

## INFLUENCE OF MAGNESIUM COMPOUNDS ON SODIUM, POTASSIUM AND CALCIUM LEVELS IN DIFFERENT MICE ORGANS

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### Abstract

The administration of  $Mg^{2+}$  determines not only the increase of  $Mg^{2+}$ , but also induces changes in the tissular levels of  $Ca^{2+}$ ,  $K^+$  and  $Na^+$ . The effects of dietary  $Mg^{2+}$  on macro-elements ( $Ca^{2+}$ ,  $K^+$ ,  $Na^+$ ) levels in mice tissues (heart, liver, spleen, kidney and lung) were investigated in a murine study. Doses of 300, 200, 100, 50 and 25 mg of different Mg compounds (orotate, sulphate, oxide, chloride, carbonate, citrate) were administered by gavage. The results showed that  $Na^+$  and  $K^+$  levels increase, while  $Ca^{2+}$  levels decrease with the increase of the  $Mg^{2+}$  level. In all organs, macro-elements levels decrease in the following order:  $K^+ > Na^+ > Ca^{2+}$ . The highest intracellular  $Na^+$ ,  $K^+$  and  $Ca^{2+}$  levels were obtained in the case of Mg-orotate administration, while no significant changes in the intracellular  $Na^+$ ,  $K^+$  and  $Ca^{2+}$  levels were obtained by Mg supplementation as oxide, citrate or carbonate. The principal component analysis confirmed that the increase of intracellular  $Na^+$  is accompanied by the increase of intracellular  $K^+$  and *vice versa*. Also, high intracellular  $Ca^{2+}$  levels are expected at low  $Mg^{2+}$  doses.

### Rezumat

Administrarea de  $Mg^{2+}$  determină nu numai o creștere a conținutului de  $Mg^{2+}$ , ci și modificări ale nivelurilor de  $Ca^{2+}$ ,  $K^+$  și  $Na^+$  în țesuturi. În această lucrare s-a studiat influența compușilor cu  $Mg^{2+}$  asupra macro-elementelor ( $Ca^{2+}$ ,  $K^+$ ,  $Na^+$ ) în țesuturile (inimă, ficat, splină, rinichi și plămâni) de șoareci. Au fost administrate doze de 300, 200, 100, 50 și 25 mg de diferiți compuși de Mg (orotat, sulfat, oxid, clorură, carbonat, citrat) prin gavaj. Rezultatele indică o creștere a nivelurilor de  $Na^+$  și  $K^+$ , în timp ce nivelul de  $Ca^{2+}$  scade odată cu creșterea nivelului de  $Mg^{2+}$ . În toate organele, nivelul de macro-elemente scade în următoarea ordine:  $K^+ > Na^+ > Ca^{2+}$ . Cele mai mari niveluri intracelulare de  $Na^+$ ,  $K^+$  și  $Ca^{2+}$  au fost obținute în cazul administrării de orotat de Mg, în timp ce, ca urmare a administrării de  $Mg^{2+}$  sub formă de oxid, citrat sau carbonat, nu au fost observate schimbări semnificative în nivelul intracelular de  $Na^+$ ,  $K^+$  și  $Ca^{2+}$ . Analiza componentelor principale a confirmat creșterea  $K^+$  intracelular odată cu creșterea  $Na^+$  și *vice-versa*. De asemenea, concentrații ridicate de  $Ca^{2+}$  intracelular apar la administrarea de doze mici de  $Mg^{2+}$ .

**Keywords:** magnesium compounds, tissue uptake, mice, calcium, potassium, sodium

### Introduction

The major dietary nutrients needed by humans are grouped into macro-nutrients (proteins, carbohydrates and fat) and micronutrients (vitamins and minerals) [1]. The minerals are present in all body tissues and fluids, their presence being necessary to maintain the physicochemical processes that are essential for life [8, 19]. Dietary supplements are ingested in order to supply micro- and macro- nutrients that are lacking in the diet, to maintain or improve health, to support a particular body function (like immunity or cardiovascular status), to reduce health risks and to prevent diseases [9, 14, 23].

