menta HEART™

Advanced Heart-Brain Axis Nutrition*

amare® GLOBAL
THE MENTAL WELLNESS COMPANY

TECHNICAL DATA

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

menta HEART™

The first product of its kind to support mental wellness through the heart-brain axis, MentaHeart features key ingredients backed by multiple clinical studies shown to help optimize the heart, the body's third brain.*

Studies have now shown that the heart is the body's third brain, containing approximately 40,000 neurons that can sense, feel, learn, and remember. Similar to the gut-brain axis, the heart and brain are also closely connected via the heart-brain axis. The heart-brain axis refers to the close intuitive connection between what we feel (heart/emotions) and what we know (brain/intelligence). Signals across the heart-brain axis underlie cellular coherence — the concept that optimal function in one tissue (heart) can optimize function in another tissue (brain) — via electrical, hormonal and other signals transmitted between tissues.

The heart contains a complex and intrinsic nervous system similar to our brain and sends emotional and intuitive signals to the brain on a continuous millisecond by millisecond basis. Like the gut (with its enteric nervous system), the heart has its own independent complex nervous system that permits it to function without direct input from the brain. MentaHeart is the first product of its kind to support mental wellness through the heart-brain axis.

MentaHeart helps people infuse emotions with intelligence — helping us effectively manage our emotions in the midst of life's challenges and the 21st century stress epidemic. Negative emotions disrupt nervous system balance and interfere with normal heart rhythms, whereas positive emotions improve nervous system balance and enhance heart signaling to the brain.

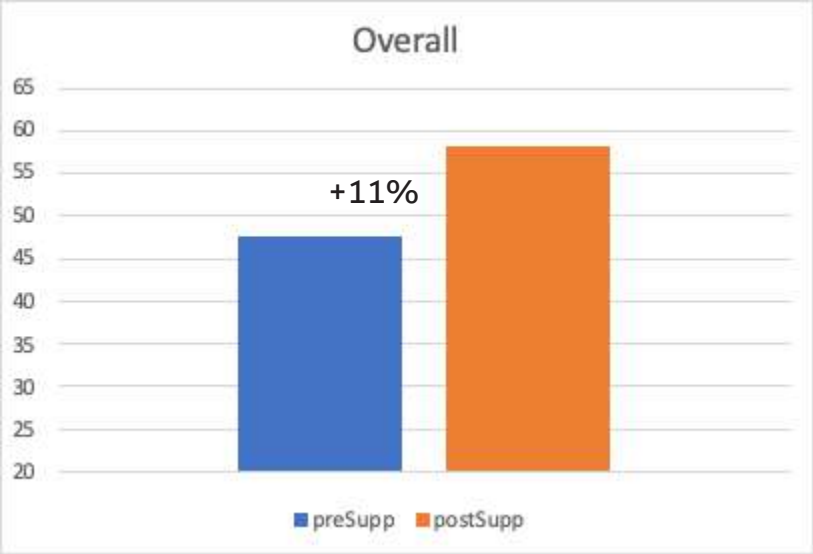
A recent pilot clinical trial on MentaHeart showed dramatic differences in "physical health" benefits such as cardiac efficiency, heart rate variability, and parasympathetic nervous system tone; as well as improvements in "mental fitness" parameters such as stress, focus, and motivation (see graphs below). This data will be presented at the upcoming International Society for Nutritional Psychiatry Research Conference in London.

"Physical" heart benefits and "mental" brain benefits are related via the psychophysiological "heart-brain-axis" with simultaneous improvements in both physical and mental wellness. Our studies have shown targeted supplementation to improve parameters associated with heart health (antioxidant, fat oxidation, endurance) and brain health (neuro-inflammation, cognition, antidepressant/anxiolytic) — with further previously-undescribed benefits for psychological mood state (depression, fatigue, vigor).

MentaHeart Clinical Pilot Study

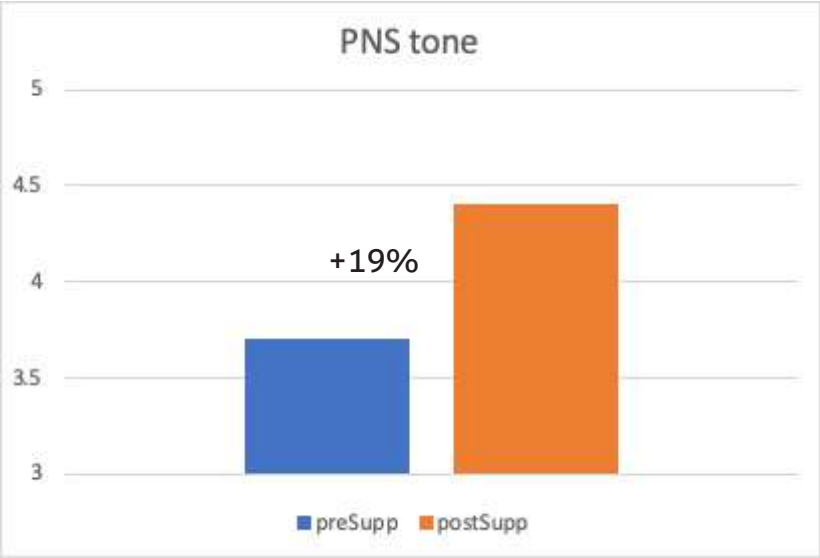
HRV / SDNN (msec)

