ALBION®
HUMAN NUTRITION

RESEARCH NOTES

A COMPILATION OF VITAL RESEARCH UPDATES ON HUMAN NUTRITION

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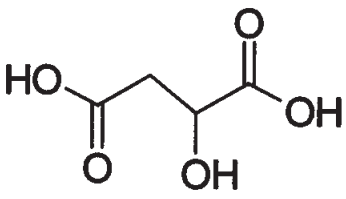
MALIC ACID CAN BE THE RIGHT LIGAND FOR CERTAIN APPLICATIONS

Malic acid, a natural constituent of many fruits and vegetables, is one of a group of acids known as alpha hydroxy acids. These are weak organic acids. The molecular structure for malic acid is depicted below in Figure 1.

Figure 1

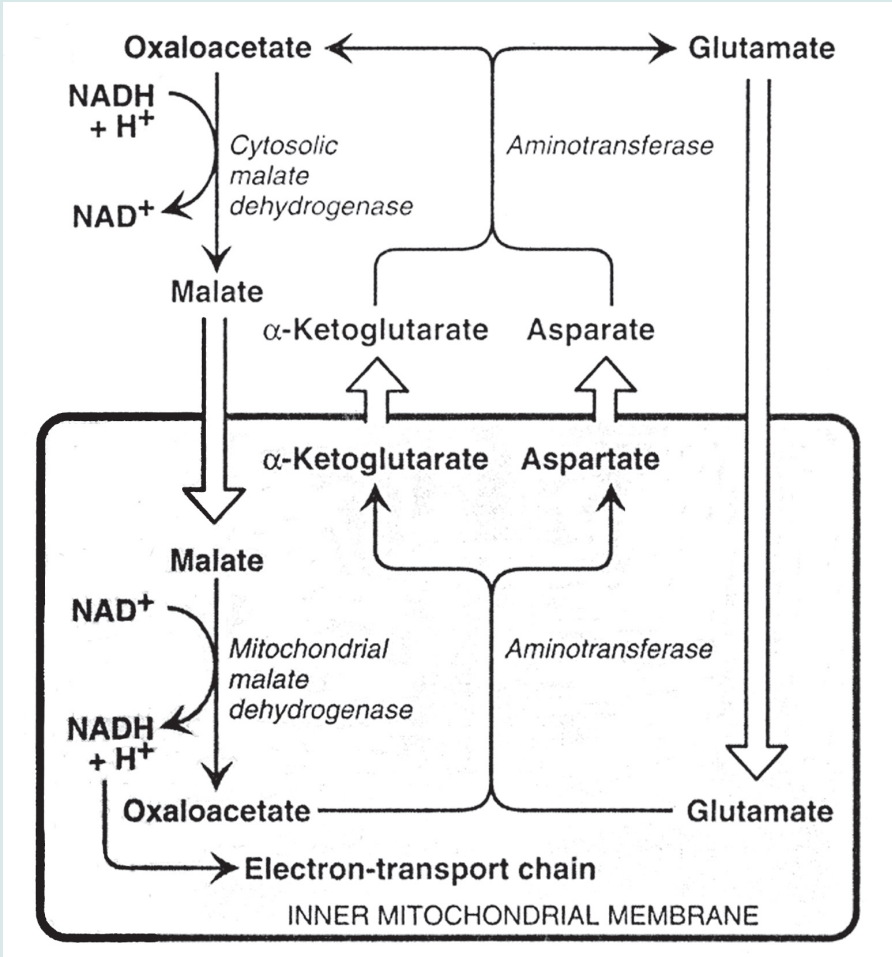


Malic Acid

Malic acid can be derived from food sources, as well as synthesized by the body through the citric acid cycle (Kreb's Cycle). It is involved in the production of energy in the body under both aerobic and anaerobic conditions. Malic acid is involved in the production of energy through the malate-aspartate redox shuttle (Figure 2) in the electron transport chain. During anaerobic conditions, malic acid's ability to remove the accumulation of reducing equivalents through its simultaneous reduction to succinate and oxidation to oxaloacetate (Figure 3) allows it to reverse hypoxia's inhibition of glycolysis and energy production. It is this action (in the Kreb's Cycle) under anaerobic conditions that may allow malic acid to improve energy production in fibromyalgia, reversing the negative effect of the relative hypoxia seen in these patients.

As a result of malic acid's role in the malate-aspartate redox shuttle and the Kreb's cycle, NADH is produced. Each

Figure 2



Lippincott's Illustrated Reviews: Biochemistry 2nd Edition, PC Champe and PA Harvey 1994.

