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Magnesium citrate: potential and current approaches in pharmacy

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ABSTRACT: Magnesium, the fourth most abundant cation in the human body and the second most abundant intracellular cation after potassium, is an essential mineral. Therefore, magnesium deficiency can lead to various symptoms and manifestations in the body. Today, to address magnesium deficiency, various dosage forms (powder, tablet, capsule, sachet, lozenge, etc.) are available on the market. These dosage forms contain different forms of magnesium. Among them, magnesium citrate is the most extensively researched and most frequently used form by individuals. To date, numerous studies have been conducted in the literature on magnesium citrate. This review presents information about magnesium citrate and summarizes various studies conducted on this topic.

KEYWORDS: Magnesium; Forms of magnesium; Magnesium citrate; Magnesium in pharmacy.

1. INTRODUCTION

Magnesium, which is most commonly found in oceans and rivers on Earth, is the eighth most abundant element on our planet [1]. The ionic form of magnesium has a very high solubility in water. This makes magnesium the third most abundant dissolved element in seawater. Since its salt forms dissolve easily in water, it is readily utilized by organisms. Magnesium's importance is clearly demonstrated by being the fourth most abundant cation in our body and the second most abundant intracellular cation after potassium [2]. The total magnesium content in the body of an average adult weighing 70 kg with 20% (w/w) body fat is approximately 24 grams. About 50-60% of this amount is found in the bones, while the majority of the remaining portion is located in the muscles and soft tissues (Table 1) [1, 2, 3, 6].

Table 1. Magnesium distribution in an adult human [2, 3, 6].

Tissue	Weight (Kg wet wt)	Concentration (mmol/Kg wet wt)	Content (mmol)	% of total body magnesium
Serum	3.0	0.85	2.6	0.3
Red blood cells	2.0	2.5	5.0	0.5
Soft tissue	22.7	8.5	193.0	19.3
Muscle	30.0	9.0	270.0	27.0
Bone	12.3	43.2	530.1	52.9
Total	70.0		1000.7	100

As seen in Table 1, the serum magnesium level reflects approximately 1% of the body's total magnesium content. This is because most of the magnesium is stored in the muscles, bones, and soft tissues. Therefore, even if serum levels are within the normal range, severe magnesium deficiency can occur in the body, and its clinical impact may be significantly underestimated [44, 49]. Magnesium balance in the human body is maintained by the regulation of magnesium reabsorption by the kidneys [3]. Primarily found within cells, magnesium acts as an ion for ATP, the main source of cellular energy transfer, and nucleic acids. Serving as a cofactor in more than 300 enzymatic reactions, magnesium plays a role in numerous processes in the body, and its deficiency can lead to various physiological problems (Table 2).

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Table 2. Physiological functions of magnesium [3].

Enzyme function	Enzyme substrate (ATPmg, GTPmg)
Direct enzyme activation	Phosphofructokinase
	Creatine kinase
	5-phosphoribosyl-pyrophosphate synthetase
	Adenylate cyclase
	Na+,K+-ATPase
Membrane function	Cell adhesion
	Transmembrane electrolyte flux
Calcium antagonist	Muscle contraction/relaxation
	Neurotransmitter release
	Action potential conduction in nodal tissue
Structural function	Protein
	Polyribosomes
	Nucleic acids
	Multiple enzyme complexes
	Mitochondria

To address magnesium deficiency in the body, regular intake of this mineral is necessary. According to the literature, the minimum daily magnesium requirement for humans is 350 mg for men and between 280-300 mg for women. It is recommended that the minimum daily dose for women during pregnancy and lactation be 355 mg [4]. Reduced dietary intake, malabsorption in the gastrointestinal system, kidney dysfunction, alcohol consumption, diabetes, smoking, stress, and the use of certain medications can lead to magnesium deficiency in the body [5]. Clinical symptoms of magnesium deficiency include various issues such as cramps, tremors, arrhythmia, depression, psychosis, hypokalemia, and hypocalcemia (Table 3) [1, 5, 7].

Table 3. Symptoms and signs of magnesium deficiency [7].