SDNN = standard deviation of N-N intervals

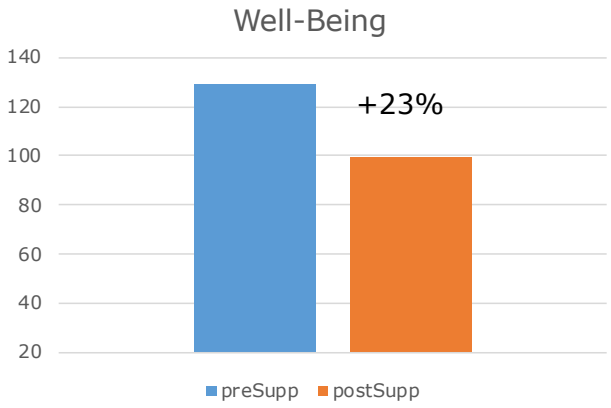


HRV / RMSSD

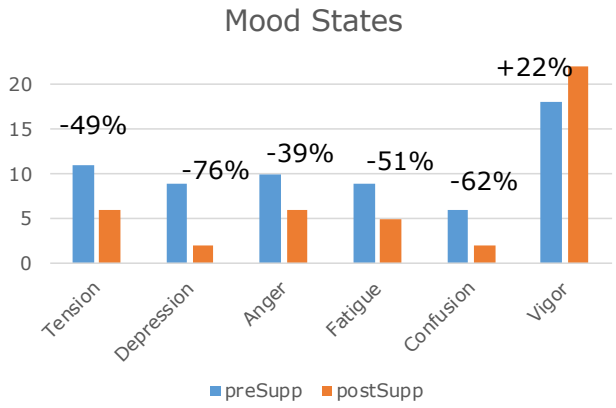
RMSSD – root mean square of successive differences



Global Mood State



POMS Sub-Scales



SDNN = standard deviation of N-N intervals
RMSSD – root mean square of successive differences

KEY INGREDIENTS

PFBc™ Palm Fruit Bioactives Complex — Is a 100% natural, non-GMO and water-soluble complex isolated from the fruit of the oil palm tree that supports optimal total cardiac output, a decreased workload or pressure on the heart, and a reduction of oxidative stress to help preserve mental wellness.*

Bergavit® 40 — Is a bergamot fruit extract that supports cardiovascular health, promotes wellness for metabolic processes, supports cholesterol levels already in the normal range, and helps provide antioxidant protection.*

Astazine® Astaxanthin — Promotes brain health, provides cardiovascular support, decreases some oxidative stress markers, and improves cognitive function. High-Astaxanthin Algae extract (Astazine 10% oleoresin) is an antioxidant, astaxanthin that is said to have many health benefits. It's been linked to healthier skin, endurance, heart health, joint pain, and may even have a future in cancer treatment.*

CoQ10 (Aquacelle) — Improves the absorption of nutrients and It helps provide energy to cells. Coenzyme Q10 also seems to have antioxidant activity. People with certain diseases, such as heart failure, high blood pressure, gum disease, Parkinson's disease, blood infections, certain diseases of the muscles, and HIV infection, might have lower levels of coenzyme Q10.*

ThymoQuin™ Black Cumin Seed Oil — Helps support already normal blood sugar and cholesterol levels, and enhances memory and cognitive health. In addition, it favorably affects several parameters related to heart disease risk including lowering total and LDL cholesterol, reducing inflammation, lowering blood pressure, reducing plaque formation. It also reduces blood glucose, as well as diabetic-associated complications such as neuropathy.*

CLINICAL STUDIES

Effect of Astaxanthin Supplementation on Psychophysiological Heart-Brain Axis Dynamics in Healthy Subjects.

Functional Foods in Health & Disease. FFHD: Online ISSN: 2160-3855 Vol 9, No 8 (2019).

Abstract

Objective: Marine microalgae is the predominant source of natural astaxanthin (NAX), a red-orange carotenoid with powerful antioxidant and anti-inflammatory properties. Previous studies suggest that NAX supplementation improves antioxidant capacity and reduces oxidative stress, while also enhancing fat utilization, exercise endurance, cardiovascular function, and neurological parameters. The purpose of this study was to assess the effects of NAX on the psychophysiological "heart-brain-axis" while nutrition (astaxanthin) may impact physiology (cardiovascular function) and psychology (mood state) in a coordinated manner.

Methods:

Using a double-blind parallel design, 28 healthy subjects (male=14, female=14, age=42) were supplemented for 8 weeks with NAX (12mg/day Haematococcus pluvialis algal extract) or a matching placebo. Before and after supplementation, subjects performed a cardiovascular stress test (VO2max) and completed a validated Profile of Mood States (POMS) survey to assess global mood state (GM) and related subscales: Vigor (V), Tension (T), Depression (D), Anger (A), Fatigue (F), and Confusion (C).

