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Research Digest

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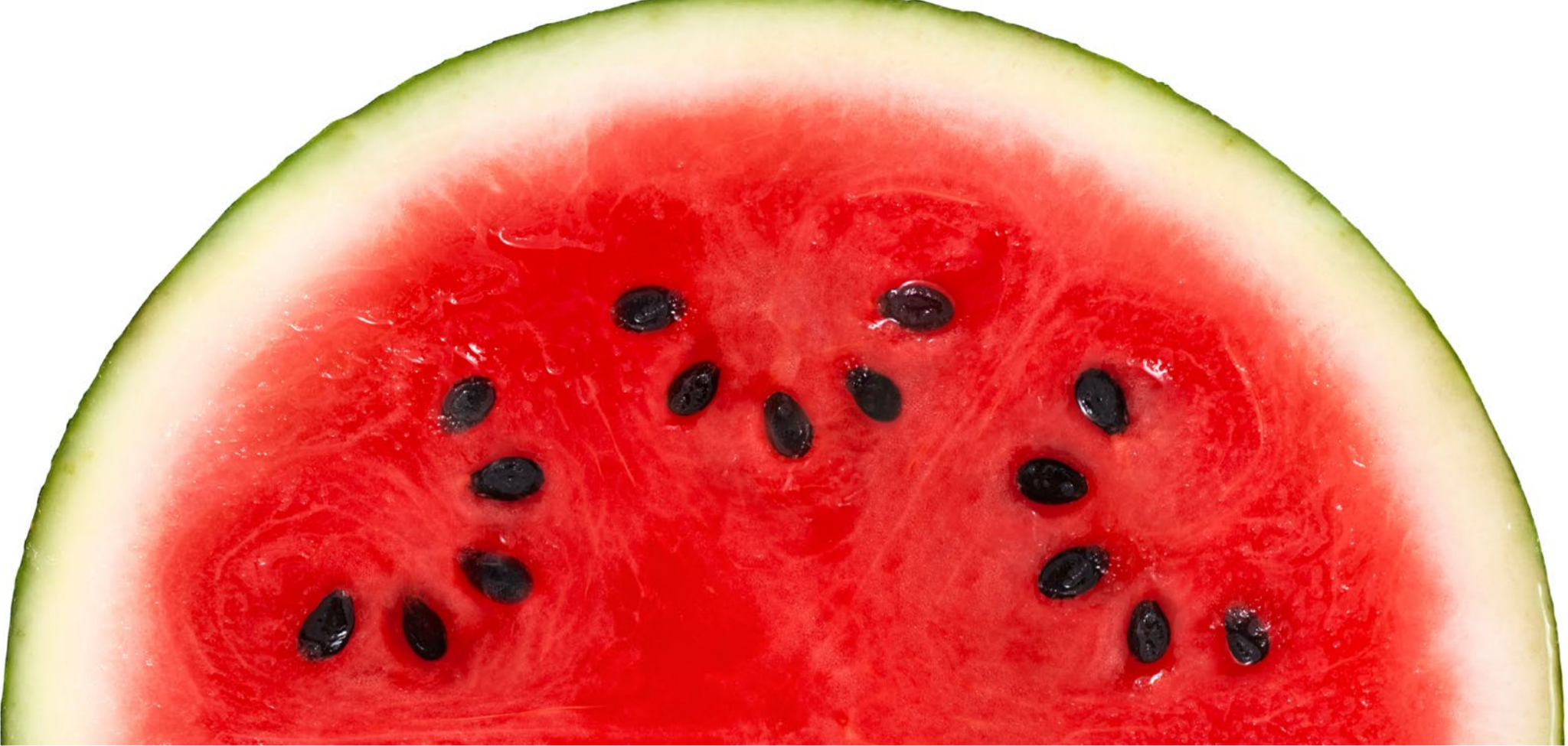
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