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The bioaccessibility and tolerability of marine-derived sources of magnesium and calcium

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A B S T R A C T

It is generally accepted that mineral deficiencies, including magnesium and calcium, are widespread globally. Dietary supplementation may be an effective approach to combat such deficiencies. However, challenges associated with limited mineral solubility in the digestive system can impede effective dissolution and hinder absorption, leading to deficiency, and undesirable gastrointestinal disturbances including diarrhoea. Seawater is considered to be a rich source of bioactive magnesium, calcium, and 72 other trace minerals. In this study, we examine two different marine-derived multimineral products as potential dietary supplements. Aquamin-Mg, sourced from seawater is rich in magnesium (12%), and Aquamin F, a seaweed-derived multimineral is rich in calcium (32%). Both products also contain a diverse array of over 72 minerals, characteristic of their oceanic origin. Our study comprises two experiments. The first experiment evaluates and compares the solubility of Aquamin-Mg, commercially available magnesium bisglycinate, and Pure Magnesium Bisglycinate (PrizMAG) during *in vitro* digestion using the INFOGEST method. Results demonstrate that Aquamin-Mg exhibits superior solubility than the other magnesium sources during the gastric and intestinal phases, particularly when administered alongside food materials. The second experiment is a randomized, double-blind, placebo-controlled study in a small cohort of healthy older aged adults to assess the tolerability of a combined Aquamin-Mg/Aquamin-F supplement over a 12-week period. The findings indicate that this combination supplement is well-tolerated, with no significant adverse events reported, emphasizing its potential as a means of addressing mineral deficiencies.

1. Introduction

Suboptimal dietary practices, intensive agricultural techniques, and the diminished nutritional value of foods are common factors that contribute to mineral deficiencies [1]. These deficiencies may lead to numerous health issues such as migraines, fatigue, neuromuscular irritability, anxiety, arrythmia and nausea [2–6]. While dietary supplementation is an effective strategy to address insufficiencies and deficiencies [7,8], many magnesium and calcium supplements on the market suffer from limited solubility, tolerability and bioavailability, compromising their efficacy. For instance, magnesium oxide, despite its high elemental magnesium concentration, has low solubility and bioavailability [9], while other sources like magnesium citrate offer better solubility but lower levels of elemental magnesium [10]. These differences arise because magnesium oxide is an inorganic magnesium salt, whereas magnesium citrate is an organic magnesium salt. Studies indicate that organic magnesium salts boast higher solubility and bioavailability compared to inorganic magnesium salts [11,12]. The solubility of a supplement directly affects its dissolution and absorption in the digestive system [13]. Magnesium supplements that do not dissolve effectively, often have limited absorption and tolerability. Unabsorbed magnesium salts exert high osmotic activity in the large intestine, potentially causing undesired gastrointestinal distress [14]. Balancing the need to deliver an adequate amount of elemental magnesium in a supplement that can efficiently dissolve in the gastrointestinal tract, while simultaneously guaranteeing optimal absorption without causing undesired side effects, presents a notable challenge.

Magnesium and calcium are essential minerals that are involved in numerous physiological processes in the human body. Magnesium is required for over 300 enzymatic reactions, including DNA synthesis, energy production, muscle and nerve function [15], while calcium plays a critical role in blood clotting, muscle contraction, nerve function, and bone health [16]. In the USA, the recommended daily allowance (RDA) for magnesium is 320 mg/day and 420 mg/day for adult females and males [17], respectively, while the recommended intake for calcium for both males and females is 1000 – 1200 mg/day [18].