Results:

Subjects in the NAX group showed a significant ~10% lower average heart rate at submaximal exercise intensities compared to those in the placebo group (aerobic threshold, AeT; NAX 130+17 v. PL 145+14; and anaerobic threshold, AT; NAX 139+20 v. PL 154+11, $p<0.05$). Significant improvements were found in the NAX group for both positive mood state parameters: GM (+11%, $p<0.05$) & V (+5%, NS); and negative mood state parameters: T (-20%, NS), D (-57%, $p<0.05$), A (-12%, NS), F (-36%, $p<0.05$), and C (-28%, NS).

Conclusions:

NAX supplementation lowered average heart rate at submaximal endurance intensities (suggesting a "physical" heart benefit) and improved mood state parameters (suggesting a "mental" brain benefit). While previous studies have shown NAX supplementation to improve parameters associated with heart health (antioxidant, fat oxidation, endurance) and brain health (neuro-inflammation, cognition, antidepressant/anxiolytic), these results suggest that natural astaxanthin supplementation supports the psychophysiological "heart-brain-axis" with simultaneous improvements in both physical and mental wellness.

Keywords: Antioxidant; Carotenoid; Cardiovascular; Mood State; Mental Wellness

Astaxanthin Supplementation Reduces Depression and Fatigue in Healthy Subjects.

EC Nutrition 14.3 (2019): 239-246. Talbott, Hantla, Capelli, Ding, Li, and Artaria.

Abstract

Objective:

Natural Astaxanthin from Haematococcus pluvialis microalgae (NAX) has been researched in hundreds of clinical trials, pre-clinical animal studies and in-vitro surveys for various bioactive properties that indicate potential preventive and therapeutic health benefits. Among the most widely-researched properties of astaxanthin in the literature are broad-spectrum anti-inflammato- ry activity and powerful antioxidant capacity. In addition, both human and animal research have revealed a wide range of potential benefits for neurological and eye health, cardiovascular function, exercise endurance, enhancement of the immune response and skin health. This study's goal was to explore the effects of a daily dose of 12 mg per day of NAX on psychological mood state in healthy subjects.

Methods:

This study employed placebo control and parallel design under double blind conditions. A total of 28 healthy subjects, half male and half female, with a median age of 42, supplemented with 12 mg per day of NAX or placebo. Before Day 0 and again at the end of the 8-week supplementation period, subjects completed a validated Profile of Mood States (POMS) survey to assess global mood state (GM) and related subscales: Vigor (V), Tension (T), Depression (D), Anger (A), Fatigue (F) and Confusion (C).

Results:

Significant improvements were found in the NAX treatment group for positive mood state parameters: GM (+11%, $p < 0.05$) and V (+5%, NS); and negative mood state parameters: D (-57%, $p < 0.05$), F (-36%, $p < 0.05$), T (-20%, NS), A (-12%, NS), and C (-28%, NS).

Conclusions:

While previous studies have shown NAX supplementation to improve parameters associated with brain health (neuro- inflammation and cognition), these data are the first to suggest that natural astaxanthin supplementation reduces negative mood state parameters (depression and fatigue) and improves global mood state and thus supports mental wellness.

Effect of Astaxanthin Supplementation on Cardiorespiratory Function in Runners.

EC Nutrition 11.6 (2016): 253-259. Talbott, Hantla, Capelli, Ding, Li, and Artaria.

Abstract

Purpose:

Marine microalgae is the predominant source of natural astaxanthin (NAX), a red-orange carotenoid with powerful antioxi- dant and anti-inflammatory properties. Studies in both rodents and humans suggest that NAX supplementation improves antioxidant capacity and reduces oxidative stress, while also improving fat utilization and exercise endurance. The purpose of this study was to assess the effects of a moderate dose of NAX supplementation (12mg/day for 8 weeks) on cardiorespiratory function during both higher and lower intensity exercise in recreational runners.

Patients and Methods: Using a double-blind parallel design, 28 recreational runners (male = 14, female = 14, age = 42) were supplemented with NAX (Haematococcus pluvialis algal extract) or a placebo. Before and after the supplementation period, subjects per- formed a maximal running test (VO2max on treadmill) and a maximal cycling test (watts on cycle ergometer).

Results: There was no improvement in maximal oxygen uptake (running VO max) or maximal power output (cycling watts) with NAX supplementation. However, subjects in the NAX group showed a significant ~10% lower average heart rate at submaximal run-

ning intensities compared to placebo (aerobic threshold, AeT; NAX 130+17 v. PL 145+14; and anaerobic threshold, AT; NAX 139+20 v. PL 154+11, $p < 0.05$).

Conclusion:

Supplementation with 12 mg/day of NAX for 8 weeks reduced average heart rate at submaximal endurance intensities (AeT and AT), but not at higher “peak” intensities. These results suggest that NAX may be a beneficial ergogenic aid for long/ultra- distance endurance athletes, but not necessarily for athletes competing in shorter higher intensity efforts. In addition, these data are also suggestive of a general “cardiotonic” effect of NAX, that should be investigated in non-athletic populations including elderly subjects and those with cardiac complications including post-myocardial infarction, heart failure, statin usage, mitochondrial dys- function, chronic fatigue, and related conditions.

Keywords: Antioxidant; Cardiovascular; Carotenoid; Athlete; Endurance Introduction

Astaxanthin sources: Suitability for human health and nutrition.

