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RESEARCH PAPER

A Comparative Study on the Influence of Maple Syrup and Gold Nanoparticles on Kidney Stone Biomarkers in Female Albino Rats

Etin Diah Permanasari [1], Ali Hamid AbdulHussein [2]*, Ola Hamad Salah [3], Rand Mohammed [4], Ghazi Mohamed Ramadan [5], Mohammed Jawad Alnajar [6], Mohammed Qasim Alasheqi [7], Ibrokhim B. Sapayev [8,9], Nilufar Esanmurodova [8,9]

[1] *Master of Pharmaceutical Sciences, Postgraduate School, Universitas Muhammadiyah Prof DR HAMKA, Jakarta, Indonesia*

[2] *Department of Pharmaceutics, College of Pharmacy, University of Al-Ameed, Karbala, Iraq*

[3] *Al-Manara College For Medical Sciences, Maysan, Iraq*

[4] *Department of Dentistry, Al-Hadi University College, Baghdad, 10011, Iraq*

[5] *College of MLT, Ahl Al Bayt University, Kerbala, Iraq*

[6] *Anesthesia techniques, Al–Nisour University College, Iraq*

[7] *National University of Science and Technology, Dhi Qar, Iraq*

[8] *Tashkent Institute of Irrigation and Agricultural Mechanization Engineers, National Research University, Tashkent, Uzbekistan*

[9] *Western Caspian University, Baku, Azerbaijan*

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ABSTRACT

This study investigates the comparative effects of maple syrup and gold nanoparticles (AuNPs) on blood biochemical indicators in female albino rats with induced kidney stone disease. Maple syrup, rich in antioxidants, and AuNPs, known for their biomedical applications, were evaluated for their potential therapeutic benefits or risks in renal health. Twenty sexually mature female albino rats were divided into five groups, including two control groups and three treatment groups. The treatment groups received varying concentrations of ethylene glycol to induce kidney stones, with or without maple syrup or AuNPs. Blood urea nitrogen, creatinine, and albumin levels were measured, along with urinary oxalate and calcium concentrations. The group treated with maple syrup plus 100 mg/kg ethylene glycol showed a significant decrease in blood urea nitrogen levels compared to the negative control group ($p<0.05$), and a marked reduction in urinary oxalate and calcium levels ($p<0.001$). Conversely, the group treated with maple syrup plus 200 mg/kg ethylene glycol and AuNPs did not exhibit significant differences from the negative control. These findings suggest that maple syrup, particularly at lower concentrations of ethylene glycol, may have protective effects against kidney stone pathology, potentially due to its antioxidant properties. However, further research is needed to understand the implications of AuNPs and higher concentrations of ethylene glycol in such treatments.

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* *Corresponding Author Email: alihamidabdulhussein@outlook.com*

INTRODUCTION

Maple syrup, a delightful natural sweetener obtained from the sap of sugar maple trees, is not just a culinary favorite but also harbors compounds with potential medicinal benefits [1,2]. Notably, it boasts a significant antioxidant capacity, with research indicating the presence of 24 different antioxidants [3]. These substances play a crucial role in neutralizing free radicals, thereby potentially reducing the risk of chronic diseases associated with oxidative stress [4].

In terms of nutritional value, maple syrup is a noteworthy source of essential minerals. A serving of approximately 1/3 cup (80 ml) can provide 7% of the Recommended Daily Intake (RDI) for calcium, 6% for potassium, 7% for iron, 28% for zinc, and a remarkable 165% for manganese [5]. However, it is also high in sugar, containing around 60 g in the same serving size, primarily in the form of sucrose. This underscores the importance of moderate consumption, given the health risks associated with excessive sugar intake.

Emerging research suggests that dark-colored maple syrup may exhibit anti-cancer properties, particularly in inhibiting the growth of certain cancer cells, such as those found in colorectal and gastrointestinal cancers [6]. Additionally, compounds in maple syrup have been studied for their potential to slow down carbohydrate breakdown in the digestive tract, which could have positive implications for blood sugar regulation and anti-diabetic effects [7].

