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Comparative Efficacy of Aqueous Mentha spicata Extract and Green-Synthesized Silver Nanoparticles in Protecting Rats from KCl-Induced Hypomagnesemia

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Abstract | This study investigated the protective effects of Mentha Spicata extract and green-synthesized silver nanoparticles in rats induced hypomagnesemia. Twenty-four adult female rats were randomly divided into four equal groups: The control group (G1) gavage with distilled water; Magnesium deficiency induced rats in three other groups by giving them potassium chloride at a dose of 1.39 mg/kg through gavage, the G2 group was given potassium chloride only, G3 and G4 were treatment group orally given mint extract at dosage 5.25 ml/kg B.W per day and AgMSNPs at dosage 12.5µg/kg B.W per day. Blood samples were collected from the rats after 28 days from the beginning of the experiment in order to evaluate potassium, magnesium, sodium, calcium, and chloride content. All rats were sacrificed and bone samples were collected for histological study. For the potassium, there was a significant increase in G2 and there was a non-significant difference between other groups when compared with the control. The results of magnesium showed a significant reduction in G2, G3, and G4 compared with the control. There was a non-significant difference between control group and G2 for sodium and there was a significant decrease in sodium in other groups compared with the control group. The oral intubation with potassium chloride caused a significant reduction in calcium in G2, but the other groups, mint extract and AgMSNPs, did not show any significant difference in calcium. Chloride had a significant elevation in G2 and there was a non-significant difference in chloride in G3 and G4 when compared with the control. In conclusion, both Mentha spicata extract (G3) and green-synthesized AgMSNPs (G4) successfully restored serum magnesium levels to control values in KCl-induced hypomagnesemia. Notably, AgMSNPs provided superior protection of bone tissue integrity on histopathological examination, demonstrating enhanced therapeutic potential over the crude extract.

Keywords | Biogenic silver nanoparticle, Bone, Hypomagnesemia, Potassium chloride

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INTRODUCTION

Magnesium deficiency is a dietary problem that alters cellular function and molecular activity in the body Magnesium deficiency is also associated with the occurrence of metabolic diseases linked to inflammation. In the body of adult humans, there is 1 mole of Mg, half of the Mg content is found in bone whereas the other half is found in soft tissue (Fiorentini *et al*., 2021). More specifically, the serum contains 0.3% of the total magnesium, erythrocytes include 0.5%, soft tissues contain 19.3%, muscles contain 27%, and bones contain 52.9%. One-third of the magnesium in serum is linked to proteins. 25% of this total is tied to albumin, whereas 8% is linked to globulins. The remaining magnesium is composed of around 80% free ion 55% of total magnesium and approximately 20% associated with phosphate, citrate, and other molecules (Zhou and Yao, 2025). Magnesium homeostasis in the body depends on how much is consumed, how much is absorbed by the intestines, how much is excreted by the kidneys, and what different tissues need (Barbagallo *et al*., 2021).

In osteoporosis animals, dietary intake of Mg and other bone-essential minerals is often suboptimal (Muñoz-Garach *et al*., 2020; Juesas *et al*., 2023). Bone mineral serves as a store for calcium (Ca) and other elements, crucial amounts of which must be maintained in cells and fluids throughout the body. Appropriate support function requires the formation and maintenance of sufficient bone, both in quantity and quality, to sustain the body during life and withstand normal pressures to which skeletal components are exposed (Hart *et al*., 2020; Yao *et al*., 2022). Hyperkalemia is one of the most serious metabolic problems since it may create electrophysiological disturbances with serious clinical consequences including death (Hayes *et al*., 2012; Simon *et al*., 2023). Because potassium plays such an important function in the body organ like bone, kidney and heart, the impact of KCl injection on plasma Mg concentration and urine Mg excretion must investigate in animal. The increasing dietary K intake reduces Mg absorption through the rumen epithelium in the ruminant and apparent Mg digestibility (Oberson *et al*., 2019). As a result, oral KCl treatment can lower plasma Mg concentration in ruminant and rats (Obaid and Khalil, 2019; Merschmann *et al*., 2025). The addition of potassium chloride to a feed of fresh cut grass in dairy calves lowered apparent Mg absorption (Doncel *et al*., 2019). The cows given a lot of K had lower urine Mg excretion and higher fecal excretion (Tebbe and Weiss, 2018) and in rat (Obaid and Khalil, 2021).