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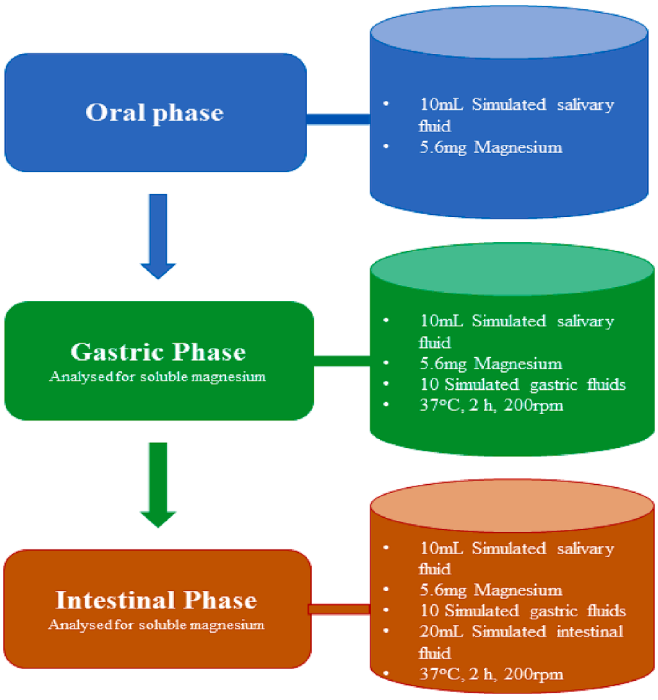

Fig. 1. *In vitro* digestion workflow used to simulate digestion and release of Magnesium from different magnesium supplements.

However, nearly half (48 %) of the US population falls short of the recommended dietary intake of magnesium, while 42 % do not meet the recommended calcium intake from their food [19,20]. In the European Union (EU), the recommended daily intake for magnesium is 300 mg/day for women and 350 mg/day for men [17], while the recommended calcium intake is 1000 mg/day for adult men and women [21]. Similar to the USA, individuals living in the EU also face challenges in meeting the recommended intakes for both calcium and magnesium [22,23].

It has recently been demonstrated that it is possible to extract magnesium from ocean water (Aquamin-Mg). Previous researchers have reported that Aquamin-Mg exhibits high bioavailability, comparable to other magnesium sources [24]. Most notably Aquamin-Mg shows significantly better bioavailability than magnesium oxide and a similar profile to the more bioavailable magnesium chloride. Additionally, the *Lithothamnion sp*. of red seaweed serves as a valuable source of bioavailable calcium known as Aquamin-F. This supplement has previously been shown to have health benefits in terms of bone [25,26], joint [27,28] and digestive health [29–31]. Both products also contain a 'mineral tail' of over 72 minerals, present in small amounts and characteristic of their oceanic origin. The bioavailability of Aquamin-F *in vivo* has been previously established [32]. The combination of Aquamin-Mg and Aquamin-F, known as MMB (Marine Mineral Blend) was chosen as magnesium and calcium deficiencies are common in older adult populations [33,34] and often older adults have reduced ability to digest and absorb nutrients [35]. Aquamin MMB has been tested previously in rodents [36,37].

This study aimed to first evaluate and compare the solubility of Aquamin-Mg with two commonly available commercial magnesium supplements, using the INFOGEST *in vitro* digestion method. The second aim of the study was to evaluate the tolerability of a combination of Aquamin-Mg and Aquamin-F (MMB) in a randomized, double-blind, placebo-controlled study involving a small cohort of healthy older aged adults.

2. Materials and methods

2.1. Solubility of magnesium supplements in water

Magnesium supplement solubility was evaluated at 1 %w/v and 5 % w/v concentration. Fig. 1. shows *in vitro* digestion workflow used to simulate digestion and release of Magnesium from different magnesium supplements. 500 mg (M) and 2500 mg (M) from each of the magnesium supplements were weighed into labelled 50 mL plastic tubes. 50 mL of distilled water was added to the tube and mixed by shaking vigorously. After mixing, the solution was filtered through pre-weighed (M1) 11 μm filter paper (Whatman). The filter paper was dried in the oven at 100 °C overnight. After drying, the filter was placed in a desiccator to cool before weighing (M2). Solubility was calculated as the ratio of soluble fraction [M – (M2-M1)] to initial sample weight (M) and multiplied by 100. Whatman 11 μm filter paper has a molecular weight cutoff as high as 100KDa and intestinal permeability studies are done using molecules ranging between 0.15KDa and 3.35KDa which exhibit high permeability [38]. The molecular weight of the magnesium forms (hydroxide and bisglycinate) in the tested supplements are within this range.