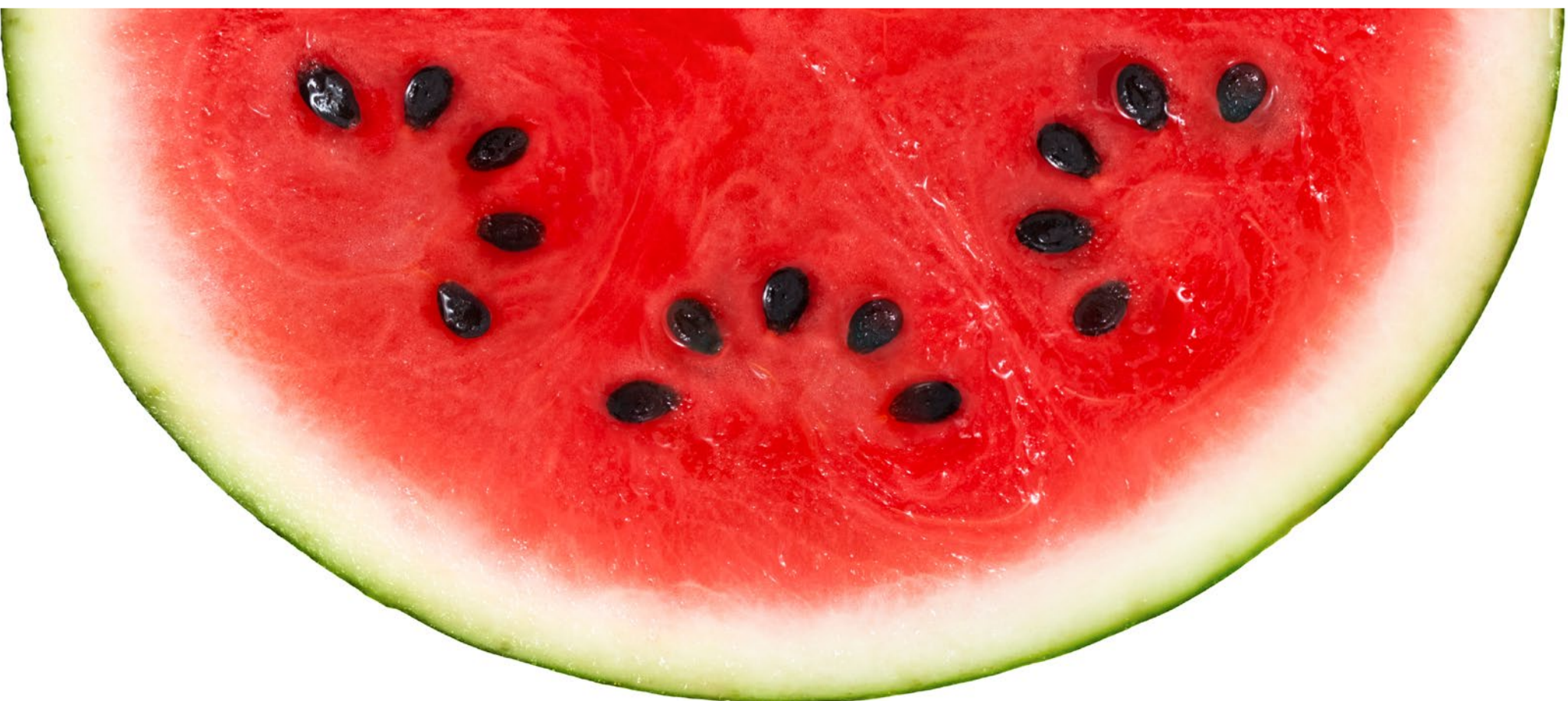
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Fish oil isn't necessarily benign ... it turns out that certain fatty acids might partially negate chemotherapy