Calcium ( $Ca^{2+}$ ), magnesium ( $Mg^{2+}$ ), sodium ( $Na^+$ ) and potassium ( $K^+$ ) have important roles in numerous biologic and cellular functions [4].  $Mg^{2+}$  and  $K^+$  are the main intracellular cations, while  $Na^+$  and  $Ca^{2+}$  are mainly extracellular ions, but only some of their compounds exhibit good intracellular absorption [10, 14, 24].  $K^+$  plays a vital role in the heart and skeletal muscle contraction, nerve conduction and renal function, while  $Ca^{2+}$  mediates muscle contraction and controls the exocrine, endocrine and neurocrine functions.  $Mg^{2+}$  has an important role in enzyme activation, energy metabolism, synthesis of proteins and DNA,  $Ca^{2+}$

and  $K^+$  flux regulation, bone formation, neuromuscular excitability, while  $Na^+$  has a crucial role in the excitability of muscles and neurons and in the regulation of body fluids [4, 17, 18]. These elements are absorbed from the gastrointestinal tract and excreted by the kidneys, their homeostasis being balanced by these mechanisms. The main  $Mg^{2+}$  reserves are kept in the skeletal muscle, while the main  $Ca^{2+}$  reserves in the structural bones [17]. When the body reserves of electrolytes ( $Na^+$ ,  $K^+$ ,  $Ca^{2+}$  and  $Mg^{2+}$ ) decrease, the gastrointestinal absorption, bone and renal resorption increase to normalize their levels [4].  $K^+$  and  $Mg^{2+}$  deficiency significantly alters the functions of cell membranes, in terms of ionic permeability. Small changes in the serum  $K^+$  can affect various body functions like heart rhythm and skeletal muscle function. In the case of hypomagnesemia, it is impossible to correct the intracellular  $K^+$  deficiency [7, 11, 13, 16].

There is no correlation between the plasma and intracellular electrolyte content [21].  $Ca^{2+}$  antagonizes the effects of  $K^+$  and  $Mg^{2+}$  at the cell membranes, being very useful in the treatment of hyperkalemia and hypermagnesemia [7, 13, 16]. The effect of micronutrients in the body's physiological need is not entirely understood through all organs and systems. Usually, the micronutrients are required in the cells and tissues and might undergo a specific metabolic route within the cells. Although the blood is the main delivery route for almost all nutrients toward cells and tissues, its composition may not reflect the real nutrient status of cells. Moreover, the traditional targets as blood, urine and hair do not always reflect correctly the nutrients level in the body. As a result, there is a need to develop suitable methods to determine the nutritional status [3]. As the serum concentration does not correlate with the tissular  $Ca^{2+}$  or  $Mg^{2+}$ , deficiencies are difficult to identify, due to their easy migration into bones, muscles, soft tissue and other body parts. Only 0.3% of the total body  $Mg^{2+}$  is present in serum and 1% in the extracellular fluids; the highest part represents free  $Mg^{2+}$ , the other part being bonded to plasmatic proteins. A similar situation was observed for  $Ca^{2+}$  [20]. Moreover,  $Mg^{2+}$  strongly interacts with  $Ca^{2+}$  and  $K^+$ , the deficiency-excess of one cation influencing the effects of the others [5, 12, 22, 26].

A large part of the population is confronting stress, sleeping disorders and chronic fatigue. In half of the cases, besides this symptoms Mg deficiency also appears. This finding made magnesium supplements gaining much attention. Moreover, magnesium formulations are among the most commonly used supplements. Our previous studies described the  $Mg^{2+}$  levels of mice tissues (heart, liver, spleen, kidneys and lungs) after administration of different  $Mg^{2+}$  compounds

(orotate, sulphate, oxide, chloride, carbonate, citrate). Despite the fact that translating the results of animal experiments to humans is sometime difficult or subject to failure, mice models allow elucidating the role of supplements in the organism, give insights on their metabolism and allow identification of their function in key biochemical and physiologic processes. Small changes in plasma  $Mg^{2+}$  level induce modifications of other ions ( $K^+$ ,  $Na^+$  and  $Ca^{2+}$ ). The treatment of  $Mg^{2+}$  deficiency and assurance of optimum intracellular levels of  $Ca^{2+}$ ,  $K^+$  and  $Na^+$  depend on the  $Mg^{2+}$  source utilized in the therapy. In this study, the influence of most frequently used  $Mg^{2+}$  supplements on  $K^+$ ,  $Na^+$  and  $Ca^{2+}$  levels in different mice tissues has been investigated. Furthermore, Principal Component Analysis (PCA) was used to reveal the relationships between the levels of different macrominerals and to differentiate the supplements by dose and formulation.

### Materials and Methods

$Mg^{2+}$  compounds (orotate, sulphate, oxide, chloride, carbonate, citrate), 65%  $HNO_3$  and 30%  $H_2O_2$  were purchased from Merck, Germany. A multi-elemental standard solution of 1000 mg/L (Merck, Germany) containing the analysed elements ( $Na^+$ ,  $K^+$  and  $Ca^{2+}$ ) was used for inductively coupled plasma optical emission spectrometer (ICP-OES) calibration. For all dilutions, ultrapure water (18.2 M $\Omega$ /cm) obtained from a Millipore Direct-Q3 UV system (Millipore, France) was used.