General: Anxiety, drowsiness, fatigue, agitation, depression, dysmenorrhea, hyperactivity, headache, irritability, poor concentration, low stress tolerance, insomnia, nausea, tinnitus, physical dysfunctions, impaired athletic performance.
Muscular System: Muscle spasms, cramps in the soles of the feet, leg cramps, facial muscle twitches, muscle weakness, pain in chewing muscles and teeth, carpopedal spasms, back pain, neck pain, advanced spasms, tetany caused by magnesium deficiency.
Nervous System/CNS: Irritability, increased sensitivity of NMDA receptors to excitatory neurotransmitters, migraines, depression, myasthenia, paresthesia, memory impairment, seizures, tremors, vertigo.
Gastrointestinal System: Constipation.
Cardiovascular System: Arrhythmias, supraventricular or ventricular arrhythmias, hypertension, coronary spasm, reduced myocardial pump function, digitalis sensitivity, Torsades de Pointes, increased risk of death due to heart disease.
Electrolytes: Hypokalemia, hypocalcemia, sodium retention.
Metabolism: Dyslipoproteinemia (increased blood triglycerides and cholesterol), reduced glucose tolerance, insulin resistance, increased risk of metabolic syndrome, disruption in bone and vitamin D metabolism, PTH resistance, low active PTH levels (hypoparathyroidism), associated with low serum 25(OH)D levels, triggered osteoclast damage.
Miscellaneous: Asthma, chronic fatigue syndrome, osteoporosis, hypertension, impaired glucose homeostasis.
Pregnancy: Pregnancy complications (e.g., miscarriage, preterm birth, eclampsia).

Magnesium, which is primarily absorbed in the small intestine, is also partially absorbed in the large intestine. Studies using radiolabeled magnesium have shown that the ileum and jejunum are the primary sites of magnesium absorption, and this process occurs uniformly along the small intestine [6]. Absorption varies depending on physiological factors, as well as the administered dose, formulation, and the type of magnesium complex. An increase in magnesium absorption is observed as the administered dose increases and when taken on an empty stomach [7]. Magnesium has been used for many years as a complementary medication in various pharmaceutical dosage forms to relieve pain and address conditions such as

depression, insomnia, and stress associated with pain [47]. The use of magnesium in acute and chronic pain is due to its role as a blocker of a receptor called N-methyl-D-aspartate receptor (NMDAR) [8]. This receptor plays a significant role in pain amplification and in cognitive functions such as learning and memory [9]. It is also possible to state that magnesium provides benefits in terms of cardiovascular diseases [48, 51]. Cardiovascular diseases (CVD) account for nearly half of deaths associated with chronic kidney disease (CKD). Hypomagnesemia has been linked to various cardiovascular disorders and predicts a decline in kidney function that leads to end-stage renal disease (ESRD). For instance, a study aimed at investigating the importance of magnesium in cardiovascular and renal functions, the clinical outcomes of hypomagnesemia on CVD and CKD, and the benefits of magnesium supplementation in managing CVD and CKD concluded that magnesium protects against various cardiovascular diseases and delays the progression of chronic kidney disease [41].

2. FORMS OF MAGNESIUM

In cases of magnesium deficiency in the body, addressing this deficiency by consuming foods rich in magnesium requires a series of complex enzymatic processes. Instead, taking magnesium in an isolated form yields more effective results in terms of bioavailability. The metabolism of magnesium in the body and the form in which it will be used are among the parameters that need to be considered in the treatment approach [51]. The most commonly used organic magnesium supplements include magnesium citrate, magnesium glycinate, magnesium threonate, magnesium malate, and magnesium taurate, while inorganic magnesium supplements include magnesium oxide and magnesium sulfate. Inorganic magnesium supplements are cheaper to produce and easier to digest [13]. However, the bioavailability of organic magnesium salts is better than that of inorganic magnesium salts. Table 4 summarizes the forms of magnesium available in pharmacies, both as prescription and over-the-counter products, the dosage forms in which these are offered to patients, and their intended uses.

Magnesium Citrate: This is one of the most commonly used forms of magnesium with high absorption. It is used for chronic constipation [34], cramps [35], kidney stones [36], regulating nerve and muscle functions [19], and intracellular energy metabolism. As a reliable option, this form is included in the composition of most supplements available on the market.