Citrulline wants to pump you up!

*Effects of supplemental citrulline malate
ingestion during repeated bouts of lower-
body exercise in advanced weightlifters* 📌



Introduction

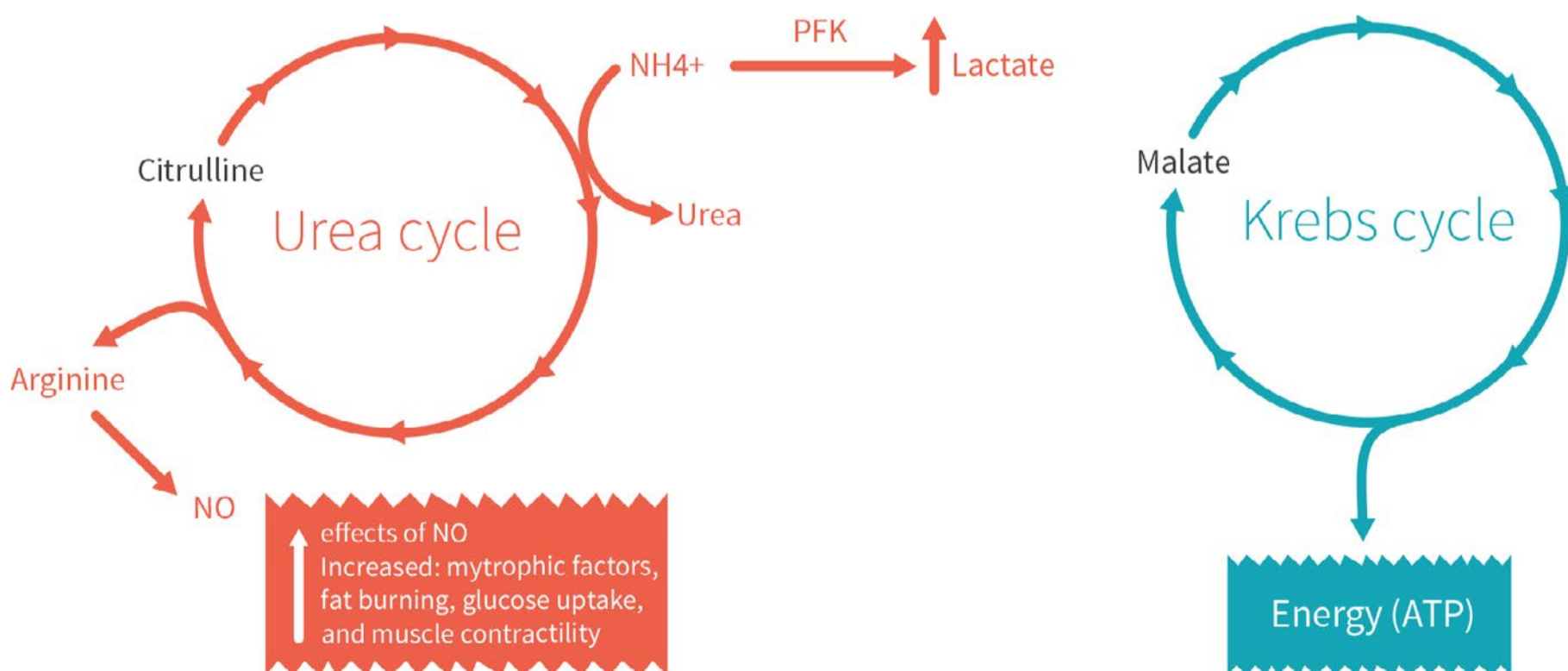
Competitive athletes are always on the lookout for a new supplement that can make them stronger or improve their performance, even if that supplement is not backed by a whole lot of scientific research. Similar to previous studies covered in the ERD on both HMB and sodium phosphate supplementation, citrulline malate is a relatively new ergogenic aid that has limited but promising research behind it.

As the name suggests, citrulline malate is made up of L-citrulline and malate. Citrulline is an amino acid made by the body. It is synthesized from glutamine, as well as from the conversion of arginine to nitric oxide. Watermelon is the only common food source that contains significant amounts of citrulline, with amounts ranging from [0.7 to 3.6 milligrams per gram of fresh weight](#). Citrulline supplementation actually raises plasma arginine more than actually taking supplemental arginine. This is because oral arginine is broken down in the small intestine and liver, while oral citrulline bypasses liver metabolism and roughly 80% of the ingested dose can be converted to arginine in the kidneys.

The major effects of citrulline malate are depicted in Figure 1. By way of raising plasma arginine levels, some scientists hypothesize that citrulline may [increase nitric oxide production](#). Nitric oxide is an important molecule involved in cell processes, including vasodilation (widening of the blood vessels, which increases blood flow, lowers blood pressure, and gets more blood to working muscles). Citrulline is also [recycled to arginine](#) by endothelial cells, which is important for the muscle pump because it means that they produce their own nitric oxide substrate, which can lead to increased muscle glucose uptake and fat burning, as well as improved muscle growth. Malate is an intermediate molecule in the Krebs cycle and plays a role in energy (ATP) production and the metabolism of carbs, fats, and proteins.

