rich in purine-heavy foods, such as red meat, organ meats, and sea foods, significantly increase uric acid production and the risk of gout flares, particularly in individuals predisposed to hyperuricemia (Aydın et al., 2024; Chi et al., 2024). Also high-fructose corn syrup and other fructose-rich foods, commonly present in sugary beverages, promotes uric acid production, whereas low-fat dairy products may exert a protective effect by lowering serum urate levels (Aydın et al., 2024; Koguchi, 2021). Alcohol consumption, especially beer and liquor, further exacerbates risk by increasing uric acid production and reducing its renal excretion, with beer posing the greatest hazard (Asghari et al., 2024). Beyond diet, genetic predisposition plays a major role, with heritability estimates for serum urate levels ranging from 45% to 73% (Singh & Gaffo, 2020). Genome-wide association studies have identified variants in uric acid transport genes such as SLC2A9 and ABCG2 that increase susceptibility, with certain high risk alleles being more common in specific ethnic groups, contributing to variations in gout prevalence across populations (Tin & Köttgen, 2020).

A 2024 systematic analysis of the global burden of gout from 35 countries showed that in 2020, about 55 million people globally had gout, with an age standardised prevalence of around 660 cases per 100.000, corresponding to an increase of 22.5% over the last 30 years (Punzi *et al.*, 2025). The total number of prevalent cases of gout is estimated to reach 95.8 million in 2050 (Gout collaborators, 2021).

If not treated adequately, gout is a debilitating disease with systemic manifestations, such as monosodium urate crystal deposition in organs and worsening of cardiorenal function (Bursill *et al.*, 2019). Clinical studies have shown that gout flares are related to the transient increase in cardiovascular events after a gout attack (Cipolletta *et al.*, 2022) and are independently associated with an increased risk of death from kidney disease (Borghi *et al.*, 2020), these factors causing the patients to suffer greatly.

The crystallisation of uric acid, often related to relatively high levels in the blood, is the underlying cause of gout. Underexcretion of uric acid by the kidney is the primary cause of hyperuricemia in about 90% of cases, while overproduction is the cause in less than 10%. About 10% of people with hyperuricemia develop gout at some point in their lifetimes (Ebrahimpour-Koujan *et al.*, 2020).

Potassium oxonate, a competitive uricase inhibitor, produces hyperuricemia in rodents. The enzyme uricase, also known as uric oxidase, transforms uric acid to allantoin, a water-soluble material that allows uric acid to be excreted more readily through the urine. The basic principle of increasing the source of uric acid, reducing uric acid excretion and inhibiting uricase is used to establish the rodent model of hyperuricemia.

Punica granatum L., commonly known as pomegranate, is a perishable superfruit grown globally, originating from the Mediterranean regions (Puneeth and Sharath, 2020). In South Africa, it is planted as a hedge, attracting bluebirds during winter and autumn (Pienaar, 2021). Though exotic to South Africa, it adapts well to various climates. The plant, belonging to the family Lythraceae, is referred to as "granaat" in Afrikaans and "kgarenate" in Sesotho (Schutte-Vlok and Raimondo, 2020). Known for its health, nutritional and therapeutic benefits, the pomegranate tree grows up to 4–5 metres, featuring thorny branches, flaky bark and shiny crumpled leaves (Guerrero-Solano *et al.*, 2020), making it highly cultivated and in demand worldwide. Pomegranates have antimicrobial, antioxidants, anti-atherosclerosis, anti-viral, anti-inflammatory and anti-

cancerous pharmacological activities which are due to the richness of flavonoids bioactive compounds in pomegranates (Maphetu *et al.*, 2022).

This study was therefore carried out to evaluate the effect of *Punica granatum* leaf tea on Potassium oxonate induced gout in male wistar rats.

MATERIALS AND METHODS

Materials and Reagents

Microplate reader (Spectra Max M2, USA), centrifuge (Hettich D, 78532), vernier calliper (Mitutoyo, Japan), UV–vis spectrophotometer (PerkinElmer Lambda 25, USA), microtiter plates (Corning, USA), microtiter plates for ELISA (Costar, USA), incubator (Thermo Scientific, USA), analytical balance (Ohaus, USA), water bath (Thermo Scientific, USA), pH metre (Hanna Instruments, USA), vortex mixer (Vortex-Genie 2, USA) and biosafety cabinet (Thermo Scientific, USA), micro-CT scanner (Skyscan 1076 Bruker, MA, USA, Sodium pyrophosphate buffer (100 mM, pH 7.5), potassium oxonate, 0.9% saline solution, DMSO (Dimethyl sulfoxide), allopurinol, uricase enzyme, Tris(hydroxymethyl)aminomethane (TRIS) buffer, uric acid, picric acid, sodium hydroxide (NaOH), 10% trichloroacetic acid (TCA), commercial ELISA kits for IL-1beta, IL-6 and TNF-α, xanthine, phosphate buffer (50 mM, pH 7.5), hydrochloric acid (HCl). All reagents were of analytical grade.