Capelli, Talbott, Ding. Functional Foods in Health & Disease; FFHD: Online ISSN: 2160-3855 Vol 9, No 6 (2019)

Abstract

Background:

Astaxanthin (AX) has been consumed as a nutritional supplement for approximately twenty years. The primary source has been a natural plant-based supplement from the single-cell alga Haematococcus pluvialis (NAT-AX). Recently, Astaxanthin from other sources has entered the marketplace. The primary alternative source in the human nutritional supplement market has been a synthetic form of Astaxanthin produced from petrochemicals (SYN-AX). Additionally, a very small amount of Astaxanthin from a genetically-manipulated yeast Xanthophyllomyces dendrorhous (former nomenclature Phaffia rhodozyma, still commonly referred to as "Phaffia") (PH-AX) is also available in some supplement products. The three forms have substantial chemical differences. In addition to the chemical differences between sources of AX, in-vitro research has demonstrated profound differences in antioxidant strength and animal research has revealed fundamental differences in health benefits. In all cases, NAT-AX has proven more biologically active than the other sources. This review is designed to assist readers in understanding which form(s) of AX are suitable for consumers desiring preventive or therapeutic health benefits.

Results:

In head-to-head antioxidant experiments, NAT-AX demonstrated 14X to 90X greater antioxidant activity than SYN-AX. In numerous animal trials in diverse species, NAT-AX in esterified form has demonstrated superior efficacy in increasing lifespan; treating skin cancer; preventing the formation of gastric ulcers; improving resistance to stress; decreasing reactive oxygen species (ROS); increasing retinol conversion in the liver; augmenting enzyme levels; increasing growth rates; and improving exercise endurance.

From a safety perspective, NAT-AX has been the subject of human clinical trials demonstrating safety and a wide variety of health benefits. In addition, no documented adverse events have surfaced during its twenty years of distribution as a food supplement for humans. SYN-AX and PH-AX have not been proven safe for direct human consumption and have not demonstrated any health benefits in clinical trials. Due to these facts, SYN-AX and PH-AX have not been allowed for human consumption by government regulators in many countries while NAT-AX is widely accepted in most countries around the world.

Conclusion:

Based on our review of the literature below, we recommend NAT-AX as the sole form of AX for human consumption until SYN-AX and PH-AX have been proven safe and efficacious through human clinical research.

Astaxanthin, oxidative stress, inflammation and cardiovascular disease.

Future Cardiol. 2009 Jul;5(4):333-42. Fassett RG1, Coombes JS.

Abstract

It is accepted that oxidative stress and inflammation play an integral role in the pathophysiology of many chronic diseases including atherosclerotic cardiovascular disease. The xanthophyll carotenoid dietary supplement astaxanthin has demonstrated potential as an antioxidant and anti-inflammatory therapeutic agent in models of cardiovascular disease. There have been at least eight clinical studies conducted in over 180 humans using astaxanthin to assess its safety, bioavailability and clinical aspects relevant to oxidative stress, inflammation or the cardiovascular system. There have been no adverse outcomes reported. Studies have demonstrated reduced markers of oxidative stress and inflammation and improved blood rheology. A larger number of experimental studies have been performed using astaxanthin. In particular, studies in a variety of animals using a model of myocardial ischemia and reperfusion have demonstrated protective effects from prior administration of astaxanthin both intravenously and orally. Future clinical studies and trials will help determine the efficacy of antioxidants such as astaxanthin on vascular structure, function, oxidative stress and inflammation in a variety of patients at risk of, or with, established cardiovascular disease. These may lead to large intervention trials assessing cardiovascular morbidity and mortality.

Grace, S.C. Phenolics as antioxidants in Antioxidants and reactive oxygen species in plants (ed. Mirnoff, N.) 141–159 (Oxford: Blackwell Publishing).

Sambanthamurthi, R. et al. Oil palm vegetation liquor: a new source of phenolic bioactives. Br. J. Nutr. 106, 1655–1663 (2011).

Sambanthamurthi, R., Tan, Y.A., Sundram, K. Treatment of liquors derived from oil-bearing mesocarps, for example oil palm fruit mesocarp, and products thereof. United States Patent Application No. 20030031740 (2003).

Sambanthamurthi, R., Tan, Y.A. & Sundram, K. Treatment of liquors derived from oil-bearing mesocarps, for example oil palm fruit mesocarp, and products thereof. Malaysian Patent Application No. PI 980 4378 (1998).

Sambanthamurthi, R., Tan, Y.A. & Sundram, K. Treatment of liquors derived from oil-bearing mesocarps, for example oil palm fruit mesocarp, and products thereof. Indonesia Patent Application #P-990892 (1999).

Zern, T. L. & Fernandez, M. L. Cardioprotective effects of dietary polyphenols. J. Nutr. 135, 2291–2294 (2005).

Balasundram, N., Tan, Y. A., Sambanthamurthi, R., Sundram, K. & Samman, S. Antioxidant properties of palm fruit extracts. Asia Pac. J. Clin. Nutr. 4, 319–324 (2005).

Sambanthamurthi, R. et al. Positive outcomes of oil palm phenolics on degenerative diseases in animal models. Br. J. Nutr. 106, 1664–1675 (2011).

Leow, S. S., Sekaran, S. D., Sundram, K., Tan, Y. A. & Sambanthamurthi, R. Differential transcriptomic profiles effected by oil palm phenolics indicate novel health outcome. BMC Genomics. 12, 432 (2011).