2.2. In vitro digestion of magnesium supplements

The magnesium supplements were subjected to *in vitro* digestion in triplicate according to the INFOGEST protocol as described previously [24,39]. The protocol involved the simulation of oral, gastric, and intestinal digestive phases. All chemicals and enzymes used for the preparation of simulated salivary, gastric, and intestinal fluids were purchased from Sigma Aldrich. The quantity of magnesium digested was calculated based on the NIH Office Of Dietary Supplement. The USA recommended dietary allowance for men (RDA) is set at 420 mg/day, which based on the food bolus used in the digestion protocol was equivalent to 5.6 mg (per body weight of a 75Kg male) of Magnesium from the three sources (commercial magnesium bisglycinate (CMB) (Monarch Nutraceuticals, North Dock Ogden, Utah, United States), Pure Magnesium Bisglycinate (PrizMAG) (ITL Health, Sarnia, Ontario, Canada), and Aquamin-Mg (Marigot Ltd, Carrigaline, Cork, Ireland)). All tested supplements were supplied by Marigot Group Limited, Strand Farm, Curraghbinny, Carrigaline, Co. Cork, Ireland. The oral digestive phase involved the use of simulated salivary fluid containing 15.1 mM KCl, 3.7 mM KH_2PO_4, 13.6 mM $NaHCO_3$, 0.15 mM $MgCl_2(H_2O)_6$, 0.5 mM $(NH_4)_2CO_3$, 1.1 mM HCl and 1.5 mM $CaCl_2(H_2O)_2$ in final volume of 10 mL, adjusted with distilled water. This was followed by the addition of simulated gastric fluid; 6.9 mM KCl, 0.9 mM KH_2PO_4, 25 mM $NaHCO_3$, 47.2 mM NaCl, 0.1 mM $MgCl_2(H_2O)_6$, 0.5 mM $(NH_4)_2CO_3$ to replicate the gastric environment. All chemicals used were laboratory grade. Pepsin (Sigma Aldrich, St. Louis, Missouri, United States) and $CaCl_2$ were included to achieve a final concentration of 2000 U/mL and 0.15 mM in the final volume of the gastric phase (20 mL), respectively. To acidify the mixture to pH 3, hydrochloric acid (HCl, 6 M) was added, followed by water to reach a final volume of 20 mL. Samples were then incubated in a shaking bath (37 °C and 200 rpm) for 2 h. The pH was measured and re-adjusted to pH 3 at 1 h of incubation and 1 mL sample was taken after the 2-hour incubation period and stored in a −20 °C freezer for subsequent elemental analysis.

After the oral and gastric incubation, simulated intestinal fluid (composition: 6.8 mM KCl, 0.8 mM KH_2PO_4, 85 mM $NaHCO_3$, 38.4 mM NaCl, 0.33 mM $MgCl_2(H_2O)_6$) was added together with pancreatin (Sigma Aldrich, St. Louis, Missouri, United States), to achieve a trypsin activity of 100 U/mL, and bile salts (10 mM) (Sigma Aldrich, St. Louis, Missouri, United States). Calcium chloride was added to reach a concentration of 0.6 mM. The pH was adjusted to 7 (NaOH, 1 M) followed by water to reach a final volume of 40 mL. Samples were incubated in a shaking water bath (37 °C and 200 rpm) for an additional 2 h. The pH was measured and adjusted to pH 7 at 1 h of incubation. At the end of the 2-hour incubation period, 1 mL aliquots of each sample were taken and

Table 1
Comparison between the demographics, health status and nutritional status of participants supplemented with placebo or Aquamin MMB.

		Placebo	Aquamin MMB
Demographics	**Gender (no. (%))**		
	Male	7 (24 %)	6 (21 %)
	Female	6 (21 %)	10 (34 %)
	Age (years ± SD)		
	Male	71. 3 ± 7.3	72.8 ± 6.7
	Female	72.0 ± 4.4	75.0 ± 3.8
	Total	71.62 ± 5.92	74.19 ± 5.01
	Race (%)		
	Caucasian	100	100
	Years Education ≥ 13 (no. (%))	10 (77)	15 (94)
Health Status	Weight (kg)	77.9 ± 8.9	71.8 ± 15.2
	BMI (kg/m^2)	27.1 ± 2.6	26.7 ± 4.6
	Alcohol Intake (ml/day)	8.33 ± 9.06	11.33 ± 14.93
	Smoking (no. (%))		
	Non-smoker	6 (46)	10 (62.5)
	Smoker	0 (0)	1 (6.25)
	Former smoker	7 (44)	5 (31.25)
	Physical Activity (MET-min/week ± SD)	3500 ± 2215	6065 ± 5414
Nutritional Status	Caloric Intake (kcal/day)	2393 ± 686.3	2075 ± 604.1
	Dietary Magnesium Intake (mg/day)	400.6 ± 124.0	336.2 ± 101.8
	Dietary Calcium Intake (mg/day)	1081 ± 343.2	1045 ± 580.6