Animal Source

Thirty (30) Wistar rats, weighing 110 ± 5 g were purchased from National Veterinary Research Institute, Plateau State, Nigeria. The animals were housed under standard room temperature and 12 hours of light/dark cycle and were fed with commercial pellet diet (and water ad libitum for two weeks to acclimatise to the environment before the commencement of the study.

Establishment of the hyperuricemia mouse model and drug administration

Gout was experimentally induced in male Wistar rats through the administration of potassium oxonate (K.O) according to the method described by Sarvaiya et al. (2015). All animals, except for the vehicle control group, received K.O. at a dosage of 250 mg/kg body weight. The potassium oxonate was dissolved in 0.9% saline solution and administered intraperitoneally (I.P.) to the rats. This procedure was carried out once daily

for 14 days. All treatment groups received their respective test compounds (Punica granatum leaf tea or standard drug) 1 hour after each K.O. administration.

Animal Sacrifice and Biological Sample Collection

At the end of the treatment period (day 15), 12 hours after the last administration, the rats were humanely sacrificed by placing them in a closed chamber containing a cotton ball soaked with chloroform to induce deep anaesthesia. Once unresponsive, the necks of the rats were severed using a sterile scalpel to ensure humane euthanasia and allow for blood collection. The blood was allowed to clot at room temperature for 30 minutes and then centrifuged at 3,000 rpm for 15 minutes to separate the serum. The serum was stored at a cool temperature in a refrigerator until further analysis (Lin et al., 2014).

Determination of serum uric acid levels

The determination of the uric acid method was based on the ACA method described by Elin *et al.* (1982).

Determination of urea

Serum urea quantification was performed using a kinetic diacetyl monoxime (DAM) reaction as described by (Sabiullah, 2019).

Determination of serum Creatinine levels

Serum creatinine was measured by an alkaline picrate colorimetric method based on Jaffe's reaction as modified by Greg Miller et al., (2005).

Determination of IL-1beta and IL-6 Levels

The levels of interleukin (IL)-1beta and IL-6 was quantified by enzyme immunoassay using commercially available rat IL-1beta and IL-6 ELISA kits (Koma Biotech) as described by Han et al., (2014).

Determination of tumour necrosis factor-alpha (TNF-α) levels

Tumour necrosis factor-alpha (TNF-α) concentration in serum and liver homogenate was estimated using commercially available rat specific TNF-α ELISA kit (Krishgen Biosystems) as described by Löbenberg and Amidon, 2000.

Determination of Xanthine Oxidase inhibitory activity

Xanthine oxidase (XO) activity was measured spectrophotometrically using the method described by Yuk et al. (2018).

Determination of Aspartate Transaminase (AST) Activity

The activity of aspartate aminotransferase (AST) was assayed using the method of (Reitman and Frankel, 1957) as modified by (Schmidt, 1961).

Determination of Alanine Transaminase (ALT) Activity

The activity of alanine aminotransferase (ALT) was determined using the method of Reitman and Frankel (1957) as modified by Schmidt (1961).

Determination of Alkaline Phosphatase Activity

Alkaline phosphatase activity was determined according to the method described by Roy (1970).

Statistical Analysis

Results were evaluated using SPSS software (version 28.0) using one-way Analysis of Variance (ANOVA) followed by Tukey's post hoc test to separate the means that are statistically different. Results were expressed as mean ± SEM, and *P* values of <0.05 were considered significant.

RESULTS

Table 1 shows the effect of *Punica granatum* leaf tea on serum uric acid, urea, and creatinine levels across different groups. The negative control group showed a significantly higher ($p<0.05$) uric acid, urea, and creatinine levels compared to the normal control. Treatment with *P. granatum* reduced these parameters in a dose-dependent manner with the 30mg/kg.bw group showing the most significant decrease.