Furthermore, the polyphenol antioxidants in maple syrup may exert anti-inflammatory effects, which could be beneficial in preventing conditions like arthritis, inflammatory bowel disease, and heart disease [8,9]. While these findings are promising, it is essential to consume maple syrup in moderation due to its high sugar content, which can contribute to obesity, type 2 diabetes, and heart disease if consumed in excess. As such, maple syrup should be enjoyed as part of a balanced diet, with careful consideration of overall sugar consumption.

Gold nanoparticles (AuNPs) have emerged as a versatile tool in the field of medicine, offering a range of potential therapeutic and diagnostic applications. Their unique physical and chemical properties, such as high surface area-to-volume ratio, ease of functionalization, and optical characteristics, make them particularly suitable for biomedical uses [10,11].

One of the most notable properties of AuNPs is their localized surface plasmon resonance (LSPR), which can be utilized in the diagnosis and treatment of tumors [12]. The LSPR property allows AuNPs to absorb and scatter light, making them excellent contrast agents for imaging techniques1. Additionally, AuNPs have been used to enhance the efficacy of radiotherapy due to their high X-ray absorption coefficient, which can lead to improved tumor destruction while minimizing damage to surrounding healthy tissue [13].

AuNPs have been explored for their potential in cancer therapy, particularly in the targeted delivery of anticancer drugs. For example, antibody-functionalized AuNPs were used to deliver gemcitabine to pancreatic adenocarcinoma cells, resulting in increased cytotoxicity compared to non-targeted drug delivery [14]. Other chemotherapeutic drugs, such as doxorubicin, oxaliplatin, and docetaxel, have also been bound to AuNPs to enhance their delivery and efficacy [15,16].

The ability to functionalize the surface of AuNPs with various ligands and biomolecules has opened up possibilities for targeted drug delivery. This functionalization allows for the immobilization of chemical groups or biological molecules, such as genes, proteins, and small molecules, onto the gold surface. As a result, AuNPs can serve as carriers, delivering therapeutic content to specific tissues or cells with increased precision [17].

AuNPs have been employed in photothermal therapy (PTT), where they are used to convert light into heat to destroy cancer cells. The nanoparticles absorb light and generate localized heat, which can ablate tumor cells while sparing healthy ones. This approach has shown promise in preclinical studies and is being explored for its potential in clinical applications [18–20].

Despite the promising medicinal effects of AuNPs, it is important to consider their biocompatibility and potential health threats. Due to their low clearance rate from circulation streams and tissues, prolonged exposure to AuNPs may lead to health problems [21].

The accumulation of AuNPs in the body could potentially result in unforeseen long-term effects, which are still being studied. The cytotoxicity of AuNPs can vary depending on their size, shape, surface charge, and the presence of functional groups. Studies have shown that

certain functionalized AuNPs can affect cellular internalization, accumulation, and targeting efficiency, which may influence their toxicity. For instance, the conjugation of antibody fragments to AuNPs for PTT displayed cytotoxicity upon irradiation that varied with the expression of the epidermal growth factor receptor (EGFR) [22,23]. This indicates that the design and functionalization of AuNPs need to be carefully tailored to minimize potential adverse effects. Another concern is the immunogenic effect of AuNPs, particularly when they are conjugated with biological molecules. The presence of certain regions in these molecules, such as the fragment crystallizable region of antibodies, can trigger an immune response in the body [24]. This could lead to complications, especially in therapeutic applications where the immune system's reaction to the nanoparticles could negate their beneficial effects.

Kidney stones, or renal calculi, are a growing health concern in developed countries, with lifestyle, medical conditions, and medications playing a role in their formation [25]. Research links diabetes and obesity to kidney stones, and men are more likely than women to develop them. The risk of recurrence is high, with a 50% chance within five years and two-thirds within ten years [26].

Patients often endure severe flank pain, hematuria, and sandy urinary sediment. Complications can include urinary retention and nausea. Evaluations should cover past kidney issues, infections, medical history, medications, family history, and lifestyle. Laboratory tests check electrolytes, creatinine, calcium, phosphorus, and uric acid levels, while urinalysis assesses pH, hematuria, infections, and crystal types. Most kidney stones are calcium-based, primarily calcium oxalate, followed by calcium phosphate. Oxalate, a byproduct of glycine and ascorbic acid metabolism, becomes risky when excreted above 25 mg/day [27].