stored in a −20 °C freezer for subsequent elemental analysis. In the digestive simulation involving food material, 5.6 mg of magnesium from each supplement was added to a food sample (In this case, Cottage pie (Dunnes stores, Tralee, County Kerry, Ireland)) to a final weight of 5g [28] and masticated manually prior to being subjected to the digestive simulation. The cottage pie is a mix of Irish beef, onion, gravy, and mashed potatoes and contains 104Kcal/100g, 4.9g/100g total fat, 13.2g/100g total carbohydrate, 1.1g/100g fibre, 3.8g/100g protein, and 0.9g/100g salt. A control was included in the simulation involving pie and magnesium which only contained the food sample and no magnesium supplement. The choice of cottage pie for this experiment was based on the frequency of global consumption of its major ingredients, for example potato is the third most important crop in the world [33] and beef is globally consumed by millions.

2.3. Magnesium quantification using inductively coupled plasma mass spectroscopy

Magnesium concentration of samples taken from the gastric phase and intestinal phase, were analysed using an inductively coupled mass spectrometry system (ICP-MS). Prior to analysis, aliquots taken from the gastric and intestinal phase of digestion were centrifuged (10,000 rpm for 10mins) and digested in a microwave digester (CEM corporation) with a digestant (1:1 water to Nitric acid (65 % Nitric acid), for the digestion 9 mL digestant was added to 1 mL sample in a CEM microwave Teflon tubes). The digestion dissolves the minerals and large molecules present in the sample prior to analysis. The digested samples were filtered and diluted appropriately with diluent containing 2 % and 0.5 % ICP-MS grade nitric acid and hydrochloric acid in ultrapure water (18.2mΩ·cm), respectively. Diluted samples were analysed on the inductively coupled plasma mass spectroscopy instrument (Agilent7800 ICP-MS, Santa Clara, CA 95051, USA). Agilent ICP-MS calibration standards (5, 10, 20, 50, 100, 500, 1000, 2000 ppb, and R square of 0.999) were used for the analysis (Agilent, 5301 Santa Clara, CA 95051, United States).

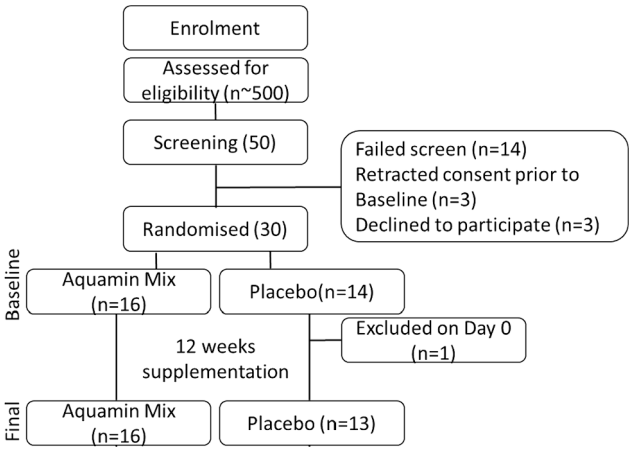

Fig. 2. Flow diagram of subjects/participants.

2.4. In vivo study population

The study protocol (YN001) and all procedures were approved by the Cork Teaching Hospitals Ethics Committee and conducted in accordance with the ICH Guidelines on Good Clinical Practice, and the Declaration of Helsinki. Study participants were male and female between 65 and 82 years of age (Table 1) and were recruited from the carers/loved-ones of patients attending the Assessment and Treatment Centre, St. Finbarr's Hospital Cork, Ireland. Participants were screened for suitability for study inclusion and were scheduled to attend three study visits at the Assessment and Treatment Centre, St. Finbarr's Hospital Cork Fig. 2.