Idris, C. A. C. et al. Oil palm phenolics and vitamin E reduce atherosclerosis in rabbits. J Func Foods. 7, 541–550 (2014).

Leow, S. S., Sekaran, S. D., Sundram, K., Tan, Y. A. & Sambanthamurthi, R. Oil palm phenolics attenuate changes caused by an atherogenic diet in mice. Eur J Nutr. 52, 443–446 (2013).

Patten, G. S., Abeywardena, M. Y., Sundram, K., Tan, Y. A. & Sambanthamurthi, R. Effect of oil palm phenolics on gastrointestinal transit, contractility and motility in the rat. J Func Foods. 17, 928–937 (2016).

Bolsinger, J., Pronzcuk, A., Sambanthamurthi, R. & Hayes, K. C. Anti diabetic effect of palm fruit juice in the nile rat (Arvicanthis niloticus). J. Nutr. Sci. 3(e5), 1–11 (2014).

Leow, S. S., Bolsinger, J., Pronczuk, A., Hayes, K. C. & Sambanthamurthi, R. Hepatic transcriptome implications for palm fruit juice deterrence of type 2 diabetes mellitus in young male Nile rats. Genes & Nutrition. 11, 29 (2016).

The impact of micelle size and increased absorption of ubiquinone using a novel delivery system (AquaCelle®)

Aim:

The objective of this study was to determine whether the use of a self-emulsifying drug delivery system AquaCelle, could improve the absorption of CoQ10. Materials & methods: Fifty-seven healthy males and females completed this study with the primary outcome as change in plasma absorption of CoQ10 over a 10-h period. Results: All AquaCelle groups signifcantly increased CoQ10 concentrations up to three-times that of the standard CoQ10 supplement. Ubiquinone with AquaCelle achieved an equivalent absorption to ubiquinol. Conclusion: The novel delivery system AquaCelle demonstrates superior absorption for the supply of ubiquinone when compared with a standard ubiquinone extract. These results further indicate that ubiquinone with AquaCelle absorbs as effectively as the typically superior absorbing ubiquinol at the same 100 mg dose.

First draft submitted:

23 May 2019; Accepted for publication: 21 August 2019; Published online: 16 September 2019

Coenzyme Q10 (CoQ10) is an endogenously occurring lipid compound essential to mitochondrial function and bioenergetics. In humans, CoQ10 is the most abundant form of coenzyme Q and is present in nearly all tissues [1]. Structurally, CoQ10 is similar to vitamin K comprising a benzoquinone ring arrangement with a unique 10-unit isoprenoid side chain [2]. In 2012, over 3 million USA adults had reported using CoQ10 as a dietary supplement in the previous 30 days; a 20% increase on the values reported in 2007 [3]. This surge in popularity for CoQ10 supplementation over the past decade is largely due to its complementary use in the treatment of various age-related diseases [4–9]. The major limitation with CoQ10 supplementation lies with its lipophilicity, resulting in poor oral absorption and difficulty obtaining plasma concentrations required for therapeutic benefit. To compensate for this poor absorption, numerous delivery systems have been made available, showing enhanced absorption of orally delivered CoQ10 when compared with pure crystalline formulas [10]. Much of this research surrounds combined oil–water formulations, which increase the hydrophilicity of crystalline CoQ10 [10]. More recently, self-emulsifying formulations have gained much interest. These systems are known to improve absorption of lipophilic agents by increasing drug dissolution in the gut and increasing gastrointestinal epithelial permeability [11]. AquaCelle is a novel example of this self-emulsifying delivery technique. CoQ10 can exist in both a reduced (ubiquinol) and oxidized (ubiquinone) state. It therefore functions as an antioxidant based on its ability for two electrons to be exchanged in a redox cycle between ubiquinol and ubiquinone [12]. The redox functions of CoQ10 extend beyond mitochondria, emphasizing its role in the management of medical conditions linked with oxidative damage [13]. Indeed, supplementation of CoQ10 has been shown to be beneficial in people with cardiovascular [4,5], neurological [6,7] and metabolic conditions [8,9]. However, these studies all stress the difficulty in achieving the plasma CoQ10 concentrations required for therapeutic benefit due to unfavourable pharmacokinetics. The oral delivery of CoQ10 is extremely challenging. In its most pure crystalline form, CoQ10 is water-insoluble and has limited absorption from the gastrointestinal tract. This is speculated to be largely due to its large molecular weight and strong lipophilicity [12]. Oral CoQ10 formulations in humans report a time to absorption of 5–10 h [14] and a plasma half-life up to 33 h [10,15,16]. However, the half-life may be difficult to assess due to the reported hepatic recirculation [16]. Given therapeutic levels of CoQ10 are only seen at two- to three-times [17,18] endogenous levels (0.5–1.7 µM) [19], improved gastrointestinal absorption is required to deliver a