Risk factors for calcium stones include high urinary calcium and oxalate, low citrate, insufficient urine volume, and diet. Microscopic urine analysis reveals cells, casts, crystals, and microbes. Acidic urine, hyperoxaluria, and ethylene glycol intoxication are linked to calcium oxalate presence. Ethylene glycol metabolizes into toxic byproducts like glycolaldehyde, increasing urinary oxalate and stone risk [28].

Gold nanoparticles are studied for their oxidative stress and free radical generation, which could target kidney stone pathology. Conversely, maple syrup's antioxidant properties may counteract AuNPs' free radicals and support the immune system. This research examines the effects of AuNPs and maple syrup on blood urea nitrogen, creatinine, and albumin levels in a model of kidney stones using female albino rats. This study aims to determine the therapeutic benefits or risks of these treatments for kidney stone disease.

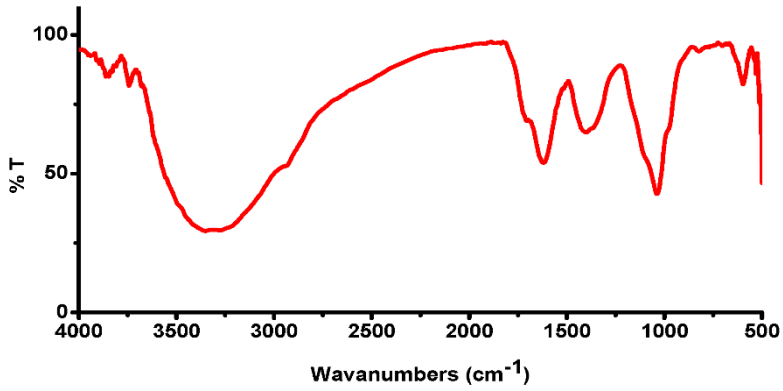
MATERIALS AND METHODS

In this experimental study, 20 female albino rats demonstrating sexual maturity at the age of three months and exhibiting a weight range of 110-150 g, were procured from the Faculty of Veterinary Medicine, University of Baghdad. The experimental subjects were provided with ad libitum access to a standard laboratory chow and water. The microenvironmental conditions were regulated to maintain a relative humidity of 25-30% and ambient temperature within 20-25°C. A photoperiod of 12:12 hours light-dark cycle was established to simulate natural conditions. Housing was facilitated using standardized transparent polycarbonate cages, and sawdust bedding was employed for its thermal insulation properties and its efficacy in absorbing excreta.

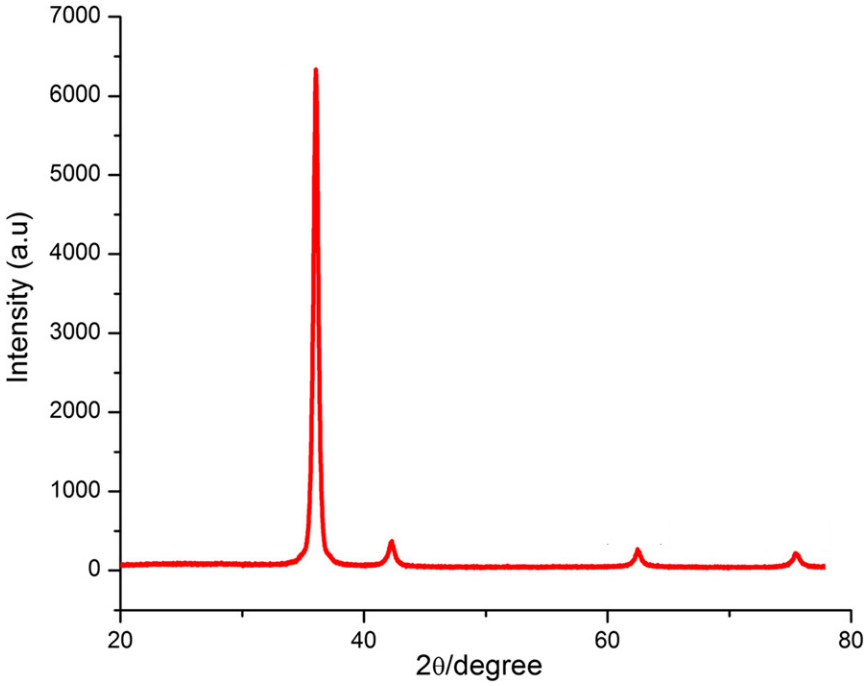
A minimum acclimatization period of two weeks was observed post-housing, prior to the initiation of experimental procedures. For the purpose of this study, the subjects were stratified into five distinct groups, each comprising four individuals. The experimental design was as follows:

- Control Group 1: Received vehicle control of 1% distilled water.
- Control Group 2: Served as the negative control, receiving 1% ethylene glycol in their drinking solution, with no additional interventions.
- Treatment Groups 3 and 4: Administered with ethylene glycol at a dosage of 100 and 200 mg/kg body weight respectively, supplemented with 1% maple syrup via oral gavage from day one until the conclusion of the study.
- Treatment Group 5: Administered with a single intraperitoneal injection of 0.5 cc of spherical AuNPs with an average diameter of 10 nanometers at a concentration of 100 ppm, which was sustained over a period of 15 days.

Pure, natural maple syrup obtained from local



(a)



(b)

Fig. 1. Analysis results of AuNPs: (a) XRD measurement, (b) FTIR spectroscopy

producers in Baghdad was utilized for gavage. Prior to administration, the body mass of each rat was recorded to calculate the appropriate dosage for a 30-day experimental period, with four rats allocated per group. The maple syrup was diluted with distilled water to the calculated concentrations and administered via gavage for the duration of the study.

Spherical AuNPs, with an average diameter of 10 nm, were procured from Sigma-Aldrich. The nanoparticles were synthesized through a chemical reduction process using sodium citrate as the reducing agent. Sodium citrate reduces gold ions in the solution to form AuNPs, and the citrate ions also act as a stabilizing agent to prevent the nanoparticles from aggregating. Serial dilution was employed to achieve the desired concentration of the AuNP colloid, which was then administered intraperitoneally to the rats in a sterile environment. Fig. 1 presents the X-ray

diffraction (XRD) analysis, and Fourier-transform infrared (FTIR) spectra of the AuNPs utilized in this study.

To induce kidney stones, ethylene glycol was incorporated into the rats' drinking water. A concentration of 0.01 ml of ethylene glycol per 0.99 ml of water was used, ensuring the total volume per dose remained at 1 ml.

Upon completion of the treatment regimen, 24-hour urine samples were meticulously collected from each subject within the group, utilizing individual metabolic cages to ensure isolation of specimens. Post-collection, the urinary output was quantified, followed by immediate refrigeration to preserve sample integrity pending biochemical analysis. The analytical focus was directed towards the quantification of urinary oxalate and calcium levels, employing enzyme assay kits (Span Diagnostics Limited, India) for oxalate determination, and the xylidyl blue calorimetric method for calcium measurement.

Concurrent with the urine analysis, cardiac puncture was performed under anesthesia to procure heart blood on the 30th day post-treatment initiation. The obtained blood specimens underwent centrifugation at 2000 rpm for a duration of 20 min to separate serum, which was subsequently dispatched to a certified medical diagnostic laboratory. Therein, the serum underwent scrutiny for key biochemical markers, specifically blood urea nitrogen, creatinine, and albumin. Quantitative assessment of these parameters was facilitated by an Autoanalyzer (Hitachi autoanalyzer, model 7600), which measured the optical density of the samples to infer concentration levels.

The statistical analysis of the data was conducted using SPSS 23.0 software, employing a one-way analysis of variance (ANOVA) to discern the differences in factors across the groups. Post-hoc comparisons were facilitated through Tukey's follow-up test to further elucidate intergroup variances. The data were articulated as the mean ± standard error (Mean ± S.E), with the threshold for statistical significance established at a p-value less than 0.05.