NADH will yield 3 ATPs, the energy currency of the human body. Malic acid is a metabolite of the Citric Acid Cycle which correlates positively with physical activity. In animal studies, exercise induced mitochondrial respiration was associated with increased malate levels only, while the other key metabolites remained unchanged. Human studies have shown that after endurance training, the athletes' muscles were characterized by a 50% increase in the malate-aspartate redox shuttle enzymes, where malate's role is pivotal. In both animals and humans, when there is an increased demand for ATP (energy), there is an additional demand and utilization of malic acid. For this reason, malic acid is also being looked at by healthy individuals, who are interested in maximizing their energy production, in an attempt to improve their performance in sports and exercise. It should be noted that both magnesium and malic acid, in close alliance, play critical roles in the production of ATP in aerobic and anaerobic (hypoxic) conditions. For some time now, researchers and clinicians have been gathering evidence that point to relative deficiencies of both magnesium and malic acid in the clinical condition of fibromyalgia.

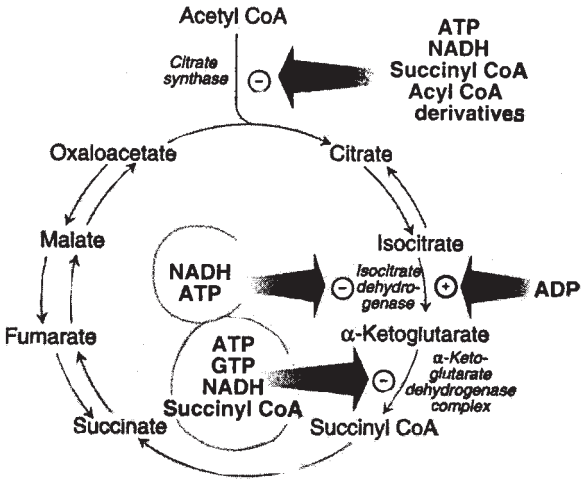
Management of Fibromyalgia: Rationale for the Use of Magnesium and Malic Acid, Abraham GE and Flechas JD, Journal of Nutritional Medicine (1992) 3, 49-59 AA

Primary fibromyalgia (FM) is a common clinical condition affecting mainly middle-aged women. Of the etiologies proposed, chronic hypoxia is one well supported by biochemical and histological findings. The researchers postulate that FM symptoms are predominantly caused by enhanced gluconeogenesis with breakdown of muscle proteins, resulting from a deficiency of oxygen and other substances needed for ATP synthesis. In this study, they presented data which supports the critical role for magnesium and malate in ATP production under aerobic and hypoxic conditions, and indirect evidence of magnesium and malate deficiency in FM. After treating 15 FM patients for an average of 8 weeks with an oral dosage form totaling 1200-1400 mg of malate and 300-600 mg of magnesium, the tender point index (TPI) scores (x +/- SE) were 19.6 +/- 2.1 prior to treatment and 8.1 +/- 1.1 and 6.5 +/- 0.74 (higher scores indicate greater pain ratings) respectively after 4 and 8 weeks on the magnesium malate combination ($p<0.001$). Subjective improvement of myalgia occurred within 48 hours of supplementation. In six FM patients, following 8 weeks of treatment, the mean TPI was 6.8 +/- 0.75. After 2 weeks on placebo tablets, the TPI values increased to a mean +/- SE of 21.5 +/- 1.4 ($p<0.001$). Again, subjective worsening of muscle pain occurs within 48 hours of placebo administration.

Treatment of fibromyalgia syndrome with Super Malic: a randomized, double blind, placebo controlled, crossover pilot study, Russell IJ; Michalek JE; Flechas JD; Abraham GE J Rheumatol 1995 May;22(5):953-8

In patients with fibromyalgia, treatment with malic acid was evaluated secondary to reported deficiencies in high-energy phosphate, including adenosine triphosphate in muscle and in erythrocytes. Malic acid and magnesium, both involved in generation of adenosine triphosphate were administered in combination to patients. In the initial phase of the study, half the patients were given a fixed dose of 1200mg of malic acid plus 300mg of magnesium, divided into two doses over 2 weeks, while the other half received a placebo. Patients were evaluated for 3 primary pain/tenderness measures. No clear treatment effect was found in the malic acid/magnesium group. In the second phase of this study, the patients were given up to 2400 mg malic acid and 600mg of magnesium per day in 2 divided doses, after a 2 week medication free washout period.

Figure 3



Lippincott's Illustrated Reviews: Biochemistry 2nd Edition, PC Champe and PA Harvey 1994.

This part of the study lasted 6 months, and was open labeled. With the dose escalation and longer duration of treatment for the patients in the second phase, significant reductions in the severity of all 3 primary pain/tenderness measures were seen. The researchers attributed the absence of a significant benefit effect in phase one of the study to the lower doses of malate and magnesium used and to the shorter length of this phase. They concluded that future evaluation should use at least a course of therapy that lasts a minimum of two months.

Other Considerations

Malic acid is considered to be nontoxic and has GRAS status. Animal studies show it to be free of any reproductive toxicity. Malic acid was found to be non-mutagenic across a wide range of genotoxicity tests. It has been shown to bind and remove aluminum from the brain.