All participants were provided with written information detailing the study involved and all participants provided full written consent prior to the study commencement. A total of 30 participants were randomly assigned to receive either Aquamin MMB or Placebo for twelve weeks. This combination was chosen as magnesium and calcium deficiencies are common in older adult populations [33,34] and often older adults have reduced ability to digest and absorb nutrients [35]. Sixteen subjects received 4 capsules of Aquamin MMB which contained 300 mg Mg^{2+}/day and 235 mg Ca^{2+}/day and fourteen subjects received maltodextrin as placebo. In Europe, the EFSA recommended daily intake for magnesium is 300 mg/day for women and 350 mg/day for men [17]. The magnesium inclusion is based on these recommendations. The EFSA recommended daily intake for calcium is 1000 mg/day for adult men and women [21] and we included calcium at 25 % of this recommendation. Adverse events were self-reported by participants.

2.5. Statistical analyses

Water solubility data are mean ± standard error of three independent water solubility experiments performed for each supplement. *In vitro* digestion data are mean ± standard error of three independent simulations (gastric and intestinal phase) for each supplement. The water solubility and *in vitro* digestion data were analysed in SigmaPlot 12.0 (Systat Software, Inc. SigmaPlot for Windows). Data were analysed using one-way analysis of variance (ANOVA) for treatment groups (different magnesium supplements), following Grubbs test for outliers and verification of normal distribution of data. All data were checked for normal distribution using Shapiro-Wilk test prior to ANOVA. Tukey's post hoc test was used for treatment group comparisons to test for significant differences between variable mean values of percentage of water soluble and *in vitro* digestible magnesium of each magnesium supplements. Differences were significant at $p < 0.05$. The *in vivo* trial data were expressed as mean ± standard deviation (SD). Statistical analysis was carried out using *t*-test. Values of $p < 0.05$ were considered statistically significant.

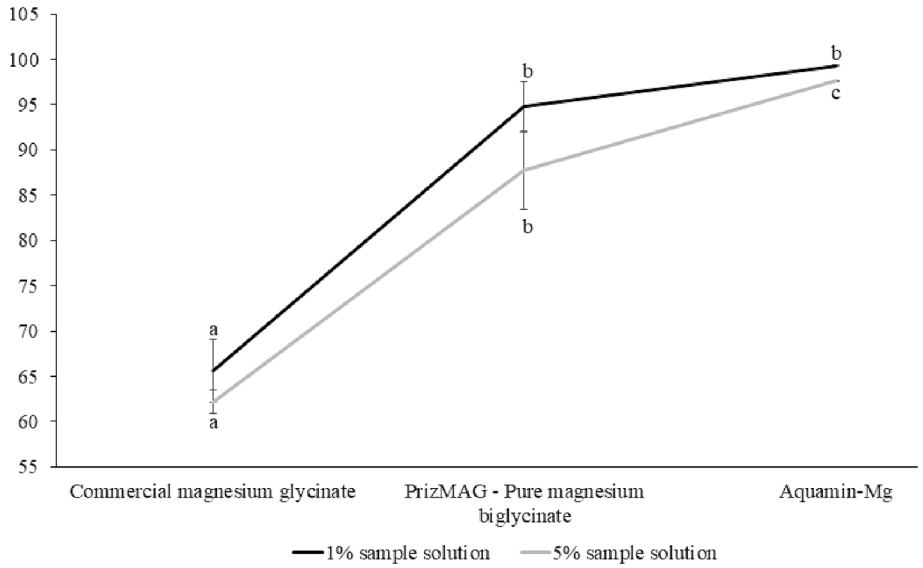

Fig. 3. The solubility of magnesium supplements, commercial magnesium bisglycinate, PrizMAG – pure magnesium bisglycinate and Aquamin-Mg at 1 % and 5 % w/v concentration in water. Samples were dissolved in distilled water, filtered, dried, and weighed, and solubility determined. The y axis demonstrates the percentage solubility of each supplement in water. The x axis indicates the three magnesium supplements being tested. Values are means, with their standard errors represented by vertical bars. N = 3, statistically significant differences determined by ANOVA have a P value < 0.001. Letters a, b, and c indicate statistical difference among sample means.