Table 1: Effect of *Punica granatum* Leaf Tea on Uric acid, Urea and Creatinine in mg/dl

Groups	Uric acid	Urea	Creatinine
Normal Control	1.15 ± 0.06	36.04 ± 0.42	0.54 ± 0.02
Negative control	7.37 ± 0.15[a]	41.82 ± 1.87[a]	0.67 ± 0.03[a]
Positive control	3.90 ± 0.06[ab]	36.51 ± 0.76	0.55 ± 0.03
P. granatum 10 mg/kg.bw	6.30 ± 0.06[abc]	41.56 ± 0.54[a]	0.57 ± 0.03
P. granatum 20 mg/kg.bw	5.30 ± 0.06[abc]	40.72 ± 2.07	0.61 ± 0.02
P. granatum 30 mg/kg.bw	4.80 ± 0.06[abc]	37.90 ± 0.28	0.45 ± 0.03[b]

Values are expressed as Mean ± S.E.M; n=5;

a = Significantly higher ($p < 0.05$) compared to normal control;

b = Significantly lower ($p < 0.05$) compared to negative control;

c = Significantly higher ($p < 0.05$) compared to positive control.

Table 2 shows the effect of *Punica granatum* leaf tea on IL-1β, TNF-α, and IL-6 levels. The negative control group showed significantly higher ($p < 0.05$) levels of all cytokines compared to the normal control. Treatment with *P. granatum* leaf tea reduced IL-1β, TNF-α, and IL-6 levels in a dose-dependent manner, with the 20 mg/kg.bw and 30 mg/kg.bw groups showing significant decreases compared to the negative control. Notably, the 30 mg/kg.bw dose produced the greatest reduction and, in some cases, showed effects comparable to or better than the positive control.

Table 2: Effect of *Punica granatum* Leaf Tea on IL-1β, TNF-α, and IL-6 in pg/mL

Groups	IL-1β	TNF-α	IL-6
Normal control	21.87 ± 0.38	7.12 ± 0.22	3.01 ± 0.24[b]
Negative control	31.45 ± 2.71[a]	14.51 ± 1.24[a]	7.10 ± 0.33[a]
Positive control	26.68 ± 0.71[b]	10.95 ± 1.87	3.41 ± 0.05[b]
P. granatum 10 mg/kg.bw	29.54 ± 2.45[a]	12.70 ± 2.19	6.02 ± 0.11[ac]
P. granatum 20 mg/kg.bw	26.70 ± 0.69[b]	8.29 ± 0.56[b]	4.78 ± 0.33[abc]
P. granatum 30 mg/kg.bw	25.41 ± 0.79[b]	7.44 ± 0.58[b]	4.03 ± 0.06[ab]

Values are expressed as Mean ± S.E.M; n=5;

a = Significantly higher ($p < 0.05$) compared to normal control;

b = Significantly lower ($p < 0.05$) compared to negative control;

c = Significantly higher ($p < 0.05$) compared to positive control.

Table 3 shows the effect of *Punica granatum* leaf tea on hepatic xanthine oxidase (HXO), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) activity. The negative control group showed significantly higher ($p < 0.05$) levels of HXO, AST, ALT, and ALP compared to the normal control. Treatment with *P. granatum* leaf tea reduced these enzyme activities in a dose-dependent manner, with the 30 mg/kg.bw group showing the most pronounced reduction, comparable to the positive control.

Table 3: Effect of *Punica granatum* Leaf Tea on Liver Parameters (HXO, AST, ALT, ALP) in U/L

Groups	HXO	AST	ALT	ALP
Normal control	4.29 ± 0.43	31.00 ± 0.71	12.75 ± 1.89	59.26 ± 3.96
Negative control	11.89 ± 1.11^{ab}	45.00 ± 1.15^{a}	25.00 ± 1.15^{a}	77.25 ± 1.86^{a}
Positive control	4.75 ± 0.26^{b}	34.33 ± 0.88^{b}	16.67 ± 0.33^{b}	68.00 ± 1.98
P. granatum 10 mg/kg.bw	8.15 ± 0.46^{abc}	43.33 ± 0.33^{ac}	19.00 ± 1.15^{abc}	75.16 ± 1.30^{ac}
P. granatum 20 mg/kg.bw	6.82 ± 0.31^{ab}	36.33 ± 0.88^{ab}	16.00 ± 1.15^{b}	69.08 ± 1.42^{a}
P. granatum 30 mg/kg.bw	5.93 ± 0.20^{b}	35.23 ± 0.82^{b}	15.67 ± 0.67^{b}	63.16 ± 2.06^{b}

Values are expressed as Mean ± S.E.M; n=5;

a = Significantly higher ($p < 0.05$) compared to normal control;

b = Significantly lower ($p < 0.05$) compared to negative control;

c = Significantly higher ($p < 0.05$) compared to positive control.