Magnesium Glycinate: This is the magnesium form with the highest bioavailability. It is used for depression [33], premenstrual syndrome [37], chronic pain [38], and sleep disorders. This form is a chelated compound in which the magnesium ion is bound to the amino acid glycine. Chelation is known as the process of binding a mineral to an organic molecule. This process enhances the absorption of magnesium in the intestines. Magnesium glycinate is known for its high bioavailability and is easily absorbed by the body. This makes it an ideal option for individuals with digestive issues. Compared to inorganic forms (e.g., magnesium oxide), it can be utilized more efficiently in the body without causing irritation to the intestines. Magnesium glycinate has particularly positive effects on the neurological and musculoskeletal systems. Glycine is a neurotransmitter known for its calming properties. Therefore, magnesium glycinate is one of the preferred forms of magnesium for managing anxiety, stress, and sleep disorders. Research has shown that this form has a soothing effect on the nervous system and can improve sleep quality. In particular, magnesium glycinate supplements taken at night may help promote deeper and uninterrupted sleep [45]. Additionally, magnesium glycinate is highly effective in preventing muscle contractions and cramps. It is particularly recommended for athletes, pregnant women, and individuals at risk of magnesium deficiency. It may help reduce muscle fatigue and accelerate recovery after intense physical activity. It is also believed to be beneficial in conditions such as chronic fatigue syndrome (CFS) and fibromyalgia. Furthermore, due to its glycine content, it may have positive effects on gut health and, according to some studies, exhibit anti-inflammatory properties. Magnesium glycinate is a suitable magnesium supplement option for many individuals due to its high bioavailability and positive effects on the nervous system. It stands out in areas such as anxiety management, sleep regulation, and muscle health maintenance [46].

Magnesium Malate: An effective form used in energy metabolism. It is utilized for conditions such as depression, migraines, fibromyalgia, and muscle pain. It also has a laxative effect. Magnesium malate is a compound formed by the binding of magnesium ions with malic acid. Malic acid is a naturally occurring organic acid in the body that plays a crucial role in the Krebs cycle, which is essential for ATP synthesis and energy production. Therefore, magnesium malate supplements stand out for their energy metabolism-supporting effects. They are particularly recommended for conditions such as fatigue, chronic energy

deficiency, and muscle pain. Due to its high bioavailability, magnesium malate can be easily absorbed by the body. This makes it a suitable option for individuals with digestive sensitivities.

Magnesium Taurate: One of the most commonly used forms, magnesium taurate is beneficial in the treatment of depression. Magnesium taurate is a compound formed by the combination of magnesium ions with the amino acid taurine. Taurine is a naturally occurring amino acid in the body that plays a crucial role in nervous system health, cardiac functions, and cellular hydration. Therefore, magnesium taurate is particularly preferred for supporting cardiovascular and nervous system health.

Magnesium Threonate: Among the magnesium forms with high absorption rates. It is effective in regulating memory and cognitive functions due to its ability to cross the blood-brain barrier [32]. This form is particularly effective for memory problems, attention disorders, anxiety, and concentration difficulties.

Magnesium Orotate: Used for maintaining heart health in the cardiovascular system and for symptoms such as bone and back pain.

Magnesium Aspartate: Used for stomach disorders and improving muscle strength.

Magnesium Oxide: Known for its strong laxative effect. However, since most of it is excreted from the body when used, it is insufficient to raise deficient magnesium levels. Therefore, it has low bioavailability.

3. MAGNESIUM FORMS AVAILABLE ON THE MARKET

The majority of orally administered drugs are in tablet form. A simple tablet consists of the active pharmaceutical ingredient and excipients. Excipients are used to ensure that the tablet achieves the desired size, is manufactured without sticking to the equipment during the production process, and disintegrates quickly in the stomach after administration to release the active ingredient. Simple tablets are produced by mixing the active ingredient with excipients and compressing the mixture in a tablet press [10]. Tablets, being a solid dosage form, have better chemical, mechanical, and microbiological stability compared to other dosage forms. When correctly formulated and properly prepared, they provide accurate and consistent dosing. Due to their small size, they are easy for patients to use and convenient to carry because of their lightweight nature. Thanks to these advantages, most dosage forms on the market are produced in tablet form. However, certain disadvantages include the difficulty some patients (such as children, the elderly, and bedridden patients) face in swallowing tablets, as well as the inability to use liquid active ingredients in tablet production.

Effervescent tablets are a type of tablet that rapidly disintegrates and releases the active ingredient into a solution as a result of a reaction between the acid and base in their formulation in an aqueous environment, producing carbon dioxide gas. Effervescent tablets are used by dissolving them in water rather than swallowing them. Due to their larger size compared to regular tablets, special presses are used during the manufacturing process [10].