All plant extracts are natural sources of non-toxic reducer/stabilizer agents; they may be beneficial in the production of nanoparticles. Mentha also contains menthol, limonene, pulegone, carvophyllene and pinene. Similar to a typical secondary alcohol, menthol interacts in a variety of ways. It can also be utilized in the biosynthesis of Ag-nanoparticles by alcohol-reducing $AgNO_3$ (Ning *et al*., 2025). Plant extracts like mint perform a dual function in the NPs production process facilitating metal salt reduction while also acting as capping agents to stabilize the generated NPs.

Nanoparticles are particles smaller than 100 nm in diameter (Kirstein *et al*., 2022). Nanomaterials can easily cross cellular barriers compared to larger particles and move to a cell or organ due to their special properties (Liga *et al*., 2025). This study aimed to evaluate the effects of aqueous extract of *Mentha spicata* leaf, and silver nanoparticle reducing by mint silver nanoparticles AgMSNPs supplementation on serum levels of K, Mg, Ca, Na, and Cl in rats exposed to KCl-induced hypomagnesaemia. Although silver does not directly modulate magnesium absorption, green-synthesized silver nanoparticles (AgMSNPs) were used to stabilize and enhance the bioavailability of Mentha spicata's active compounds, such as menthol and other phytochemicals. We hypothesized that the AgMSNPs would exhibit superior efficacy compared to the crude mint extract in restoring magnesium homeostasis and protecting against KCl-induced bone damage due to enhanced bioavailability and targeted delivery.

MATERIALS AND METHODS

Design and animals

Twenty-four adult female rats weighing 185 ± 15 g were obtained from the College of Pharmacy, Karbala University. The animals were housed in the animal facility of the Department of Physiology and Pharmacology, College of Veterinary Medicine, University of Baghdad. They were maintained under standard laboratory conditions (temperature 22 ± 2°C, relative humidity 55 ± 10%, and a 12 h light/dark cycle) and had free access to tap water and a standard commercial pellet diet throughout the experiment. The standard diet (Al-Rahma Feed Company, Baghdad, Iraq) contained approximately 22% crude protein, 4% fat, 5% fiber, 8% ash, and 1% calcium. Its mineral composition was verified according to the supplier's certificate of analysis, and the baseline magnesium and potassium contents were measured by atomic absorption spectroscopy (Mg= 320 ± 15 mg/kg; K= 6800 ± 120 mg/kg), confirming that they were within the normal range for laboratory rodents. Each cage housed five rats and was cleaned daily.

Animals were randomly allocated into four experimental groups (6 rats each, aged 10–12 weeks) for a period of four weeks. The control group (G1) received normal saline orally; group G2 received 1.39 g/kg of KCl solution orally (Obaid and Khalil, 2021). Group G3 was administered 1.39 g/kg of KCl plus the aqueous Mentha spicata leaf extract at a dose of 5.25 ml/kg (Al-Bazii *et al*., 2013) by an oral gavage. Group G4 received 1.39 g/kg of KCl plus Mentha spicata-based silver nanoparticles (AgMSNPs) at a dose of 12.5 μg/kg per day (Ali and Khalil, 2025), also by an oral gavage.