While previous [exercise studies](#) have found mixed results with citrulline supplementation alone, it is hypothesized that citrulline and malate may work together synergistically to provide an ergogenic effect. These [benefits](#) may include reduced feelings of fatigue during exercise, increased ATP production, and increased recovery rate of the short-term energy system (phosphocreatine).

Figure 1: The effects of Citrulline and Malate



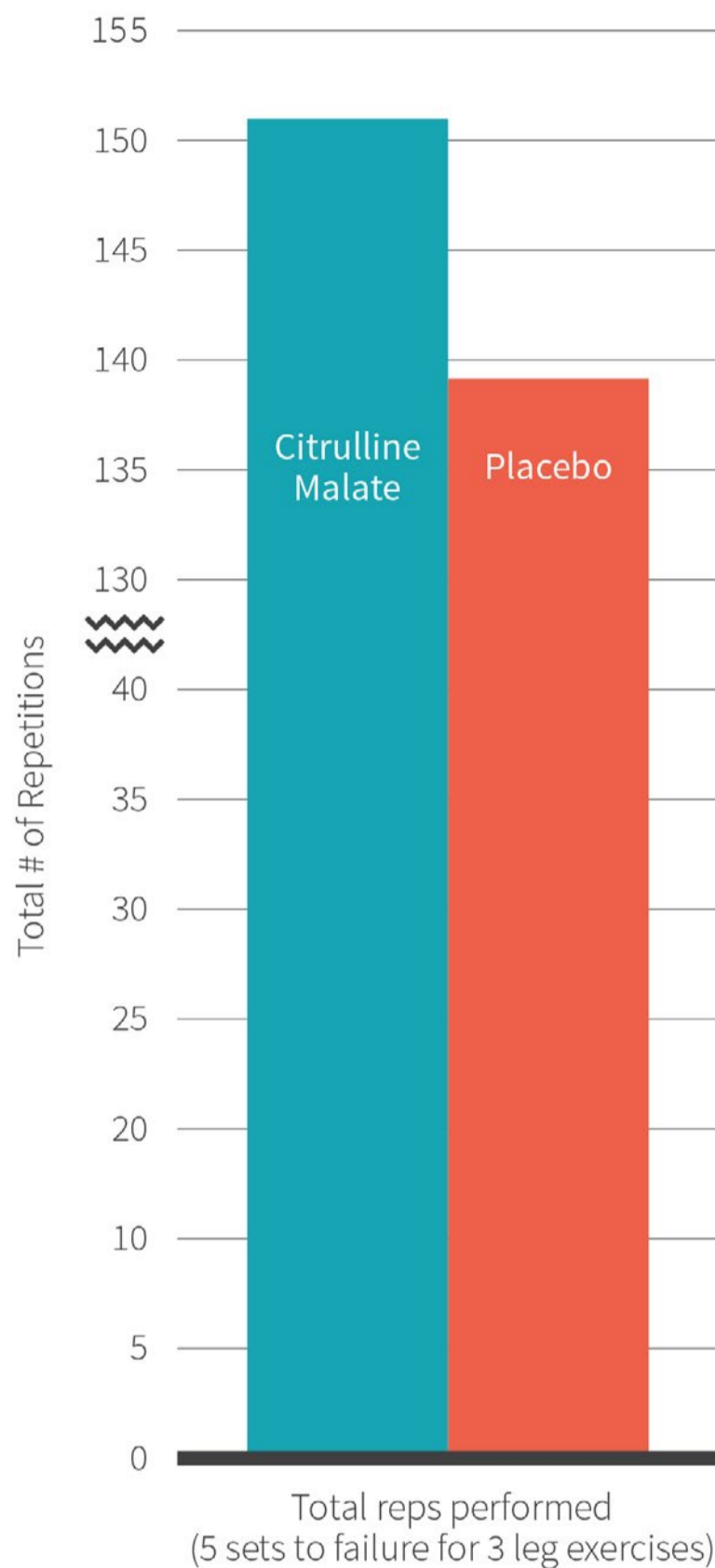
Prior to this study by Wax and colleagues, only one [study](#) has tested the effects of citrulline malate on resistance training performance and found improvements in the number of reps performed during an *upper-body* resistance training protocol. Due to its greater muscle mass, the *lower body* may actually respond more dramatically to supplementation compared with the upper body. Determining whether this hypothesis is correct was one of the goals of this study. The authors investigated the effects of acute citrulline malate supplementation on lower-body resistance exercise performance, blood lactate, heart rate, and blood pressure.