A number of 62 adult male Crl:CD1(ICR) mice with an average weight of  $26.92 \pm 0.21$  g were used in the study as previously described by Moisa *et al.* [15]. Amounts of 25, 50, 100, 200 and 300 mg of  $Mg^{2+}$  compounds were dissolved (orotate, sulphate, chloride and citrate) or suspended (carbonate, oxide) in distilled water and administered by gavage. In the case of the control group, distilled water was administered. After 48 h, the animals were euthanized by cervical dislocation. The heart, lung, liver, spleen and kidney were used [2]. In each organ, the  $Na^+$ ,  $K^+$  and  $Ca^{2+}$  concentrations were determined (mg/kg) by using Optima 5300 DV ICP-OES (Perkin Elmer, USA), after microwave digestion (MW). The digestion was performed on about 200 mg organ tissue, using  $HNO_3/H_2O_2$  (10/1, v/v) in closed polytetrafluoroethylene (PTFE) vessel MW system (Berghof MWS-3+, Eningen, Germany) according to the method described by Zhao *et al.* [25]. The operating conditions used for ICP-OES determination were: 1300 W RF power, 15 L/min plasma flow, 2.0 L/min auxiliary flow, 0.8 L/min nebulizer flow and 1.5 mL/min sample uptake rate.

The calibration standards (0.1, 0.2, 0.5, 1, 2, 4 and 6 mg/L) were prepared from multi-elemental standard after appropriate dilution. The accuracy of the analytical results was assured by analysing 3 replicates and a certified reference material (CRM). Beef/pork meat CRM (LGC7000, LGC Standards GmbH, Germany) was used for quality assurance. The recoveries (%), calculated using the average of three replicates were in the range of 90-106%.

*Statistical analysis*

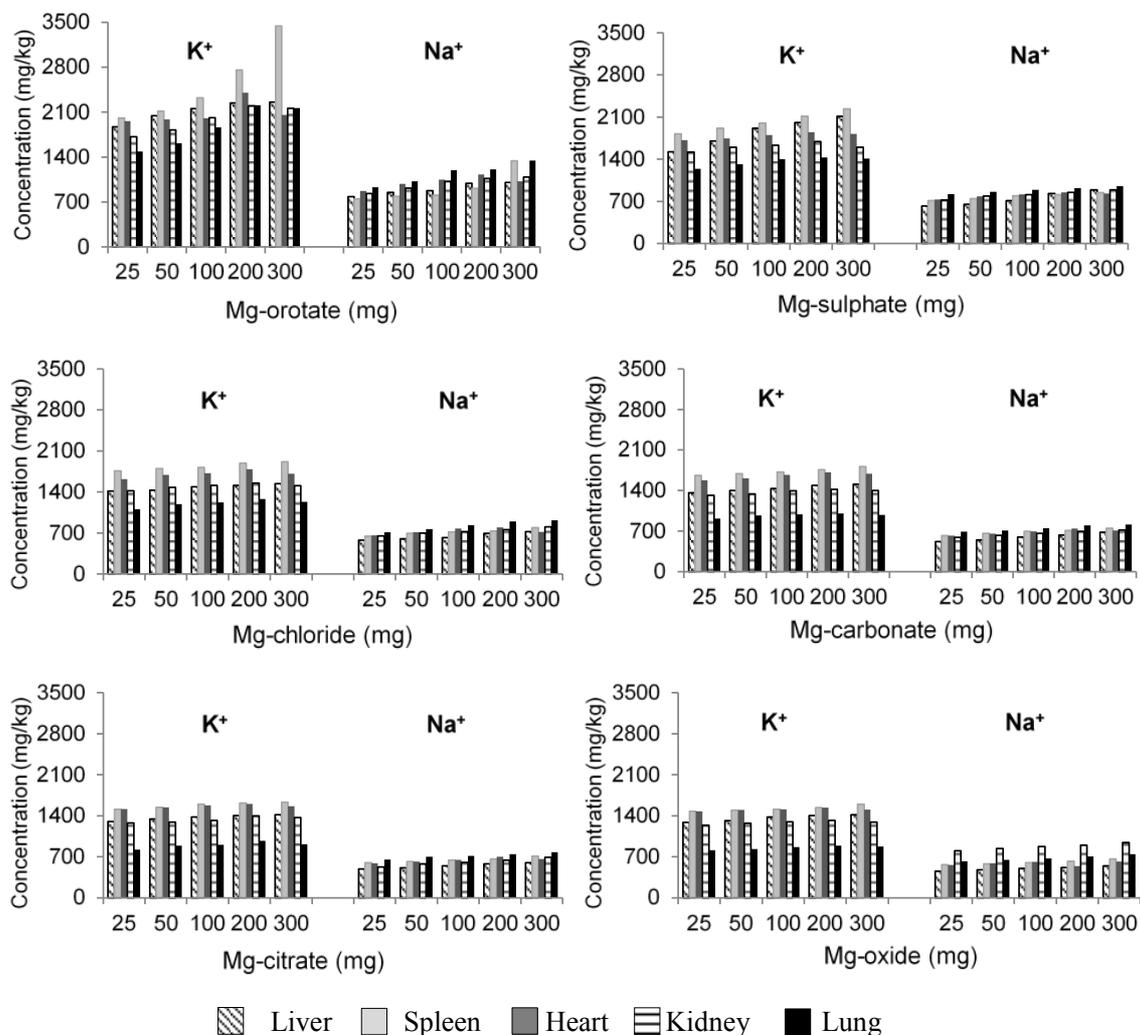
To interpret the dataset structure, principal component analysis (PCA) with varimax rotation was performed using the XL Stat Microsoft Excel plug-in (Addinsoft).