After 28 days of experiment, 5 mL of blood samples were taken from rats using the heart puncture method

(Parasuraman *et al*., 2010), sample were placed in non-heparinized gel tubes and allowed to stand for 30 minutes before being centrifuged (for 15 minutes at 3000 rpm) and stored in firmly sealed tubes for further analysis at -20°C, to the K (Agappe- Switzerland), Mg (Agappe- Switzerland), Na (Agappe- Switzerland), Ca (Agappe- Switzerland) and CL (Agappe- Switzerland) by ELISA test and animals were sacrificed for histopathological examination of bone by hematoxylin and eosin stain.

Preparation of watery extract of Mentha leaves

Spearmint leaves were cleansed three times with distilled water before being chopped into smaller pieces and air-dried before being ground into powder. Boiling distilled water was added to the powder (5g of mint/100 mL water), which was then soaked in boiling water for 60 minutes with constant shaking before being filtered through a filter paper (Whatman no. 1 paper) and immediately placed in dark bottles (Al-Bazii *et al*., 2013; Khatoon *et al*., 2018).

Preparation of biogenic AgNPs

Silver nanoparticles (AgNPs) were synthesized following the previously published method by Alwan *et al*. (2021), Ali and Khaleel (2025), which provides a detailed and validated protocol. A 1 mM aqueous solution of silver nitrate ($AgNO_3$) was prepared and used as the precursor for nanoparticle synthesis. Five milliliters of filtered aqueous leaf extract of *Mentha spicata* was added dropwise to 200 mL of the $AgNO_3$ solution under ultrasonication for 30 minutes to facilitate the reduction of Ag^+ ions to Ag^0. The reaction mixture was then incubated at room temperature for 20 minutes under vigorous magnetic stirring, during which a rapid color change was observed, indicating the formation of AgNPs. The resulting mixture was allowed to react for 72 hours under gentle stirring to ensure complete nanoparticle formation. Aliquots were collected at predetermined intervals to monitor the synthesis process (Khudiar and Sood, 2019). Biosynthesized AgNPs were previously characterized using: UV-Vis spectroscopy (Shimadzu UV-1600, Japan), X-ray diffraction (XRD) (Shimadzu, Japan), Fourier-transform infrared spectroscopy (FTIR) (Shimadzu, Japan), scanning electron microscopy (SEM) (Cyan, Belgium), and atomic force microscopy (AFM) (Toshiba, Japan). All chemicals used were of analytical grade, sourced from Sigma-Aldrich (Germany). Fresh Mentha spicata leaves were obtained from the local market for extract preparation.

Statistical analysis

Data were statistically analyzed using GraphPad Prism version 5.0 (GraphPad Software, CA, USA) and SPSS version 23.0 (IBM Corp., Armonk, NY, USA). One-way analysis of variance (ANOVA) was performed to determine significant differences among experimental groups, followed by post-hoc comparisons using either the least significant difference (LSD) test or Duncan's multiple range test, as appropriate. All data are expressed as mean ± standard error (SE), and statistical significance was considered at $p < 0.05$.

RESULTS AND DISCUSSION

According to Table 1, oral administration of KCl (G2) resulted in a significant increase ($p < 0.05$) in serum potassium and chloride concentrations and a significant decrease ($p < 0.05$) in serum magnesium and calcium compared with the control group (G1), confirming the successful induction of hypomagnesemia and associated electrolyte imbalance. Treatment with Mentha spicata extract (G3) or AgMSNPs (G4) significantly reduced serum potassium and normalized magnesium and calcium levels to values comparable with the control group ($p > 0.05$). Sodium levels showed a mild reduction in both treated groups (G3 and G4), which may reflect a protective adjustment in renal electrolyte handling. Notably, both treatments prevented the hypocalcemia observed in G2, suggesting a close link between magnesium restoration and calcium homeostasis. Overall, AgMSNPs showed slightly better stabilization of magnesium and calcium concentrations than the crude extract, which may be attributed to improved bioavailability and enhanced tissue uptake of the mint bioactive compounds in nanoform. These findings agree with previous reports:

Table 1: Effect of KCl, *Mentha spicata* extract, and AgMSNPs on serum electrolytes in rats.