positive health effect [16]. Various delivery systems have been developed in recent years to account for this poor absorption, showing that in the presence of a lipid, CoQ10 absorption can be significantly improved. Examples of these have utilised oil-based formulations, solubilized formulations and molecular complexes to improve plasma response to an oral CoQ10 supplement [20–24]. The responses to these formulations have been varied, indicating further efforts are required to effectively increase CoQ10 absorption. AquaCelle is a self micro-emulsifying drug delivery system designed to enhance the absorption of lipids to therapeutic levels. The aim of the present study is to compare the pharmacokinetics of a single dose of CoQ10 with multiple CoQ10–AquaCelle formulations to ascertain what, if any, affect micelle sizes and distributions can have on absorption. We hypothesis, that the addition of AquaCelle to CoQ10 will increase its absorption above the standard CoQ10 supplement. Furthermore, the smaller micelle particles will further enhance the absorption of CoQ10–AquaCelle. Materials & methods Design A single equivalent dose, randomized, double-blinded study was used to evaluate the pharmacokinetics of five different CoQ10 formulations. This study was with ethical approval from Bellberry Limited. Participants were screened for inclusion and exclusion criteria before providing written informed consent prior to commencing the study. Participants Healthy male and female volunteers (n = 66) aged 18–30 were recruited to take part in this study. Participants were screened against inclusion and exclusion criteria previously detailed [25]. Briefly, exclusion criteria included but was not limited to; the presence of a clinically significant medical condition (e.g., cardiovascular, neurological, psychiatric, renal disease), supplementation with CoQ10 within 3 months of testing, known gastrointestinal or absorption issues. No participant in this trial was taking prescribed medications apart from contraceptives. Screening for known allergies/adverse reactions were performed prior to test product dosing; none were reported. Study preparations The study arms were as follows:

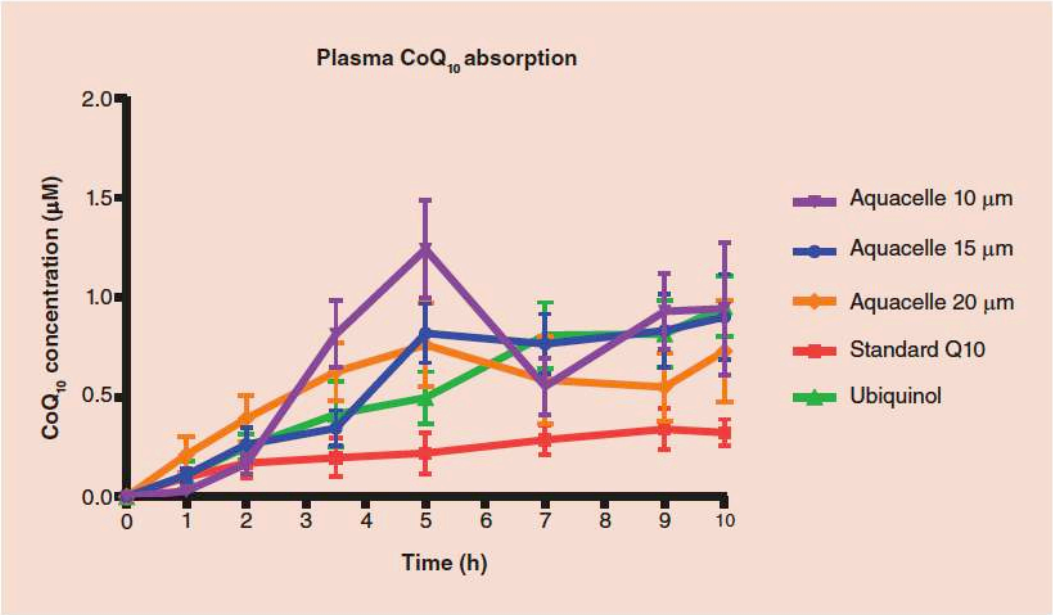
- Group 1 (AquaCelle 20) – AquaCelle CoQ10 paste: micelle size
- Group 2 (Standard)† – CoQ10 solubilized in MCT 100 mg liquid capsule (standard commercial brand)
- Group 3 (Ubiquinol) – Ubiquinol 100 mg liquid capsule (standard commercial brand)
- Group 4 (AquaCelle 10) – AquaCelle CoQ10 liquid: micelle size
- Group 5 (AquaCelle 15) – AquaCelle CoQ10 paste: micelle size

Study protocol Participants were evenly distributed to one of the five treatment groups using random allocation software (sealedenvelope.com). Blinding of participants and investigators was maintained until the completion of all plasma samples analysis

Table 2. Pharmacokinetic coenzyme Q10 parameters after a single 100 mg dose of the five study preparations.

Parameter	Group 1 Aquacelle 15 n = 10	Group 2 Standard n = 10	Group 3 Ubiquinol n = 10	Group 4 Aquacelle 10 n = 9	Group 5 Aquacelle 20 n = 9
Age	23.7 ± 3.1	22.7 ± 2.7	23.0 ± 2.0	23.0 ± 2.5	22.1 ± 3.4
Baseline	0.59 ± 0.4	0.82 ± 0.5	0.64 ± 0.4	1.36‡ ± 0.7	0.87 ± 0.6
C_{max}	1.49†,‡ ± 0.7	1.14† ± 0.6	1.60†,‡ ± 0.8	2.54†,‡ ± 1.0	1.63†,‡ ± 0.9
ΔC_{max}	0.96†,‡ ± 0.6	0.32† ± 0.3	0.95†,‡ ± 0.4	1.17†,‡ ± 0.8	0.75†,‡ ± 0.6
T_{max}	10	9	10	5	5
$AUC_{(0-10\ h)}$	5.62‡	2.21	5.24‡	6.64‡	5.34‡

Age reported in years. Values for baseline, C_{max}, ΔC_{max} are reported in μM. T_{max} is reported in hours.
†Significant compared with baseline value ($p < 0.05$).
‡Significant compared with group 2 – standard CoQ_{10} ($p < 0.05$). Values reported as mean ± standard deviation.
$AUC_{(0-10\ h)}$: Area under the curve between t = 0 and t = 10; ΔC_{max}: Maximum increase in plasma concentration; C_{max}: Peak plasma concentration; T_{max}: Time to reach peak plasma concentration.