**Results and Discussion**

Generally, for multi-elemental analysis of non-liquid samples using ICP-OES, a digestion or dissolution step should be included prior the instrumental analysis. MW digestion is a powerful

sample preparation method with considerable advantages over the conventional digestion method: low consumption of reagents and time and reduced contamination. The disadvantage of the MW method is that it is more expensive and requires some experience [6]. The main advantages of ICP-OES method is the capability for analysing almost all the elements in the periodic table, wide linear dynamic ranges, good sensitivity, limited spectral and chemical interferences, low detection limits, capacity to measure trace to high concentrations, short analysis time (1 min), low sample consumption (0.5 - 1.0 mL) and reasonable costs. The main disadvantage of ICP-OES is that the technique is sample destructive.

The tissular  $\text{Na}^+$ ,  $\text{Ca}^{2+}$  and  $\text{K}^+$  levels, after administration of different doses of various  $\text{Mg}^{2+}$  formulations are presented in Figures 1 and 2. Generally, the macro-elements contents decreases in the order  $\text{K}^+ > \text{Na}^+ > \text{Ca}^{2+}$ , in all organs.



**Figure 1.**

The  $\text{K}^+$  and  $\text{Na}^+$  concentrations in organs after the administration of various compounds and doses of Mg supplements

The  $\text{Ca}^{2+}$  content decreases, while the  $\text{Na}^+$  and  $\text{K}^+$  contents increase with the increase of the  $\text{Mg}^{2+}$  content. The lowest  $\text{K}^+$  content is found in lung (811 mg/kg), while the highest in spleen (3443 mg/kg). The median  $\text{K}^+$  concentration decreases in the order: spleen > heart > liver  $\geq$  kidney > lung. The  $\text{Na}^+$  content ranged between 453 mg/kg (liver) and 1344 mg/kg (lung), the median  $\text{Na}^+$  decreasing in the order lung  $\geq$  kidney > heart > spleen > liver. The highest concentration of  $\text{Na}^+$  is found in the

extracellular space, its homeostasis being controlled by the kidneys [16]. Moreover, the  $\text{K}^+$  increase favours the renal excretion of  $\text{Na}^+$ .

The lowest  $\text{Ca}^{2+}$  content is found in the kidney (17.3 mg/kg), while the highest in the heart (111 mg/kg), the median  $\text{Ca}^{2+}$  decreasing in the following order: heart  $\geq$  lung > spleen  $\geq$  liver > kidney, probably because  $\text{Ca}^{2+}$  is excreted in the kidney.  $\text{Ca}^{2+}$  has an opposing effect to  $\text{K}^+$  and  $\text{Mg}^{2+}$  at the cellular membrane level.