Groups	K (mmol/L)	Mg (mg/dL)	Na (mEq/L)	Ca (mg/dL)	Cl (mEq/L)
G1	4.65±0.104^a	2.4±.0912^b	138.5±0.288^a	10.7125±0.086^a	99.25±0.629^b
G2	5.9±0.1471^a	2.0325±.0137^b	140.75±0.75^a	9.25±0.392^b	106±0.645^a
G3	4.475±0.205^b	2.6475±0.062^a	122 ±2.943^b	10.615±0.511^a	95.25±2.056^b
G4	4.875±0.047^b	2.575±0.0931^a	126 ±2.798^b	11.3±0.402^a	98.5±2.217^b
P value	< 0.0001	< 0.0001	< 0.0001	0.0106	0.0014

Values are expressed as mean ± SE (n = 6). Means with different superscript letters within the same column differ significantly ($p < 0.05$). Group 1: Control negative Animals received normal saline. Group 2: Control positive Animals received KCL 1.39g/kg BW orally. Group 3: Animals received KCL 1.39g/kg BW orally + Mint 5.25ml/kg B.W orally. Group 4: Animals received KCL 1.39g/kg BW orally + AgMSNPs (12.5μg/kg B.W) orally.

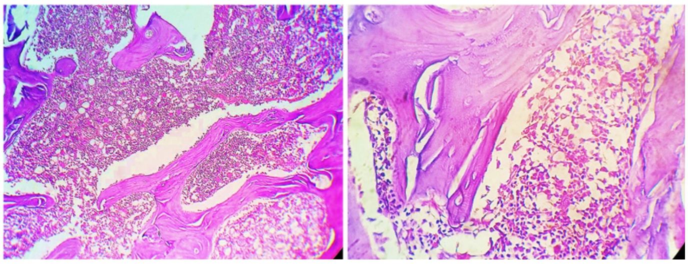

Figure 1: Histopathological section of bone in the female rat control negative group (G1) shows normal architecture. Osteocytes are easily visible within lacunae, and the compact bone has well-organized lamellae encircling Haversian canals. There is no indication of necrosis, inflammatory infiltration, or structural anomalies in the trabecular bone or bone marrow (H and E) X10.

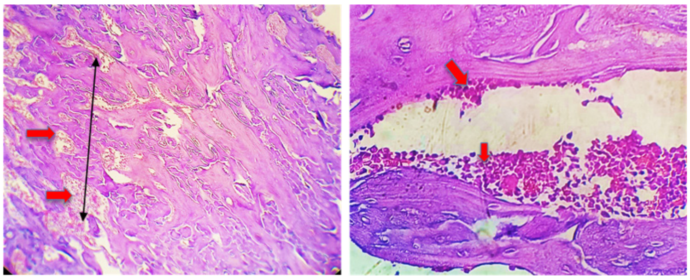

Figure 2: Histopathological section of bone in rat treated with KCI (G2) group, shows narrowing of trabecular bone (black arrow) with absent activity of osteoblast (red arrow) and hypercellularity of bone marrow, (H and E) X10.

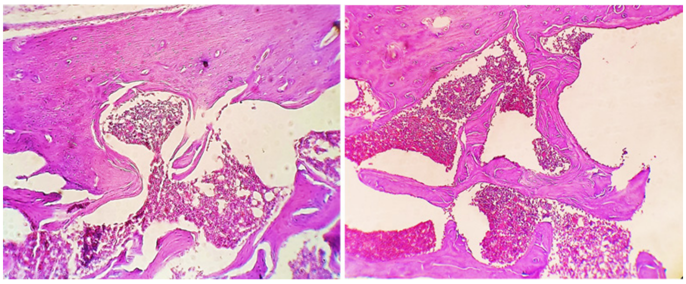

Figure 3: Histopathological section of bone in rat treated with KCl and Mint extract (G3) group shows decrease in the osteoblast, narrowing of trabecular bone and hyper cellularity of bone marrow (H and E) X10.