RESULTS AND DISCUSSION

Upon analyzing the data, it was observed that the mean blood urea nitrogen levels in the negative control group exhibited a marked elevation when contrasted with the vehicle control group ($p<0.01$). Contrastingly, the group administered with maple syrup plus 200 mg/kg ethylene glycol and AuNPs of 100 ppm did not demonstrate a statistically significant deviation from the negative control group. However, a notable reduction in the median blood urea nitrogen levels was discerned in the group receiving maple syrup plus 100 mg/kg ethylene glycol, as compared to the negative control group ($p<0.05$) (Fig. 2).

The analysis of variance for serum creatinine concentrations indicated no significant modulation across the groups. A substantial diminution in serum albumin levels was noted in the negative control group relative to the vehicle control group. Meanwhile, the group treated with maple syrup plus 200 mg/kg ethylene glycol and AuNPs of

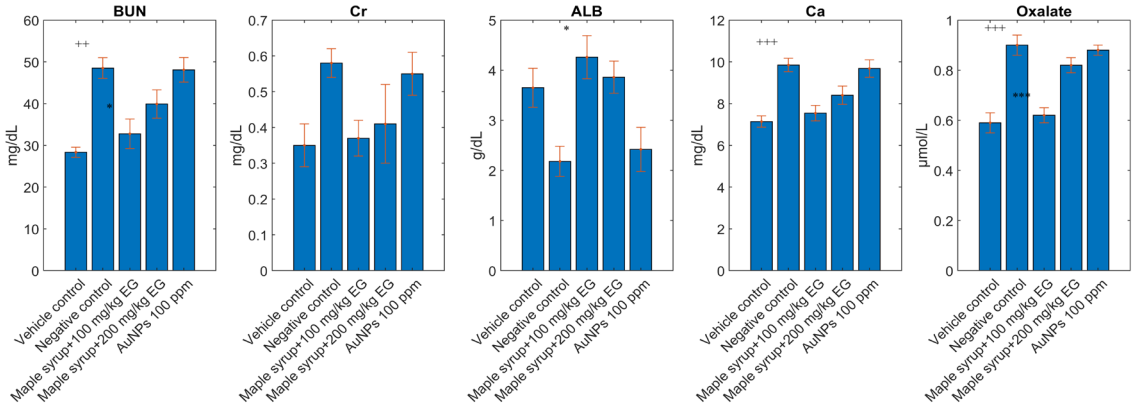


Fig. 2. Comparative analysis of serum and urinary biomarkers across various treatment concentrations (Note: BUN, blood urea nitrogen; Cr, creatinine; ALB, albumin; Ca, Calcium; EG, ethylene glycol; ++p<0.01, +++p<0.001: significant difference between the negative control group and the vehicle control group; *p<0.05, ***p<0.001: significant difference between the treatment groups compared to the negative control group)

100 ppm mirrored the negative control in terms of albumin levels, whereas the group treated with maple syrup plus 100 mg/kg ethylene glycol manifested a significant increase in albumin levels ($p<0.05$) (Fig. 2).

An assessment of urinary calcium and oxalate concentrations in the female albino rats revealed that the negative control group had significantly higher levels compared to the vehicle control group ($p<0.001$). The group treated with maple syrup plus 100 mg/kg of ethylene glycol showed a significant decrease in these urinary constituents relative to the negative control group ($p<0.001$). Conversely, the groups treated with maple syrup plus 200 mg/kg of ethylene glycol and AuNPs of 100 ppm did not exhibit a significant difference (Fig. 2).

Maple syrup, a natural sweetener derived from the xylem sap of various species of maple trees, is not only valued for its sweetness but also for its bioactive compounds, particularly phenolic substances [29]. These phenolic compounds are a subset of phytochemicals known for their antioxidant properties, which play a pivotal role in the inhibition or retardation of oxidative processes. Oxidative stress is implicated in the pathogenesis of a multitude of diseases; thus, the antioxidant capacity of phenols is of considerable interest in the context of disease prevention [30]. The pathophysiology of kidney stones involves the nucleation, growth, and aggregation of calcium oxalate crystals within the renal tubular system. The antioxidants in maple syrup may exert a protective effect against the oxidative stress that promotes the crystallization process, thereby mitigating the risk of stone formation.