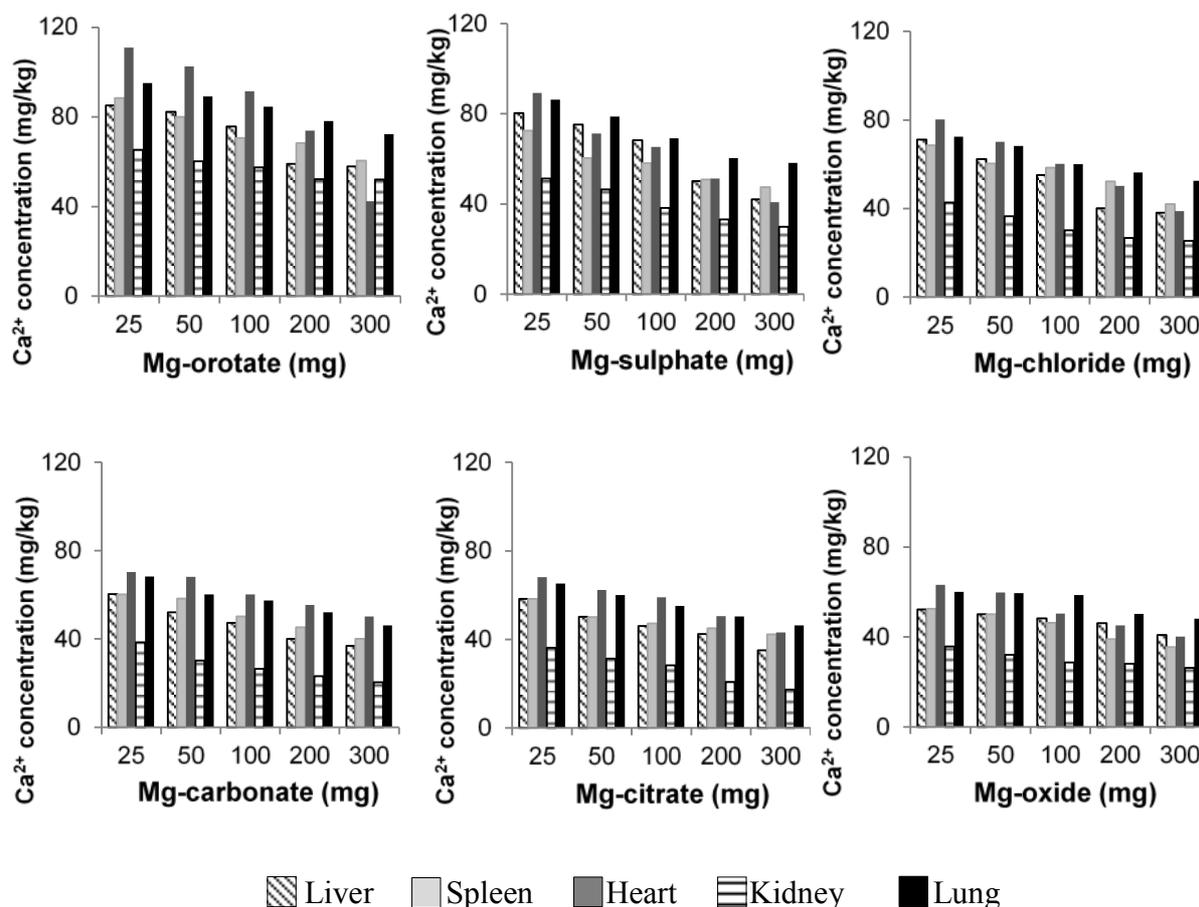
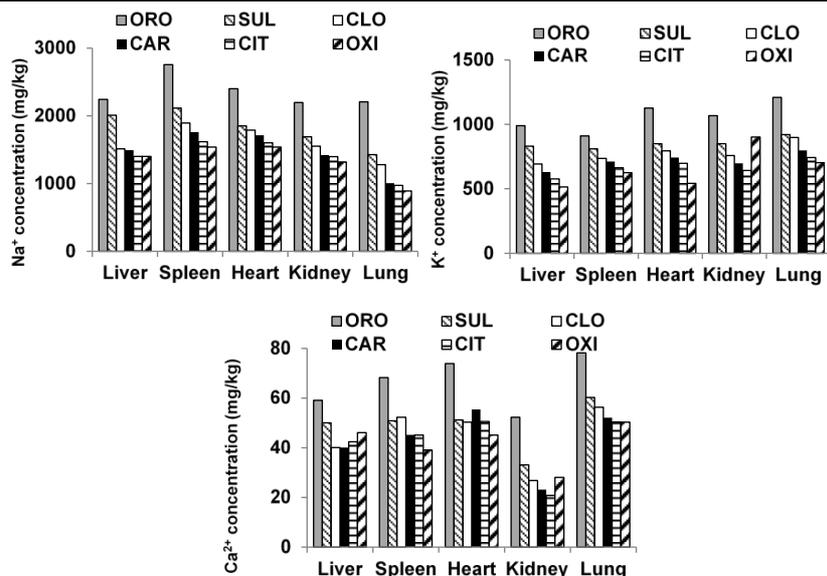


Figure 2.