Citrulline is a non-essential amino acid that may increase nitric oxide production, which could, in theory, contribute to improved athletic performance. However, tests in humans have so far had mixed results. But results in upper body resistance training when citrulline is combined with malate, a component of the Krebs cycle, were more promising. The current study tested the effects of citrulline malate on lower body resistance training.

Who and what was studied?

This double-blind study included 12 resistance-trained men. The protocol is shown in Figure 2 -- the men performed five sets of three different lower body resistance exercises at 60% of their one rep maximum after being randomly assigned to ingest eight grams of either citrulline malate or placebo. Each set was performed to failure, i.e. as many reps as could be done in each set. Participants then returned one week later to do the same set of exercises with the opposite intervention (placebo or citrulline malate). Blood lactate, heart rate, and blood pressure were measured before and after exercise. The researchers chose to use eight grams of citrulline malate to maintain consistency with the [previous study](#) (by a different research group) examining upper body resistance training.

Figure 2: Citrulline malate vs. placebo



Participants in this study needed to have a minimum of one year of serious resistance training (at least three to four times a week at a perceived high intensity), and were excluded if they had any existing injury or health problems, drank more than 10 alcoholic beverages per week, smoked, used any over-the-counter supplements in the past six months, or had ever used anabolic steroids. This appeared to have been a fairly fit group, with an average age of 22, mean height of 5'10", weight of 187

pounds, and a better-than-average body fat of 11.9%. Participants logged their dietary intake for 24 hours before the first testing session, and were instructed to duplicate the intake before the second session.

Twelve healthy men with serious resistance training experience were randomized to ingest either eight grams of citrulline malate or placebo 60 minutes before performing five sets to failure of leg presses, hack squats, and leg extensions in a double-blind manner. The number of reps were measured for each set, along with heart rate, blood pressure, and blood lactate levels. After a week, the same tests were performed, with participants who took the placebo taking citrulline malate and vice versa.

What were the findings?

As expected, the number of reps the participants were able to complete decreased during each of the five sets to failure, in both groups. As seen in Figure 3, the citrulline malate group was able to do more overall reps. When looking at the individual exercises, citrulline malate appeared to be able to mitigate some of the fatigue that occurred in the later sets of exercises. The supplementation group saw less of a performance dip in set 5 for both the leg press and leg extension, and less of a performance dip in set 4 for the hack squat. No differences were observed between groups for post-exercise heart rate or blood lactate, which were elevated

in both groups, or for blood pressure which was unchanged from baseline.

The results should be taken with many grains of salt, however. None of the individual sets nor total reps per exercise were noted to be significantly different between the control and treatment group (and this didn't appear to part of the statistical analysis). Rather, the researchers summed up all of the repetitions in all three exercises for group comparison, and also noted a few pairwise comparisons of later sets compared to earlier sets. While there is no one standard for measuring fatigue in this type of resistance exercise study, there are a lot of possible measurements that can be compared, and just because one or two turned out to be significant does not mean that citrulline malate is beneficial.

What does the study really tell us?

“Our results indicated that subjects who consumed citrulline malate experienced less fatigue to the working muscles compared with the placebo group, allowing them to perform more repetitions.”

This is the first study to show an improvement in lower body resistance training performance with citrulline malate supplementation. Participants were able to perform a higher number of reps at a given percentage of each participant's one repetition maximum weight. This would equate to a greater work capacity in any given

Figure 3: Study protocol



workout, *potentially* driving greater physiological adaptations. That being said, the results presented were not a straightforward comparison between the treatment and control groups. Rather, the researchers compared reps performed in later sets to earlier sets, but within the same group (rather than against the other group). We cannot be sure if other metrics would have shown the results in as positive of a light.

This study did not attempt to uncover a mechanism of action for the benefits, but there are several possible explanations including:

- increased energy production via the Krebs cycle
- increased nutrient delivery to muscles via nitric oxide production
- increased creatine production

The big picture

Research on citrulline malate is currently quite limited.