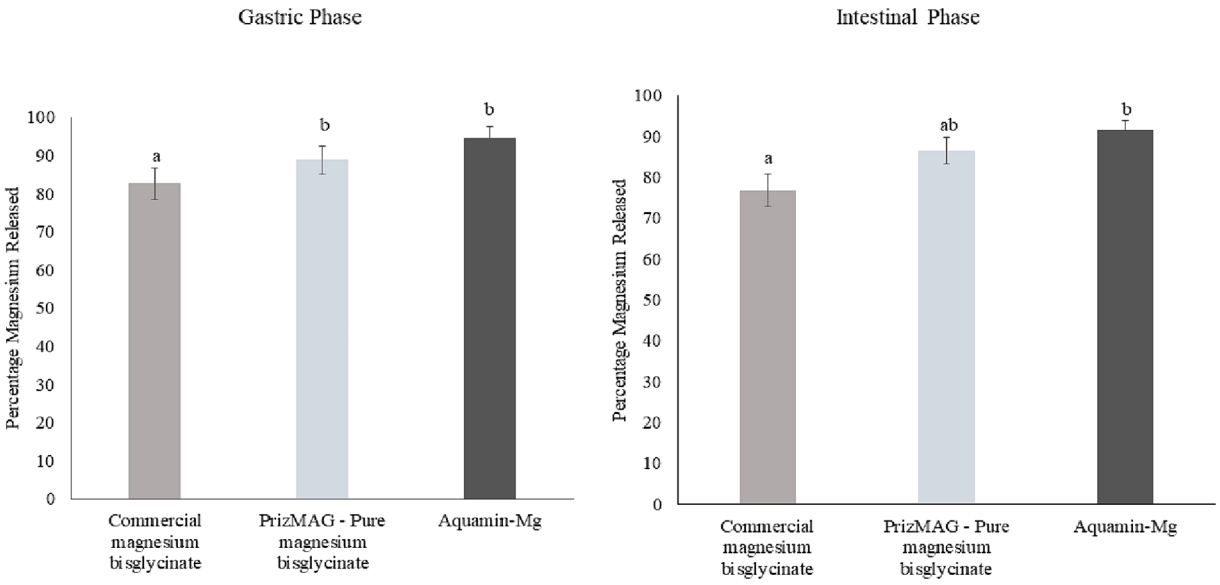

Fig. 4. A and b. Solubility of magnesium supplements, commercial magnesium bisglycinate, PrizMAG – pure magnesium bisglycinate and Aquamin-Mg. The INFOGEST protocol to simulate digestion was used to investigate the solubility of 3 different magnesium samples in the absence of food. Magnesium content was calculated based on RDA. The y axis demonstrates the percentage magnesium released in the gastric and intestinal phase. The x axis indicates the three magnesium supplements being tested. [a-b]Mean values within a row with unlike superscript letters were significantly different (P < 0.05) based on Tukey's post hoc test.

3. Results

3.1. Solubility of magnesium supplements in water

Aquamin-Mg demonstrated the highest solubility at 1 % w/v concentration in water, followed by PrizMag and commercial magnesium bisglycinate, (P < 0.001; Fig. 3). At 5 % w/v concentration in water, Aquamin-Mg demonstrated the highest solubility, followed by PrizMag and commercial magnesium bisglycinate, (P < 0.001; Fig. 3).

3.2. Magnesium recovery from magnesium supplements following in vitro digestion

Aquamin-Mg demonstrated higher solubility in the gastric stage of digestion without food material compared to CMB, but similar to PrizMAG (P = 0.004; Fig. 4**a**). In the intestinal stage of digestion without food material, Aquamin-Mg had higher solubility (94 %±3) compared to CMB (82 %±4) and PrizMAG (89 %±3), (P = 0.018; Fig. 4**b**).