HXO = Hepatic Xanthine Oxidase;

AST = Aspartate Aminotransferase;

ALT = Alanine Aminotransferase;

ALP = Alkaline Phosphatase.

DISCUSSION

This study evaluated the therapeutic potential of Punica granatum (pomegranate) leaf tea in mitigating the pathological effects of potassium oxonate-induced gout in male Wistar rats. The findings provide evidence supporting the nephroprotective, anti-inflammatory, and anti-hyperuricemic properties of P. granatum, with varying degrees of dose-dependent efficacy.

Treatment with *P. granatum* leaf tea produced a clear dose-dependent effect on key indicators of kidney function. Serum uric acid, urea, and creatinine levels were significantly elevated in the gout control group, consistent with renal dysfunction commonly observed in hyperuricemic states. Administration of *P. granatum* tea at medium and high doses led to marked reductions in uric acid and creatinine levels, with the *P. granatum 30 mg/kg.bw* group achieving results comparable to allopurinol, the standard pharmacological treatment. This finding indicates that compounds in the leaf tea may reduce uric acid synthesis or enhance its renal clearance while simultaneously protecting renal tissues from injury.

These results are in agreement with the findings of Joshi *et al.* (2025), who evaluated various Indian herbal beverages for their efficacy in managing hyperuricemia. Their study reported significant reductions in serum uric acid and creatinine levels in potassium oxonate-induced rat models after two weeks of treatment. The authors attributed these effects to increased uric acid excretion and suppression of oxidative damage in renal tubules (Joshi *et al.*, 2025).

Primarizky *et al.* (2016) reported similar benefits of pomegranate fruit extracts on uric acid levels in white rats with acute renal failure, supporting the therapeutic potential of pomegranate compounds in managing hyperuricemia. The mechanism underlying the uricosuric effect likely involves the rich polyphenolic content of pomegranate leaves, particularly ellagitannins and flavonoids, which have been demonstrated to enhance renal uric acid excretion and reduce tubular reabsorption (Eghbali *et al.*, 2021).

The improvements in serum creatinine levels, particularly with higher doses, suggest enhanced glomerular filtration capacity and kidney function preservation. This finding is consistent with previous studies demonstrating the nephroprotective properties of pomegranate extracts against various forms of kidney injury (Aksu *et al.*, 2017).

The differential response pattern in serum urea levels, with only the highest dose achieving normalisation, suggests that pomegranate's primary mechanism may be more specifically targeted toward uric acid metabolism rather than general nitrogen waste clearance. This specificity is advantageous for gout management, as it indicates a targeted therapeutic effect without compromising overall renal function. The rich phytochemical profile of pomegranate, including punicalagins, ellagic acid, and anthocyanins, contributes to its diverse pharmacological activities (Noreen et al., 2025).

The dose-dependent reduction in pro-inflammatory cytokines observed in this study supports the established anti-inflammatory properties of pomegranate extracts. The modulation of IL-1β, TNF-α, and IL-6 levels demonstrates the multi-target approach of pomegranate compounds in addressing gout-associated inflammation. These findings are consistent with recent investigations by Xu *et al.* (2017), showing that pomegranate extracts inhibit the production of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) in LPS-stimulated macrophages, indicating a broad anti-inflammatory mechanism beyond gout-specific pathways.

The reduction in TNF-α levels is particularly significant, as this cytokine plays a central role in initiating the inflammatory cascade in gout. Wang *et al.* (2020) conducted a meta-analysis and systematic review confirming that pomegranate supplementation significantly reduced TNF-α in various inflammatory conditions, supporting the clinical relevance of these findings. The mechanism likely involves the inhibition of nuclear factor-kappa B (NF-ϰB) signalling pathway, which regulates the expression of multiple inflammatory mediators involved in gout pathogenesis.

The dose-dependent efficacy observed with IL-6 reduction across all treatment groups suggests that even lower doses of pomegranate leaf tea retain anti-inflammatory activity, though optimal effects are achieved with higher concentrations. Huang *et al.*, (2024) demonstrated that punicalagin, a major bioactive compound in pomegranate, decreases interleukin-6 (IL-6) concentrations through regulation of SIRT1/STAT3 axis and Nrf2/HO-1 signalling pathways, providing mechanistic insights into the observed therapeutic effects.

The superior anti-inflammatory performance of medium and high doses compared to the positive control in certain parameters suggests that pomegranate leaf tea may offer advantages over conventional treatments through its multi-compound composition. The synergistic effects of various polyphenolic compounds, including ellagitannins, anthocyanins, and flavonoids, likely contributed to the comprehensive anti-inflammatory response observed (Tzekaki et al., 2025).