$\text{Ca}^{2+}$  concentration in organs after the administration of various compounds and doses of Mg supplements

The velocity of  $\text{K}^+$  exchange between cells and interstitial liquid vary from organ to organ, reaching the highest values in kidneys and lungs.  $\text{Ca}^{2+}$  induces cell excitability that depends on the  $\text{Na}^+$  activity. The decrease of the  $\text{Ca}^{2+}$  level has the effect of increasing the membranes permeability for  $\text{Na}^+$  [11]. A high extracellular  $\text{Na}^+$  level leads to positive electric charges accumulation outside the cell wall, as well as cell membranes tension. Any other outside stimulus determines the membrane repolarization. By increasing the  $\text{Mg}^{2+}$  orotate dose,

the  $\text{K}^+$  level increases in spleen, kidney and lung, while in the liver remains constant independently of the administered dose. A possible explanation could be the role of  $\text{Mg}^{2+}$  in the regulation of intracellular  $\text{K}^+$  level. In case of the other  $\text{Mg}^{2+}$  supplements, no significant variation of the  $\text{K}^+$  level with the increase of the  $\text{Mg}^{2+}$  dose was observed, in any of the studied organs. The  $\text{Na}^+$  level was not influenced by the administration of  $\text{Mg}^{2+}$  supplements.



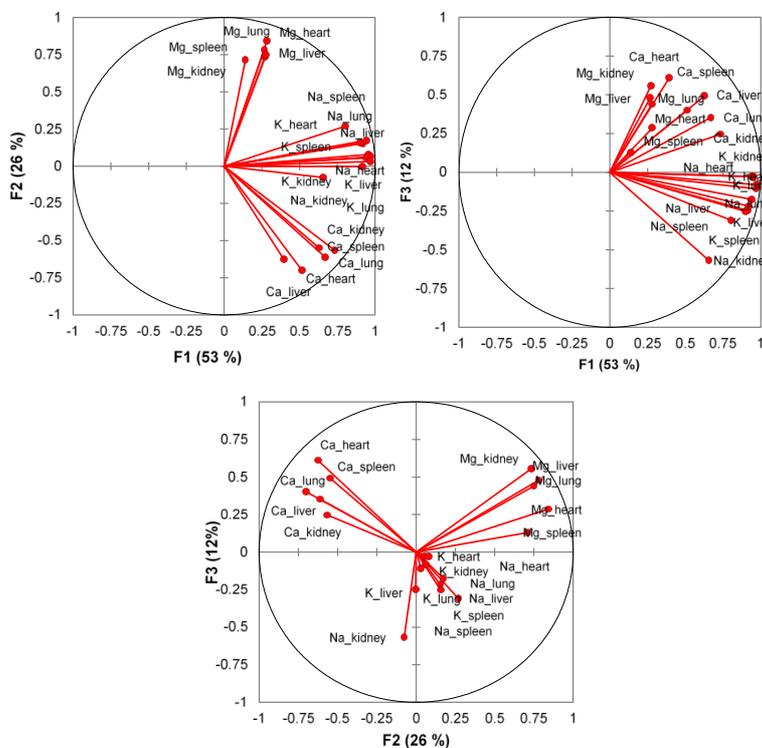
**Figure 3.**

The  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Ca}^{2+}$  concentrations in organs after the administration of 200 mg of various Mg supplements, where ORO = orotate, SUL = sulphate, CLO = chloride, CAR = carbonate, CIT = citrate, OXI = oxide

Generally, the  $\text{Ca}^{2+}$  level was not influenced by the dose of  $\text{Mg}^{2+}$  supplements; however, for all supplements, in heart, an inverse relationship between the  $\text{Mg}^{2+}$  dose and the  $\text{Ca}^{2+}$  level was registered.

In order to identify a relationship between the  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Ca}^{2+}$  levels and different salts, the Mg

supplements were compared at a single dose of 200 mg. Figure 3 shows that the highest levels of intracellular  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Ca}^{2+}$  were obtained for  $\text{Mg}^{2+}$  orotate administration. No significant changes in the intracellular  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Ca}^{2+}$  levels were obtained by dosing  $\text{Mg}^{2+}$  supplement in the form of oxide, citrate or carbonate.