In the gastric phase of digestion with food material, there was no difference in solubility between magnesium supplements, (P = 0.511; Fig. 5**a**). In the intestinal phase of digestion in the presence of food material, Aquamin-Mg had significantly higher solubility compared to

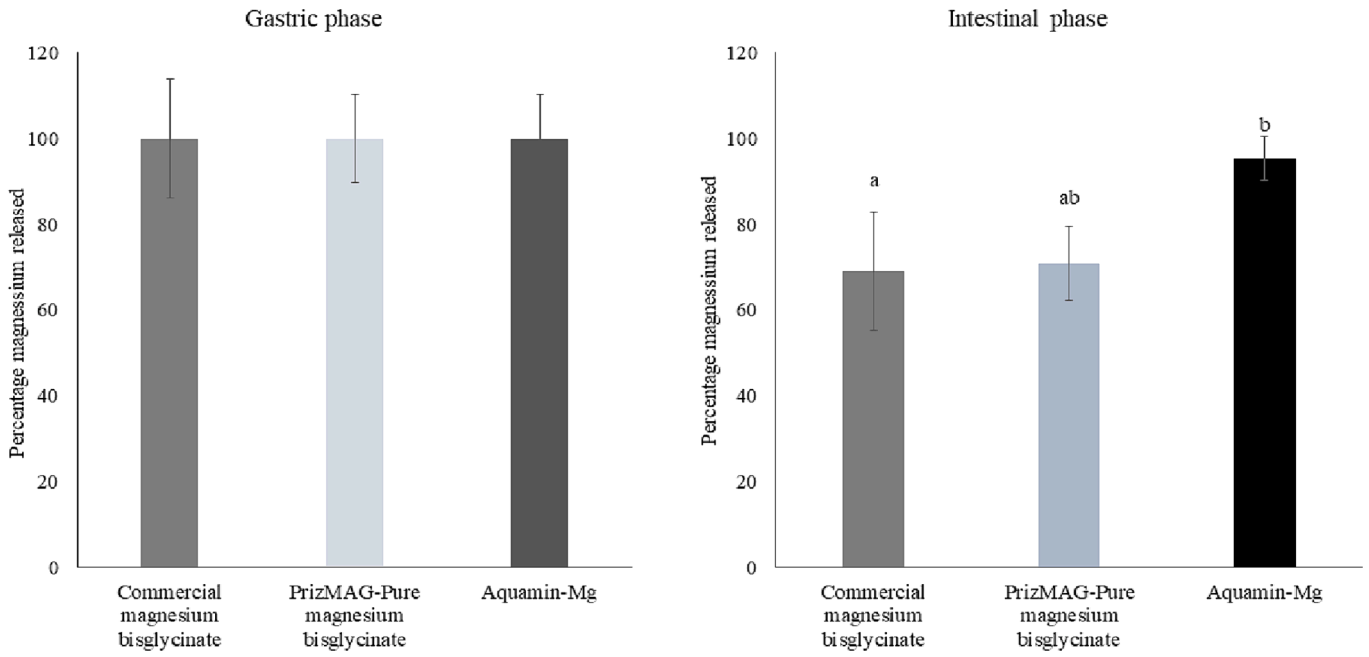

Fig. 5. A and b. Solubility of magnesium supplements, commercial magnesium bisglycinate, PrizMAG – pure magnesium bisglycinate and Aquamin-Mg. The INFOGEST protocol to simulate digestion was used to investigate the solubility of 3 different magnesium samples in the presence of food. Magnesium content was calculated based on RDA. The y axis demonstrates the percentage magnesium released in the gastric and intestinal phase. The x axis indicates the magnesium supplement being tested. [a-b]Mean values within a row with unlike superscript letters were significantly different ($P < 0.05$) based on Tukey's post hoc test.

Table 2
Participant study adherence and adverse events. This table shows the comparison between study adherence and self-reported adverse events of participants supplementing with placebo or Aquamin MMB.

		Placebo	Aquamin MMB
Study Adherence	Days on supplement (days ± SD)	83.9 ± 4.7	84.4 ± 3.8
	Compliance (%)	92.43 ± 5.080	96.79 ± 4.179
Adverse events			
	Gastrointestinal Infection	3	3
	Respiratory	3	1
	Skin	–	2
	Urinary tract infection	2	–
	Other		
	Tired	1	1
	Low mood	–	1
	Vertigo	–	1
	Muscular cramps	3	–
	Melanoma (stage I)	1	–

CMB, ($P = 0.029$; Fig. 5**b**).