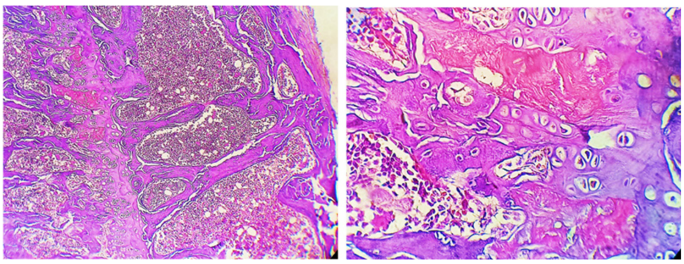

Figure 4: Histopathological section of bone in rat treated with KC1 and AgMSNPs (G4) group, shows normal bone tissues, well-organized compact and trabecular bone. Osteocytes are clearly observed within their lacunae, and the bone marrow spaces show normal cellularity. (H and E) x10 and x40.

increased potassium intake significantly reduces serum magnesium levels (Goff, 2018), and oral KCl administration for two weeks reduces plasma Mg and Ca levels (Obaid and Khalil, 2021), indicating that high K^+ intake negatively affects Mg bioavailability in the gastrointestinal tract and kidney. The inverse relationship between dietary potassium and plasma magnesium has been confirmed in both human and animal models (Van der *et al*., 2018; Zhou and Yao, 2025). The reduction in serum magnesium and concomitant fall in calcium levels in group G2 (KCl-treated) supports previous findings that magnesium deficiency disrupts calcium homeostasis because Mg acts as a natural calcium antagonist (Srinivasan *et al*., 2023). Low extracellular magnesium increases intracellular calcium accumulation, which can trigger inflammatory and apoptotic pathways (Liu *et al*., 2019). These mechanisms explain the hypocalcemia observed in KCl-treated rats.

The increase in serum chloride in G2 was also consistent with the report by Stone *et al*. (2016), who found that potassium loading increases Na^+ reabsorption and paracellular chloride reabsorption in renal tubules, thereby increasing plasma Cl^- concentrations. Similarly, Zhang *et al*. (2023) reported that high K^+ intake alters distal nephron transport activity, leading to changes in Na^+ and Cl^- handling through upregulation of epithelial sodium channels and ROMK transporters. These kidney changes can lead to electrolyte imbalance and increased blood pressure (Meng *et al*., 2022; van der *et al*., 2018).

Treatment with *Mentha spicata* extract (G3) restored serum Mg and Ca to normal values and reduced K^+ and Cl^- levels, demonstrating its mineral regulating and antioxidant properties. This is consistent with the findings of El-Menyiy *et al*. (2022), who showed that *Mentha spicata* contains significant amounts of Mg, Na and Fe in addition to phenolic antioxidants that support electrolyte homeostasis and protect against oxidative stress. Subramanian *et al*. (2012) also reported that *Mentha spicata* leaves contain essential macro and micronutrients that help maintain mineral balance and reduce oxidative damage. These beneficial effects may also explain the improvement in bone structure in G3, as magnesium and plant-derived polyphenols are known to stimulate osteogenesis and reduce bone resorption (Aune *et al*., 2017; Miranda *et al*., 2019).