Results:

Of the 66 volunteers recruited for this study, 57 participants completed all required components. The average participant age was 23.1 years; all within normal BMI range (20–25), nonsmokers and otherwise healthy. Six participants withdrew during the study due to an inability to provide an adequate blood sample (poor veins, aversion to venepuncture). One participant withdrew due to an unrelated sickness following the 5-h blood sample. Two nonresponders were excluded from the statistical analysis. No adverse events due to the product were reported during the study. Maximum CoQ10 concentration (Cmax) significantly increased from baseline for all treatment groups (Table 2; $p < 0.05$). Compared with the standard CoQ10 preparation (Group 2), AUC(0–10H), Cmax and !Cmax were significantly higher in Groups 1, 3, 4 and 5 ($p < 0.05$). The AquaCelle CoQ10 liquid preparation (Group 4) showed the greatest Cmax and !Cmax (Table 2). There were no between-group differences for baseline concentrations of CoQ10 apart from those seen in Group 4. Pharmacokinetic parameters for CoQ10 across all five treatment arms are reported in Table 2. Figure 1 shows the temporal change in CoQ10 concentration between 0 and 10 h. The time of peak concentration ranged from 5 to 10 h. An additional peak in CoQ10 concentration was seen at 24 h, however, these data have not been presented, nor included in statistical analysis (more on this in the discussion below). AUC(0–10 h) (Figure 2) was significantly greater in all AquaCelle preparations (Groups 1, 4, 5) and Ubiquinol (Group 3) compared with the solubilized CoQ10 preparation (Group 2). Of these, the AquaCelle CoQ10 liquid preparation (Group 4) showed the greatest absorption with an AUC(0–10 h) reported to be threefold greater, when compared with the solubilized CoQ10 preparation (Group 2). Group 2 and 5 reported a 2.5- and 2.4-fold higher absorption respectively compared with Group 2.

Discussion:

In the current study, we compared three different AquaCelle CoQ10 formulations with two different commercially available CoQ10 products. All trial conditions were standardised to control exogenous CoQ10 both prior to, and during the study. Apart from AquaCelle CoQ10 liquid preparation (Group 4), baseline CoQ10 concentrations were consistent and reflect endogenous levels previously reported in humans [11]. The disparity between Group 4 and the remaining groups was largely due to two participants having significantly higher baseline CoQ10 concentrations compared with the rest of participants. Given

there were no significant differences in participant age, the disparity seen in Group 4 is unusual and may reflect poor compliance to the preparticipation protocols. Nevertheless, !Cmax can still be used as a comparative measure of absorption in this group. The AquaCelle formulations delivered !Cmax values threefold (Group 4), 2.5-fold (Group 1) and 2.4-fold (Group 5) greater than the solubilized CoQ10 preparation (Group 2). These findings support earlier research which highlights the efficacy of self-emulsifying drug-delivery formulations (like AquaCelle) over solubilized. formulations such as those used in the solubilized CoQ10 preparation [11,14]. According to Artursson et al. [29], the rate limiting factor for drug absorption is the single layer of epithelium covering the gastrointestinal lumen. Further, a pre-epithelial aqueous barrier exists which impedes absorption of water insoluble drugs [29]. Considering this, superiority of self-emulsifying agents may be due to; greater surface area for drug delivery provided by the emulsion droplets and formation of mixed micelles; improved diffusion of the emulsion droplets/micelles across the pre-epithelial aqueous layer of the gastrointestinal tract; and increased gastrointestinal epithelial permeability due to the surfactant in self-emulsifying systems [14]. Not surprisingly, all formulations included in this trial delivered greater absorption compared with the standard CoQ10 (Group 2) which was without the aid of a delivery system. The superiority of self-emulsifying drugs to cross the aqueous gastrointestinal tract is further supported by the evidence showing the particle sizes and distribution of particles under 10 microns, appear to be directly related to CoQ10 absorption (Figure 2 – three AquaCelle groups). The formulation comprising predominantly of particles under 10 microns (Group 4 AquaCelle 10) increased 10 h AUC by 18 and 24% above Group 1 (AquaCelle 15) and Group 5 (AquaCelle 20). In our current study, we found that two of the AquaCelle formulations (Group 1 and 4) were shown to have equivalent absorption (!Cmax) when compared with ubiquinol (Group 3). Given that ubiquinol has previously been shown to have greater absorption than ubiquinone when delivered orally [30], our findings warrant further discussion. Our findings are therefore promising, showing that the AquaCelle delivery system strengthens the absorption of CoQ10 (ubiquinone) to a level consistent with ubiquinol; a product that has previously been considered to have pharmacokinetic dominance over ubiquinone [31]. Much of the literature investigating the pharmacokinetics of CoQ10 report a biphasic response to an orally delivered dose. An initial peak in plasma concentration is seen between 5 and 10 h postsupplementation, with a secondary peak of similar magnitude arising around the 24-h mark [16,22,24,31]. Our results from the present study support these temporal CoQ10 dynamics. The supplementary peak is thought to occur because of both enter-hepatic recycling of CoQ10 and a redistribution of the compound from hepatic stores to the circulation [16]. This suggests that the secondary peak is unlikely to result directly from acute CoQ10 oral supplementation. Because of this, we have excluded the 24-h data from our report. The slow absorption of CoQ10 from the gastrointestinal tract is possibly due to its high molecular weight and water insolubility. As such, it has been suggested that Tmax will remain somewhat consistent irrespective of its delivery system [16]. Our findings conflict with this, reporting Tmax levels of 5 h in Groups 4 and 5 (compared with ~10 h in the remaining groups) despite containing equivalent doses of CoQ10. The polysorbate present in the Group 5 formulation may explain this; increasing the lipophilicity of that CoQ10 dose and upregulating its absorption time. The explanation for the 5-h Tmax reported in Group 4 is less clear. Given that all our Tmax values were still within the range recorded in other studies [16,22,24,31], the variation we reported could merely result from the physiological differences in gastrointestinal epithelium. Therapeutic effects of CoQ10 have been reported at a plasma level change of approximately 2–4 μM in patients with chronic heart failure [32] and neurodegenerative diseases such as Parkinson's [18]. However, plasma concentrations of CoQ10 may need to be higher for some tissues [33] and may not be a direct measure of tissue specific concentrations of CoQ10 [34]. The impact this may have on any potential benefit for specific diseases is still uncertain.