3.3. Study adherence and self-reported adverse events

Study adherence and adverse events are shown in Table 2**.** There were no statistical differences in total adverse events, gastrointestinal events, infection events or other events between participants supplemented with Aquamin MMB and those supplemented with placebo.

4. Discussion

A limitation of commercially available magnesium supplements is their low water solubility, limiting potential for effectiveness [12]. This limitation cannot be accounted for by using high-dose magnesium supplements due to potential aggravation of negative gastrointestinal symptoms such as diarrhoea [40]. In this study, Aquamin Mg showed superior solubility in water compared to the two tested commercial magnesium bisglycinates. Also, using the Infogest *in vitro* digestion model, Aquamin Mg was highly soluble compared to a commercial magnesium bisglycinate (CMB) but similar to PrizMAG in both the gastric and intestinal phase of digestion without food. Results of this study showed similar solubility in the gastric phase of digestion among all tested products in the presence of a food material. As the simulation progressed to the intestinal stage of digestion, Aquamin Mg was highly soluble compared to a commercial magnesium bisglycinate but similar to PrizMAG. We then tested the combination of Aquamin-Mg and Aquamin-F (Aquamin MMB) in a population of older healthy adults and demonstrated that this combination supplement was well-tolerated, with no significant adverse events reported.

The solubility of magnesium in the gastrointestinal tract is crucial for its absorption, as minerals must be soluble to be assimilated by the body [12]. Previous assessments of the bioavailability of Aquamin-Mg revealed similar results to $MgCl_2$ [24]. The high solubility of Aquamin-Mg is attributed not only to its natural composition but also to the presence of its multi-mineral tail. Prior research suggests that minerals exhibit enhanced performance when they are combined rather than taken individually [41]. Our findings here demonstrate that magnesium from Aquamin-Mg exhibits higher solubility during the intestinal phase of digestion in the presence of food, compared to CMB but similar to PrizMAG, at equivalent concentrations, suggesting a very bioavailable form of this mineral. Studies on how different forms of magnesium interact with digestion fluids either *in vitro* or *in vivo* remain sparse. There is evidence that magnesium supplements may have different level of bioavailability depending on their method of preparation [42]. It is likely that the higher pH in the intestinal phase of digestion in the presence of food is where interaction with other dietary components is most likely possible and so to have the biggest influence on magnesium solubility [43]. Interactions which can lead to insoluble magnesium containing components are less likely to occur during the gastric phase of digestion. This is due to the higher hydrogen ion content competing with the magnesium for binding sites [44]. Considering these findings and the additional potential health benefits of a multimineral

supplement, Aquamin-Mg emerges as a unique and effective source of magnesium.

Aquamin-Mg having shown promising results in the *in vitro* experiment, was combined with Aquamin F, an Icelandic seaweed derived functional food ingredient, and assessed in older healthy adults. This combination known as Aquamin MMB, was chosen as magnesium and calcium deficiencies are common in older adult populations [33,34]. Our interpretation of the results was that the Aquamin MMB was well tolerated, as no significant differences in adverse events were observed between groups. This is likely due to its high solubility, facilitating mineral absorption by the body, in contrast to unabsorbed magnesium salts known to cause diarrhoea due to intestinal osmotic activity [14]. Additionally, Aquamin MMB may compare favourably with the other supplements tested due to the additional 72-trace minerals it contains. It is known that minerals often synergize, potentially enhancing their bioavailability [41]. Several limitations were noted in this study. In the *in vitro* study, there was a limited range of foods examined, while in the *in vivo* study, limitations included a small sample size, participant age, and lack of bioavailability verification.

In conclusion, our data suggests that Aquamin-Mg has greater solubility than commercial magnesium bisglycinate but similar to PrizMAG – pure magnesium bisglycinate. Further trials will be required to further evaluate the efficacy and bioavailability of Aquamin-Mg *in vivo*.

5. Author statement

Y.N. and C.M.L.S. designed the human study, received funding, interpreted the results and assisted in manuscript preparation. S.O.C. and O.D. designed the *in vitro* study. A.D., S.O.C. and O.D. assisted in data analysis, interpretation of results, and manuscript writing. D.M.O. G. assisted in experimental design, interpretation of results and manuscript preparation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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