Capsules are single-dose solid drug forms prepared by filling the active ingredient into a soluble container or shell of various shapes and capacities. They are designed to mask the taste and/or smell of the active ingredient. Compared to tablets, capsules have a higher likelihood of adhering to the esophagus after swallowing. Therefore, it is recommended to take them with a sufficient amount of water while standing [11].

Powders are rarely encountered as finished products. They are produced by mixing the active ingredient with other excipients. The resulting powder mixtures can be taken orally using a spoon or presented to the patient in forms such as packets, sachets, or pouches [12].

It is known that magnesium is also offered to patients in various dosage forms. Table 4 provides the dosage forms and intended uses of different magnesium salts available on the market.

Table 4. Magnesium forms available on the market [13].

Magnesium Form	Dosage Forms	Intended Purposes
Magnesium Citrate	Tablet, Capsule, Sachet, Lozenge	Acute and chronic constipation, cramps, kidney stones, intracellular energy metabolism, regulation of nerve and muscle functions
Magnesium Glycinate	Tablet, Capsule	Depression, premenstrual syndrome, chronic pain, and sleep disorders
Magnesium Malate	Tablet, Capsule, Sachet	Depression, migraines, fibromyalgia, and muscle pain. Also has a laxative effect.
Magnesium Threonate	Tablet, Capsule	Memory problems, attention disorders, anxiety, and concentration difficulties
Magnesium Orotate	Powder, Capsule	Maintaining heart health in the cardiovascular system, bone and back pain
Magnesium Aspartate	Powder, Capsule	Stomach disorders and muscle strength enhancement
Magnesium Oxide	Effervescent Tablet, Sachet, Tablet	Treatment of mild hypomagnesemia
Magnesium Taurate	Capsule	Depression
Magnesium Sulfate	Ampoule	Pain

4. MAGNESIUM CITRATE

Magnesium citrate, classified among organic magnesium salts, is a commonly used form known to provide benefits for various conditions such as constipation, cramps, and musculoskeletal pain. Compared to other forms, magnesium citrate offers certain advantages. To date, numerous studies have been conducted in the literature regarding magnesium citrate. These studies have examined a variety of topics, including arterial stiffness and blood pressure [14], asthma [15], bioavailability [16, 17], chronic inflammatory stress [18], fibromyalgia [19], migraine [20], leg cramps during pregnancy [21], preterm birth [22], pregnancy-induced hypertension [23], diabetes [24], COPD [25], osteoporosis [26], colonoscopy [27], acute low back pain [28], and muscle pain [29]. Recent studies on magnesium citrate reveal that, similar to earlier research, various topics across different fields continue to be investigated.

Magnesium is one of the recommended treatment options for hyperoxaluric patients who form calcium oxalate stones. In a study conducted by Taheri et al., the effects of magnesium oxide and magnesium citrate on 24-hour urinary metabolites and calcium oxalate supersaturation index were compared with a placebo. This clinical trial was randomized, double-blind, and placebo-controlled, including idiopathic hyperoxaluric patients recruited from a tertiary kidney stone prevention clinic. Patients were randomly assigned to three groups to receive either 120 mg of magnesium oxide, 120 mg of magnesium citrate, or a placebo (supplements were administered three times a day with meals). The study concluded that both magnesium oxide and magnesium citrate supplementation significantly reduced urinary metabolites and the calcium oxalate supersaturation index compared to the placebo [30].

Nocturnal Leg Cramps are known as painful, involuntary contractions of the lower extremity muscles occurring during prolonged periods of rest. Magnesium is thought to be effective in the treatment of nocturnal leg cramps, as one of the triggering factors for this condition is the deficiency of certain minerals, such as low magnesium levels. A study evaluating the efficacy of magnesium as an adjunct therapy in reducing the intensity of cramp pain in patients with nocturnal leg cramps was conducted as a randomized,

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clinical, open-label, controlled group trial over a 2-week period. A total of 30 diagnosed patients were divided into two groups. The first group received standard treatment for nocturnal leg cramps (calcium and gabapentin) along with one 100 mg tablet of magnesium citrate daily as adjunct therapy. The second group received only the standard treatment for nocturnal leg cramps. Nocturnal leg cramp pain was measured before the treatment (baseline) and two weeks after the treatment using the Numeric Rating Scale (NRS). The results indicated that adding magnesium to the standard treatment significantly reduced the intensity of cramp pain between pre- and post-treatment measurements. However, the study concluded that magnesium as adjunct therapy was not significantly more effective than standard medication alone in reducing cramp pain in patients with nocturnal leg cramps [31].