One of the two other pertinent studies comes right from the same research group. In that [study](#), Wax et al. tested the effect of eight grams of citrulline malate on upper body resistance exercise and found that supplementation increased the amount of reps performed for each exercise. Similar beneficial effects were observed in a [study](#) by scientists from the University of Córdoba, who found that the same dose of eight grams of citrul-

line malate increased the number of reps to failure during a bench press by 19%.

This study adds to the body of work produced by a series of previous studies, which primarily tested citrulline malate's effect on recovery after exercise. One such [study](#) in 2002 used six grams of citrulline a day. After 16 days, researchers reported a 34% increase in the rate of oxidative ATP production during exercise and a 20% increase in the rate of phosphocreatine recovery after exercise. However, this study was not blinded, did not include a control group, used sedentary males as participants, and the "exercise" was three minutes of finger flexion. Its practical significance is questionable.

A more practical [study](#) of 72 highly trained teenage athletes tested either three or six grams of citrulline malate per day during two weeks of high intensity training. The results showed a faster recovery of blood lactate and lower levels of perceived fatigue. These human studies also have a basis in animal studies. One such [animal study](#) from 2011 showed that citrulline malate improved muscle efficiency in rats, by lowering the metabolic 'cost' of contractions. Citrulline malate had no effect on phosphocreatine resynthesis or oxidative ATP synthesis capacity, however.

Another human study was performed that assessed citrulline malate's effect on aerobic exercise. This [study](#) was conducted by the U.S. Air Force (but was published

“ Citrulline alone (without malate) has also been studied in both animals in humans, with somewhat poor results. ”

internally, i.e. did not go through a peer-review process) and found that 14 days of citrulline malate supplementation (six grams a day) had *no influence* on aerobic exercise performance as measured by VO2 max, time to exhaustion, maximum power output, lactate threshold, or perceived exertion ratings during exercise.

This testing protocol only used a VO2max test that lasted about eight to 12 minutes, so a direct comparison of these results to endurance exercise or repeated anaerobic sprints or resistance exercise is unwarranted.

Citrulline alone (without malate) has also been studied in both animals in humans, with somewhat poor results. Animal models have shown citrulline supplementation resulting in [decreased production of lactate](#) and [increased time to exhaustion](#). Also, a 2006 [study](#) in healthy men and women showed that ingesting citrulline actually led to a *decrease* in performance on a treadmill exercise test to exhaustion. In view of the fact that most people use citrulline for its purported nitric oxide boosting effects, it is also worth mentioning that this effect was not found.

Similarly, the results of a 2014 [study](#) did not find any effect of a single six gram dose of citrulline in 11 men and 11 women for total number of reps for chest press, time to exhaustion, VO2max, or anaerobic threshold. Differences between male and female study participants weren't observed, either.

Lastly, it is worth mentioning that studies suggest that

“ Another possible explanation is related to citrulline's role in the urea cycle, which eliminates ammonia from the body. ”

citrulline may stimulate an increase in [intramuscular creatine](#) concentrations. This effect could partly explain the benefits seen during resistance exercises with shortened rest periods. Another possible explanation is related to citrulline's role in the urea cycle, which eliminates ammonia from the body.

Ammonia is produced as a byproduct of ATP re-synthesis. Because [ammonia build-up](#) during long duration endurance exercise contributes to fatigue, it is conceivable that citrulline could also be beneficial for longer duration endurance activities.

The research on citrulline malate is still in its early stages, but the results so far seem to indicate that it works better than citrulline alone for recovery from exercise. In addition to the mechanisms mentioned earlier, citrulline may work by increasing intramuscular creatine. It's also mechanistically possible that supplementation could be beneficial for longer-term endurance, although no studies have put this to the test yet.

Frequently asked questions

Do I need to follow a loading protocol or is a single dose effective when supplementing citrulline malate?

Much more research is needed to determine optimal dosing protocols, since both single dosage and loading have been used in studies. If you are a resistance trained male, this current study offers an argument that a single

dose might be effective. Two studies have used a single six gram dose of citrulline malate two hours before endurance exercise, and three studies have used a single eight gram dose of citrulline malate one hour before resistance exercise, and each of these studies found some positive results. Three studies that used six grams a day for 12-14 days found improvements in sedentary men and teenage athletes, and no changes in trained men and women. These differences are likely a result of the differences in study population, testing protocol, and exercise modalities.