Histopathological examination of the femur was performed using three sections from each animal. Analysis was performed by a qualified histopathologist in a blinded manner to eliminate any observer bias. To provide a more objective assessment of bone changes, a semiquantitative scoring system (0–3) was used to evaluate the degree of structural damage, trabecular thinning and osteoblastic activity. The scoring criteria were as follows: 0= normal architecture, 1= mild degeneration or slight reduction in osteoblast number, 2= moderate trabecular thinning and reduced bone cellularity, and 3= severe degeneration with marked trabecular loss and marrow hypercellularity. Rats treated with AgMSNPs (G4) showed near-complete restoration of normal bone architecture and serum magnesium levels just like the control. This suggests that AgMSNPs provided superior protection against to KCl-brought about hypomagnesemia and bone harm in comparison with the crude extract. The stronger efficacy of AgMSNPs could be attributed to their nanoscale length, which improves cell uptake and transport of *Mentha spicata* lively phytoconstituents such as rosmarinic acid, flavonoids, and terpenoids. Recent studies have proven that plant-mediated silver nanoparticles can act as efficient carriers for bioactive compounds, enhancing their stability, bioavailability, and interaction with cell membranes (Ahsan *et al*., 2025; Awlqadr *et al*., 2025). In addition, the silver core may play a biological role by modulating membrane ion channels and stimulating Mg^{2+} transporters in the kidney and intestinal epithelium. Alwan *et al*. (2021) and Ali and Khalil (2025) have previously shown that biosynthesized silver nanoparticles from *Mentha spicata* are biocompatible and have strong antioxidant and anti-inflammatory properties. It has also been reported that silver nanoparticles increase osteoblastic activity and promote collagen synthesis in bone tissue (Du *et al*., 2023). Therefore, the combination of *Mentha spicata* bioactive compounds and silver nanocarrier properties explains the stronger therapeutic effect observed in G4 compared to the crude extract.

Taken together, these results show that while both Mentha spicata extract and AgMSNPs corrected KCl-induced electrolyte disturbances, the nanoformulation provided better tissue protection, especially in bone histology. Proposed mechanisms may include increased cellular uptake of Mg^{2+}, protection against oxidative stress and stimulation of osteoblast differentiation. Future studies using molecular markers of Mg transport such as Transient Receptor Potential Melastatin 7 (TRPM6/7, Mg^{2+}/Ca^{2+} channels) and bone remodeling genes are recommended to confirm this mechanism.

CONCLUSIONS AND RECOMMENDATIONS

This study demonstrates that both aqueous Mentha spicata extract and its green-synthesized silver nanoparticles (AgMSNPs) effectively mitigate KCl-induced hypomagnesemia and associated electrolyte imbalances in rats. However, the AgMSNPs formulation proved significantly more efficacious than the crude extract, not only in normalizing serum magnesium levels but also in providing superior protection against bone histopathological damage. The enhanced therapeutic performance of AgMSNPs is likely attributable to improved bioavailability and targeted delivery of the active phytoconstituents, coupled with the intrinsic bioactivity of the nanocarrier. These findings position biogenic AgMSNPs as a promising, nano-enhanced therapeutic strategy for managing magnesium deficiency and its complications.

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NOVELTY STATEMENT

To the best of our knowledge, this is the first study to demonstrate that green-synthesized silver nanoparticles from *Mentha spicata* (AgMSNPs) are not only effective in correcting serum magnesium levels but are significantly superior to the conventional plant extract in preventing hypomagnesemia-induced bone damage. This highlights the value of nano-formulation in enhancing the therapeutic potential of herbal medicine for mineral deficiencies.

AUTHOR'S CONTRIBUTION

The first author, conducted the study and performed the experimental and analytical work. The other authors, as supervisors, oversaw the research process, provided guidance, and contributed to data interpretation and critical revision of the manuscript. All authors approved the final version.

Ethical approval

Ethical approval was obtained from the College of Veterinary Medicine, University of Baghdad and College of Pharmacy/ Karbala, Iraq (ethical approval number: COVM-6341).

Generative AI and AI-assisted technology statement

Generative AI tools (e.g., ChatGPT) were used only for minor language polishing and to improve clarity in a few non-scientific parts of the manuscript (such as the novelty statement). No AI tools were involved in generating, analyzing, or interpreting scientific data, nor in writing the Introduction, Methods, Results, or Discussion. All content was carefully reviewed by the authors, who take full responsibility for the accuracy and integrity of the final manuscript.

Conflict of interest

The authors have declared no conflict of interest.

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