The modulation of inflammatory cytokines is crucial in gout management, as chronic inflammation contributes to joint damage, cardiovascular complications, and reduced quality of life. The ability of pomegranate leaf tea to address multiple inflammatory mediators simultaneously could position it as a promising complementary therapeutic approach for comprehensive gout management.

The dose-dependent inhibition of hepatic xanthine oxidase observed in this study represents a key mechanism underlying the anti-hyperuricemic effects of pomegranate leaf tea. Xanthine oxidase is the rate-limiting enzyme in uric acid biosynthesis, and its inhibition directly reduces uric acid production, making it a primary therapeutic target in gout management. A study has demonstrated that xanthine oxidase inhibition attenuates insulin resistance and diet-induced steatohepatitis in mice (Nishikawa *et al.*, 2020).

The superior inhibitory activity achieved with higher doses of pomegranate leaf tea can be attributed to the rich flavonoid content, particularly quercetin, luteolin, and kaempferol, which have been identified as potent xanthine oxidase inhibitors. The structure-activity relationship studies have revealed that planar flavones and flavonols with a 7-hydroxyl group inhibit xanthine oxidase activity at low concentrations through mixed-type inhibition mechanisms (Chinnappan *et al.*, 2023).

The normalisation of hepatic xanthine oxidase activity with the highest dose treatment suggests that pomegranate leaf tea can effectively restore physiological enzyme levels without complete inhibition, which is advantageous for maintaining normal purine metabolism. Recent investigations have highlighted the correlation between xanthine oxidase activity and hepatic steatosis (Yagi *et al.*, 2022).

The comparable efficacy to allopurinol, the standard xanthine oxidase inhibitor, demonstrates the clinical potential of pomegranate leaf tea as a natural therapeutic alternative. The advantage of natural compounds lies in their multi-target approach and reduced risk of adverse effects compared to synthetic drugs, making them attractive options for long-term gout management and prevention of associated comorbidities.

The present study demonstrated that potassium oxonate-induced gout resulted in significant elevations of AST, ALT, and ALP levels compared to normal controls. These findings align with recent clinical observations establishing a strong association between hyperuricemia and hepatic dysfunction. A comprehensive population study by Deb and Sakharkar (2021) corroborated these findings in human subjects, demonstrating positive correlations between serum uric acid and liver transaminases. Almuqrin *et al.* (2024) also found positive correlations between ALT, AST, and total bilirubin with uric acid levels in a large cross-sectional study, with significantly increased risk of hyperuricemia in individuals with elevated liver enzymes. Recent experimental evidence confirms that following hyperuricemia induction, all rats experienced elevated levels of AST and ALT, indicating its adverse effects against liver function, supporting the observed liver enzyme elevations in the gout model.

The dose-dependent improvement in liver enzyme profiles following P. granatum leaf tea treatment represents a significant finding. The 30 mg/kg body weight dose restored AST and ALT levels to near-normal values, demonstrating substantial hepatoprotective efficacy. Bahari et al. (2024) demonstrated that pomegranate intake had a significant effect

on lowering AST levels in long-term interventions and showed significant decreases in ALT levels. Ali et al. (2021) also established the hepatoprotective potential of pomegranate in curbing acute liver injury by alleviating oxidative stress and inflammatory responses.

The ALP response pattern differed from AST and ALT, showing more gradual improvement with *P. granatum* treatment. While the highest dose achieved significant reduction, levels remained elevated compared to normal controls, suggesting that cholestatic components of liver injury may require more intensive or prolonged treatment for complete resolution.

The study demonstrates that *Punica granatum* leaf tea possesses significant anti-gout properties through multiple complementary therapeutic mechanisms including dose-dependent reductions in serum uric acid levels, inflammatory cytokines, and liver enzyme parameters. The comprehensive therapeutic approach exhibited by pomegranate leaf tea addresses the complex pathophysiology of gout through simultaneous targeting of uric acid production, and inflammation, with the 30 mg/kg body weight dose providing maximum benefits across all measured parameters. The comparable efficacy to allopurinol positions pomegranate leaf tea as a viable natural alternative or complementary treatment option, offering potential advantages over single-mechanism treatments by addressing multiple aspects of gout pathogenesis simultaneously. The findings may validate the therapeutic potential of pomegranate, providing strong evidence supporting the traditional medicinal use of pomegranate in treating inflammatory conditions.

Conflict Of Interest

The authors declared there is no conflict of interest

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