What kind of exercise would benefit the most from supplementation?

Again, more research is needed. However, considering the mechanisms and the available research, it could be speculated that anaerobic efforts featuring short rest periods (i.e. strength training or repeated sprints) as well very long duration endurance activities are most likely to benefit from citrulline malate supplementation. On the other hand, you may not experience significant benefit during exercise with a mean duration of 30 seconds to one hour.

Are there any additional (non-exercise) benefits to citrulline malate?

Luckily for men (and perhaps their partners), a [study](#)

using 1.5 grams of citrulline malate daily for a month reported improved erection hardness in men with mild erectile dysfunction. Other benefits related to nitric oxide production have not been studied directly with citrulline malate, but it is possible that there could be health benefits, including lowered blood pressure and improvements in endothelial function, given the molecular mechanisms by which citrulline malate appears to act on nitric oxide production.

What should I know?

Citrulline malate may be a useful supplement for increasing resistance exercise performance in trained men. This study adds to the small evidence base, but the way in which the results are reported prevents strong conclusions from being made. While the reasons for possible improvements remain to be explained, the benefits could be related to its ability to increase L-arginine levels, which may in turn increase nitric oxide and creatine levels. ♦

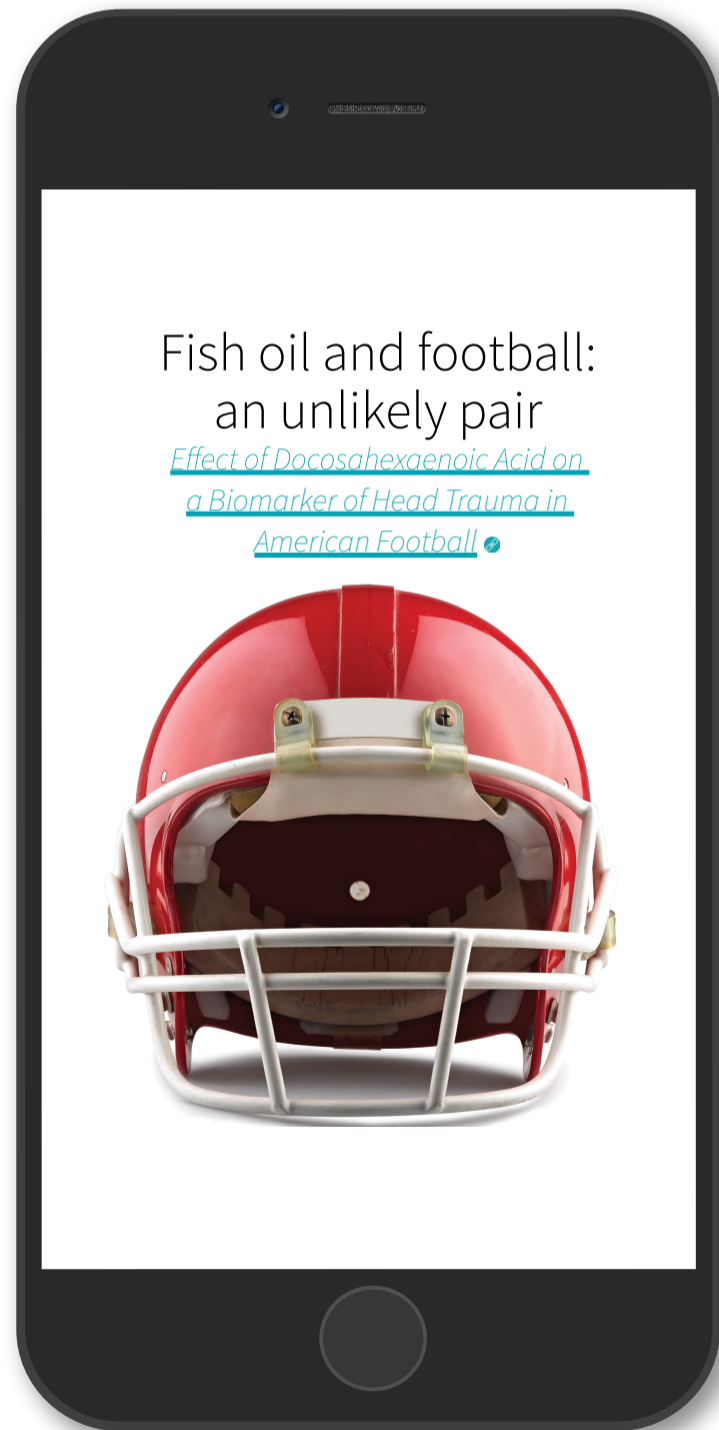
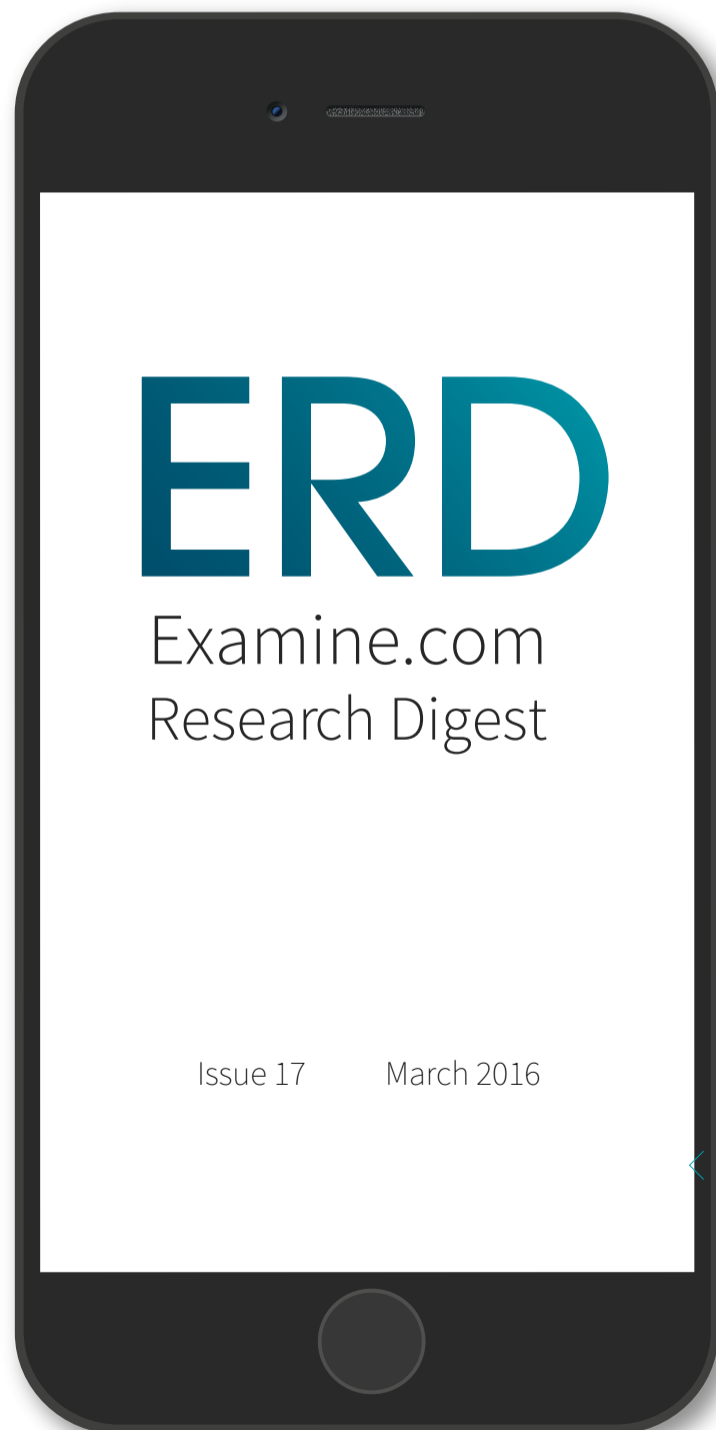
While this study doesn't provide an exact answer to the question of "Should I take citrulline malate?", it does give some clues. Talk it over in the [ERD Facebook forum](#).

“ Luckily for men (and perhaps their partners), a study using 1.5 grams of citrulline malate daily for a month reported improved erection hardness in men with mild erectile dysfunction. ”

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