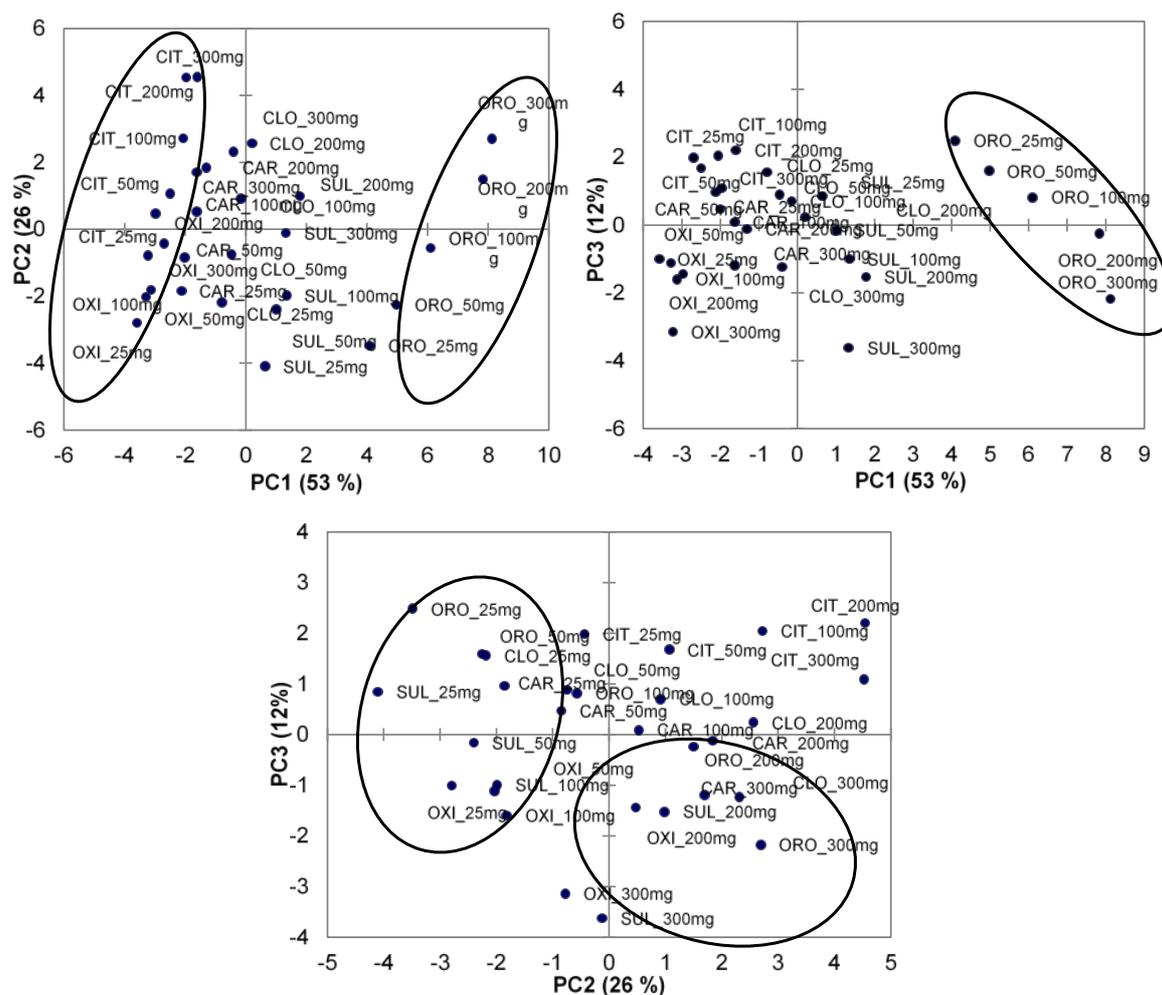


**Figure 4.**

Projection of factor loadings on the principal components

PCA was applied to intracellular levels of  $K^+$ ,  $Na^+$ ,  $Mg^{2+}$  and  $Ca^{2+}$  to reduce and visualize the data structure. The linear combinations of original variables are named principal components (PCs). According to the Kaiser criterion, only the PC's with eigenvalue higher than 1.0 was retained and subjected to varimax rotation. The varimax rotated loadings of the 3 PC's with eigenvalues  $> 1.0$  explains 91% of the system variability. The factor

loadings (Figure 4) show the correlation of PCs with the original variables and among PCs. The first factor (PC1) accounting for 53% of the total variance (loadings  $> 0.7$ ) is related to the intracellular levels of  $Na^+$  and  $K^+$ , suggesting that the increase of intracellular  $Na^+$  will be accompanied also by the increase of intracellular  $K^+$  and *vice versa*.