Magnesium deficiency is a condition that can impair physical performance. Additionally, magnesium plays a significant role in delayed-onset muscle soreness (DOMS) after workouts. Therefore, physically active individuals and sports professionals should be cautious about magnesium supplementation. A systematic review of the literature focusing on the effects of magnesium citrate on muscle pain in physically active individuals—excluding studies where magnesium was combined with other substances—demonstrated that magnesium citrate reduces muscle pain, improves performance, and provides a protective effect against muscle damage. To achieve these positive effects, it was concluded that individuals engaging in intense exercise require 10-20% more magnesium compared to sedentary individuals. This supplementation is recommended in capsule form, taken 2 hours before training. Furthermore, maintaining magnesium levels within the recommended range during the off-season is advised [32].

Metabolic syndrome increases cardiovascular morbidity and mortality. Recent studies have shown that magnesium supplementation can reduce calcium-magnesium antagonism and elevated interleukin-6 levels, decrease inflammation and atherogenic vascular damage, and thereby improve metabolic parameters. In a study conducted by Kisters et al., a double-blind, controlled, prospective trial was performed on 27 patients with metabolic syndrome to investigate the effects of magnesium on blood pressure and interleukin-6 levels. All patients, who had normal renal function, were given 400 mg of magnesium citrate orally per day. Interleukin-6 concentrations were measured before treatment and at 6 and 12 weeks after treatment. The study concluded that magnesium supplementation significantly improved systolic and diastolic blood pressure values as well as interleukin-6 levels in patients with metabolic syndrome. Magnesium demonstrated anti-inflammatory and anti-arteriosclerotic effects, thereby providing benefits, including stroke prevention, for metabolic patients at high risk of vascular damage [39].

It is estimated that approximately 3% of the population has clinically significant restless legs syndrome (RLS). In a study conducted by Gorantla et al., magnesium citrate monotherapy was found to improve symptoms of restless legs syndrome. This study included 12 untreated adults with RLS, who were administered 200 mg of magnesium citrate daily for 8 weeks. Serum magnesium levels, the International Restless Legs Syndrome Study Group Rating Scale (IRLS), the Kohnen Quality of Life Scale, and multiple suggested immobilization tests (three 1-hour tests) were performed before and after supplementation. The results of the study showed a significant reduction in IRLS scores and an improvement in Kohnen quality of life scores without a noticeable difference in serum magnesium levels [40].

The role of magnesium as a bone-strengthening mineral and an adjunct analgesic is well-documented in the literature. A study investigating the efficacy of orally administered magnesium on bone regeneration and implant stability in immediate dental implants aimed to evaluate various aspects of implant stability, correlate them with serum bone markers, establish a foundation for future research on its potential as a strong analgesic, and assess the promising effects of magnesium on osseointegration. The study concluded that oral magnesium citrate supplementation after the placement of immediate implants helps improve implant stability, reduces horizontal and vertical gaps around the implant, and possesses significant analgesic potential [42].

Magnesium is an essential mineral involved in numerous physiological processes in the human body. A deficiency in this element affects the entire body and can lead to mental disorders, including anxiety disorders. Various theories, supported by studies in both humans and animals, suggest a link between magnesium and anxiety disorders. Magnesium has been shown to influence the function of neurotransmitters involved in anxiety. Magnesium supplementation has been proven to improve health outcomes in individuals with hypomagnesemia. However, it should be noted that the bioavailability of magnesium varies among supplements available on the market, and factors such as intake frequency and dosage also influence magnesium's bioavailability. In this context, a recent study investigating the relationship between magnesium deficiency and anxiety emphasized the importance of maintaining

adequate dietary magnesium levels, given its significant impact on bodily functions and the widespread insufficient intake of this macronutrient. The study concluded that evidence linking magnesium levels to anxiety has increased interest in the potential efficacy of magnesium supplementation for alleviating anxiety symptoms [43].

4. CONCLUSION

Magnesium deficiency manifests with various signs and symptoms in the human body, which can sometimes affect an individual's quality of life. Magnesium, used for preventive or therapeutic purposes, is available on the market in various forms of dosage. Among these, magnesium citrate is the most commonly used form. Research on conditions such as cardiovascular diseases, asthma, migraines, fibromyalgia, cramps, and diabetes has concluded that magnesium citrate alleviates many symptoms in the body. In conclusion, studies demonstrate that magnesium citrate significantly improves the quality of life for individuals.

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