Whilst only one formulation group in the present study approached the limits for stated disease benefit, our results are promising, highlighting the safety and efficacy of a novel CoQ10 delivery system (AquaCelle) compared with commercially available products. It must however be noted that the aforementioned studies were long-term supplement trials whereas the present study is an acute dose. Further, given that a single 100 mg dose was used in our trial, and up to 1200 mg used in other trials, higher plasma CoQ10 concentrations would likely be achieved with continued oral CoQ10 supplementation. As the absorption of most supplements, including CoQ10, is not directly proportionate to the dose administered, effective delivery systems may optimise therapeutic concentrations in persons with chronic disease. This study was designed and conducted in accordance with good clinical practice guidelines. As such, all efforts were made to ensure all participants and samples were treated equally. However, despite best efforts, there are factors that may potentially affect results that were out of our control. First, as this study did not incorporate a crossover design, there is a potential for results to be affected by the absorption differences of individuals in each group. However, even in a crossover design, you could also say that the day-to-day and week-to-week variability of an individual person could also affect the result. This could be, for example, due to a poor night's sleep, a change in diet or emotional or physiological stress. Therefore, while we acknowledge the potential effect, the design of the study is such that these variables have been adequately accounted for and the effect stated is accurate within reason. This can also be supported by the three AquaCelle groups having a linear trend in relation to the particle size consumed (i.e., AUC increases as particle size decreases). Another factor that potentially affects the results are the treatment of outliers and nonresponders. We presented above that there were two nonresponders to supplementation and that their data were removed from analysis. We are unsure why they did not respond, but as their CoQ10 plasma concentration for each time point predominantly fell outside ±2SD of the mean, we felt it appropriate to exclude these individuals from the analysis to prevent bias of the data. Furthermore, two participants presented with high baseline levels of plasma CoQ10. However, their concentrations were still within physiologically expected values and fell within ±2SDs of the mean. We are not sure why they had elevated baseline levels, however, when we looked at the absorption profile of these two individuals, they followed a similar profile (i.e., similar baseline corrected Cmax and Tmax) to the other participants in the groups. Therefore, we felt they may naturally have high CoQ10 and that it was appropriate to include these two individuals in the analysis. A final factor in the consideration of the results is the CoQ10 raw material. This study used the same CoQ10 raw material in the standard group as the three AquaCelle groups. Therefore, the increased absorption is likely due to the addition of AquaCelle. However, as different raw materials may have different bioavailabilities, it makes comparison of this study to other studies difficult, especially when bioavailability enhancers are used. Specifically, it is unknown if the increased bioavailability observed here with AquaCelle would be seen for different raw material. It may be that different particle sizes (smaller or larger) are formed with different raw materials, and this in kind may affect the absorption.

Conclusion:

Whether the findings of this study present a CoQ10 formulation that is superior to other formulations is not the aim of this study. The aim of this study was to achieve increased absorption of CoQ10 with a novel CoQ10 delivery system, AquaCelle. Following a single 100 mg dose of CoQ10, we found three AquaCelle self-emulsifying delivery systems to have significantly higher absorption compared with standard CoQ10 in an oil–water dispersion. Further, the AquaCelle formulations were found to deliver equivalent absorption to a commercially available ubiquinol product. These results support previous reports which highlight the importance of delivery systems to aid gastrointestinal absorption of CoQ10.