**Figure 5.**

Scatter plots of the PCs

The second PC2 with a contribution of 26% was associated to  $Mg^{2+}$ , and suggests that  $Mg^{2+}$  level is directly proportional with  $Na^+$  and  $K^+$  levels and inversely proportional with  $Ca^{2+}$  levels. The third PC3 (12%) was associated to  $Ca^{2+}$  and suggests that the  $Ca^{2+}$  levels are inversely correlated with the  $Na^+$  and  $K^+$  levels. The biplots (Figure 5) reveal that  $Na^+$  and  $K^+$  intracellular level (PC1) distinguish between orotate, citrate and oxide, but does not separate the other supplements, while the  $Mg^{2+}$  levels (PC2) differentiate between orotate and the other supplements. The  $Ca^{2+}$  level (PC3) differentiates supplements by dose but not by the

salt used. Thus, in the case of  $Mg^{2+}$  orotate supplement administration, the intracellular  $Na^+$  and  $K^+$  concentrations are expected to be high, while in the case of the citrate and oxide supplements administration the  $Na^+$  and  $K^+$  concentrations are expected to be low. Also, high intracellular  $Ca^{2+}$  contents are expected at low  $Mg^{2+}$  doses and low  $Ca^{2+}$  contents at high  $Mg^{2+}$  doses.  $Na^+$ ,  $K^+$ ,  $Ca^{2+}$  and  $Mg^{2+}$  regulate the neuromuscular excitability and the coagulation mechanism; therefore, the closer monitoring of  $Mg^{2+}$  level is very important in cardiac patients. A low  $Mg^{2+}$  plasmatic concentration (hypomagnesemia)

increases the cardiac excitability, cardiac arrhythmias, while a high  $Mg^{2+}$  concentration (hypermagnesemia) suppresses the cardiac conducting system. The intracellular  $K^+$ ,  $Ca^{2+}$  and  $Mg^{2+}$  concentrations are closely linked, any deficiency influencing the other elements levels.  $Mg^{2+}$  plays an important role in maintaining adequate intracellular  $Ca^{2+}$  levels (e.g.  $Mg^{2+}$  deficiency influences the mobility of  $Ca^{2+}$  in bones) [4, 5]. Furthermore,  $Mg^{2+}$  is excreted renally, resulting in high  $Mg^{2+}$  levels in kidneys compared to other macro-elements/organs.

The obtained results indicate higher variations of intracellular  $Ca^{2+}$ ,  $K^+$  and  $Na^+$  in the studied organs after the  $Mg^{2+}$  orotate administration compared to other  $Mg^{2+}$  compounds (sulphate, oxide, chloride, carbonate and magnesium citrate). A possible explanation could be the more effective  $Mg^{2+}$  absorption, at the intracellular level, after the administration of  $Mg^{2+}$  orotate. Thus,  $Mg^{2+}$  orotate can be used to supplement the  $Mg^{2+}$  level in the human body, considering the lack of secondary effects after administration and the efficient adsorption at the intracellular level.

### Conclusions

The determination of  $Mg^{2+}$  concentration in the human body (blood, serum, tissues, skeleton) is recommended to assess the renal function, gastrointestinal disorder, electrolytes level, neuromuscular activities and cardiac function. The administration of  $Mg^{2+}$  supplements determined variations of  $K^+$ ,  $Na^+$  and  $Ca^{2+}$  in all assessed mice tissues (heart, liver, spleen, kidney and lung). The most important variations were observed after the administration of Mg-orotate, probably due to the chemical structure of this compound that allows better  $Mg^{2+}$  absorption at the intracellular level. The highest macro-elements concentrations were found in heart ( $Ca^{2+}$ ), spleen ( $K^+$ ) and lung ( $Na^+$ ) tissues. The increase of the  $Mg^{2+}$  content determines the increase of  $K^+$  and  $Na^+$  and decrease of  $Ca^{2+}$  levels in tissues. A high amount of  $Mg^{2+}$  was determined in kidney, probably due to its capacity to rapidly excrete large amounts of  $Mg^{2+}$ . Furthermore, a low  $Mg^{2+}$  level interferes with the effects of the parathyroid hormones, decreasing the amount of  $Ca^{2+}$  and  $K^+$ . Regardless of the administered  $Mg^{2+}$  dose and particular compound, the macro-elements levels decreased in the following order:  $K^+ > Na^+ > Ca^{2+}$ , but some differences between the administered  $Mg^{2+}$  compounds were noticed. The PCA revealed differences between the effect of Mg-orotate, Mg-citrate and Mg-oxide supplements on the intracellular  $Na^+$  and  $K^+$  level,

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