Ethylene glycol, an organic compound frequently encountered in antifreeze solutions, has been identified as nephrotoxic, with the kidneys being the primary target organ for its toxicity [31]. The metabolites of ethylene glycol contribute to the formation of renal cysts and an increase in hyperoxaluria, a condition characterized by elevated urinary oxalate levels that predispose to calcium oxalate stone formation [32]. Experimental models using albino rats have demonstrated that prolonged exposure to ethylene glycol can induce the formation of these stones, with the underlying biochemical mechanisms being closely linked to the increased urinary excretion of oxalate [33].

In the present study, a progressive increase in the excretion of oxalate and calcium was observed in animals with induced kidney stones, accompanied by a significant reduction in urine volume. Concurrently, a decrease in albumin synthesis, a hallmark of liver dysfunction, was noted. However, the administration of maple syrup plus 100 mg/kg of ethylene glycol was associated with an increase in albumin levels, suggesting an enhancement of hepatic function, which in turn may have a positive impact on renal health.

This study also examined the renal function parameters, specifically blood creatinine levels, which serve as an indicator of glomerular filtration rate and, by extension, kidney health. The creatinine levels in the vehicle control group aligned with established norms for rats, indicating normal renal function [34]. Conversely, elevated levels of blood urea and creatinine are indicative of renal impairment, as these waste products accumulate in the bloodstream due to inadequate renal clearance.

This investigation extended to the evaluation of AuNPs, which are increasingly utilized in various fields, including nanotechnology and medicine. Despite some assertions regarding their safety, evidence suggests that AuNPs can exert nephrotoxic effects [35]. The proposed mechanism involves the generation of ROS and oxidative stress, which can inflict damage on cellular structures and tissues. The size of the nanoparticles is a critical factor influencing their biodistribution, toxicity, and potential to induce oxidative stress [17,21,24].

Studies have reported that AuNPs, particularly those with smaller diameters, can significantly elevate ROS levels, thereby exacerbating oxidative stress and its associated toxic effects [13,17]. Despite these findings, some studies have not observed significant alterations in creatinine and blood urea nitrogen levels following exposure to AuNPs, suggesting that the impact on renal function may not always be pronounced or detectable using these biomarkers [21].

In conclusion, the interplay between the antioxidant properties of maple syrup and the oxidative potential of certain xenobiotics, such as ethylene glycol and gold nanoparticles, underscores the complexity of biological interactions and their implications for renal health. The propensity of calcium oxalate crystals to induce renal epithelial cell damage through oxidative mechanisms further highlights the relevance of antioxidants in mitigating renal stone disease. The research into the protective effects of maple syrup's phenolic

content against kidney stone formation, as well as the potential risks associated with nanomaterials, represents an important intersection of nutrition, toxicology, and nanotechnology in the pursuit of understanding and improving human health.

CONCLUSION

In conclusion, this study has provided valuable insights into the comparative effects of maple syrup and AuNPs on blood biochemical indicators in female albino rats with ethylene glycol-induced kidney stones. The research highlighted the potential therapeutic benefits of maple syrup's antioxidant properties, which may protect against oxidative stress associated with kidney stone pathology. Conversely, the study also considered the potential risks of AuNPs, particularly regarding their oxidative capacity and the subsequent impact on renal health.

One limitation of the current study is the relatively small sample size, which may affect the generalizability of the findings. Additionally, the study was conducted solely on female albino rats, which limits the applicability of the results to other genders and species, including humans. The specific dosage and form of maple syrup and AuNPs used in this study may also not directly correlate with the conditions under which humans would consume or be exposed to these substances.

Future research should aim to expand the sample size and include a more diverse population of subjects to enhance the robustness of the data. Longitudinal studies could provide more comprehensive insights into the long-term effects of both maple syrup and AuNPs on renal health. Furthermore, investigations into the molecular mechanisms underlying the observed biochemical changes would deepen our understanding of the interactions between dietary antioxidants, nanomaterials, and renal disease. The exploration of different concentrations and forms of maple syrup and AuNPs, as well as their effects on other organ systems, would also be beneficial. Ultimately, such research could lead to the development of more effective and safer therapeutic interventions for kidney stone disease and other related conditions.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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