Malic acid has a clean smooth, mellow and persistent tart taste. In supplements and powdered beverages, malic acid enhances fruit flavors by prolonging their release. The taste receptor cells are stimulated by these fruit flavors over a longer period of time, and this prolonged stimulation is translated by the brain as a stronger fruit flavor. This creates a smoother more natural tasting flavor profile. Malic acid has been shown to have a more prolonged sensation of tartness than citric acid. This prolonged tartness, in combination with malic acid's flavor blending properties helps it mask the flavor of some of the nutrients commonly found in nutritional supplements and powdered beverage mixes. It has lower hygroscopicity than citric acid and forms a more soluble calcium salt than citric acid, as well. These properties give malates some significant advantages over citrates in a wide range of dietary supplements, as well as food and beverage products.

Recent Developments at Albion

Early in 2001, Albion's Research & Development staff began developing several new mineral complexes. Specifically they looked at the process for making more advanced forms of malates than were on the market at that time. All of the malates to that point had been mono-metal malates, which were fine, but did not maximize the elemental metal content potential for the malate ligand. Since the malates have some application and nutritional advantages over the citrates, maximizing their mineral payload would enhance their usefulness. In 2002, Albion developed dimetalhydroxy malates. These new dimetalhydroxy malates are protected by a patent pending that was just filed in early December, 2002. The patent pending for Dimetalhydroxy Malate is for composition, method of making, and methods of delivery.

In the new process, Albion is attaching two metals to each molecule of malic acid. This effectively doubles the amount of metal that one can obtain from a totally reacted malate complex. The two new ingredients that Albion has introduced as dimetalhydroxy malates are:

- DiCalcium Malate (30% Ca)
- DiMagnesium Malate (19% Mg)

The molecular structures of these two new malates are illustrated below in Figures 4 and 5.

Figure 4

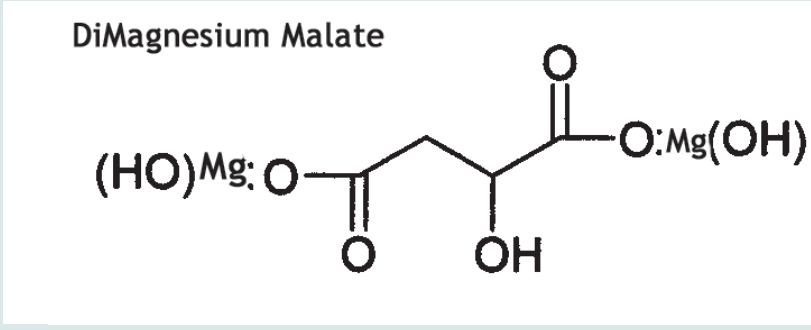
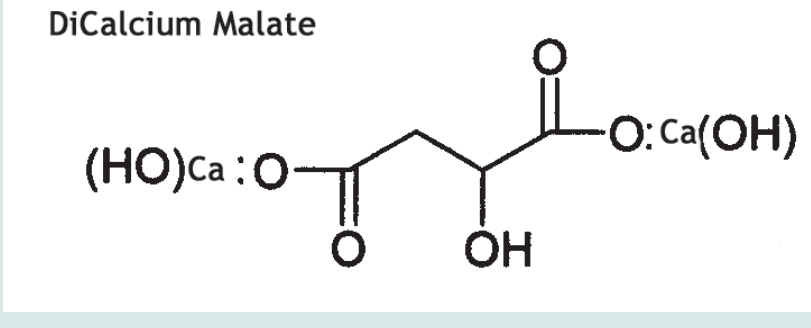


Figure 5



These two new malates are excellent sources of calcium or magnesium, as well as malic acid (malate). The elemental content of these two malates was mentioned earlier. With 30% calcium, the DiCalcium Malate offers a very high calcium content, which is well above that seen with citrates (typically, citrates contain calcium levels in the low 20% range). The DiCalcium Malate contains 64% malate by weight, while the DiMagnesium Malate offers 69% malate by weight.

These new patent pending dimetalhydroxy malates offer better solubility and miscibility than found with citrates, carbonates and oxides for the same metals, along with the advantage of extra malic acid. Malates do not react with stomach acid in the uncomfortable way that carbonates are known to do, and thus are less prone to cause the gas and acid rebound associated with carbonates.

The DiCalcium and DiMagnesium Malates are suited to a wide range of product applications:

- Bars,
- Beverages (powdered and ready-to-drink),
- Tablets,
- Capsules,
- and other foods.

Albion Human Nutrition

100 Maple Park Blvd., Suite 110
St. Clair Shores, Michigan 48081 USA
[P] 586•774•9055 | [TF] 800•222•0733
[F] 586•774•8838
[e] info@AlbionMinerals.com

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