Journal of Clinical & Experimental Ophthalmology

Paul Jr et al., J Clin Exp Ophthalmol 2019, 10:2
DOI: 10.4172/2155-9570.1000795

Research Article Open Access

A Combined Regimen of Dietary Supplements Containing Omega-3 Fish Oil and Standardized Maqui Berry Extract Improves Dry Eye Related Symptoms in a Pilot Randomized Interventional Clinical Study

Edward L Paul Jr [1*], **Anisha Patel**[2] **and Sailaja Machiraju**[3]

[1]*Paul Vision Institute, Wilmington, NC, USA*

[2]*Southern College of Optometry, Memphis, TN, USA*

[3]*Paragon BioTeck Inc., Portland, OR, USA*

[*]**Corresponding author:** Edward L Paul Jr, Paul Vision Institute, Wilmington, NC, USA, Tel: +19102328250; E-mail: epauljr@aol.com

Received date: February 26, 2019; **Accepted date:** March 13, 2019; **Published date:** March 20, 2019

Abstract

Purpose: To determine if a dietary supplement consisting of a re-esterified triglyceride form of omega-3 fish oil combined with a standardized maqui berry extract is more efficacious for the treatment of dry eye disease than omega-3 fish oil alone.

Methods: This was an institutional review board-approved, single-site, randomized, interventional, placebo-controlled, comparative, pilot clinical study. Patients with mild to moderate dry eye disease (DED) were enrolled and divided into four study groups. Group 1 (O3M) received dietary supplements of a re-esterified triglyceride form of omega-3 fish oil (O3) and a standardized maqui berry extract (M); group 2 (O3) received only the omega-3 supplements; group 3 (M) received only the maqui berry extract supplements; and group 4 received placebo capsules. Thirteen participants aged 26–78 years with DED were included. Patients were evaluated for DED by corneal staining, changes in tear osmolarity values, matrix metalloproteinase-9 (MMP-9) levels, Schirmer's test, and tear breakup time (TBUT) at baseline, week 2, week 4, week 8, and a final assessment at week 12. In addition, at each visit patients were given the Ocular Surface Disease Index (OSDI) and Dry Eye questionnaires to complete in order to assess their level of DED. Adverse events (AEs) were recorded on AE forms at each patient visit, and any serious AEs were to be reported to the sponsor within 24 hours *via* telephone.

Results: 13 patients participated in the study (77% females, 23% males), with an average age of 55 years. The highest average percent improvement in OSDI & DED scores from baseline through week 12 of study treatment was demonstrated in the O3M group (77.6% and 70.5% respectively), compared to 39.2% improvement in OSDI assessment and 44.9% in DED score for the O3 group. Schirmer's tests demonstrated an average increase in tear production over baseline of ~3.4 mm in OD and ~0.8 mm in OS after 3 months for the O3M group. In comparison, for the O3 group, the tear production decreased by ~0.6 mm in OD and increased by ~1.67 mm in OS from baseline to 3 months. TBUT improved significantly in the O3M group, from baseline to 3 months it went up by ~3.2-2.8 sec in both eyes (OD & OS), while for the O3 group TBUT values went up by ~1.66-2.0 sec in both eyes (OD&OS). Notably, there were no adverse events reported due to dietary supplement usage during the study.

Conclusion: Dietary supplements of omega-3 fish oil and standardized maqui berry extract outperformed omega-3 fish oil alone as a treatment for DED.

Keywords: Dry eye disease; Omega-3 fish oil; Maqui berry extract; Dietary supplements

Introduction

Dry eye disease (DED) is a multifactorial disorder of the ocular surface that is characterized by an imbalance of tear flow. Symptoms of DED include ocular discomfort such as foreign body sensation, stinging/burning, dryness, irritation, pain, but it also affects visual acuity [1,2]. Millions of people suffer with DED and the global prevalence is estimated to range from 7.4% to 33.7% depending on the study cited, the method of diagnosis, and which population is surveyed [3]. In the United States alone approximately 20 million people, or more, are affected with some degree of DED. The prevalence of DED is also associated with age, sex, cigarette smoking, and autoimmune disease status, among other factors. Recent studies have shown that increased screen time on digital devices such as computers, tablets, gaming devices, and smartphones leads to particularly high DED rates among a wide range of age groups [4,5].

Several studies have shown that omega-3 fish oil dietary supplements have beneficial effects on the treatment of DED [6-9]. However, there are substantial differences in commercially available omega-3 preparations, and most contain some level of alcohol which is used to detoxify the mercury and other carcinogens that the oil contains. The addition of alcohol induces a chemical change in the natural triglycerides found in fish oil, and the resulting compound known as an ethyl ester which is not easily processed or absorbed by our bodies. A process called re-esterification can be used to remove the artificially induced alcohol from the ethyl ester to produce a re-

esterified omega-3 oil which is more readily absorbed and easier to tolerate than the ethyl ester form [10]. A recent study shows that re-esterified omega-3 supplementation is associated with statistically significant improvement in DED symptoms [8].

Maqui berries are fruits from the maqui (*Aristotelia chilensis*) tree native to South America in the Valdivian temperate rainforests of Chile and adjacent regions of southern Argentina. The maqui berries have been used for centuries in traditional medicine [11], and it is the main ingredient in many functional beverages and dietary supplements due to it being recently hailed as a superfood. Maqui berries are known for their high antioxidant capacity attributable to a variety of phenolic products, anthocyanidins, other flavonoids, and phenolic acids which they contain [12]. Some of the many reported medicinal properties of maqui berries include anti-inflammatory, anti-diabetic, and analgesic effects [13].

Notably, maqui berry extracts (MBE) has been reported to be effective in treating certain ophthalmic disorders. The major anthocyanins of MBE are delphinidin 3,5-*O*-diglucoside (D3G5G) and delphinidin 3-*O*-sambubioside-5-*O*-glucoside (D3S5G), and it was reported that they were able to protect retinal cells against light-induced photoreceptor degeneration [14]. Also, in a rat animal model for dry eye it was shown that D3G5G restored tear secretion [15]. In a recent, pilot, clinical study a commercially available MBE (MaquiBright™) was effective when taken orally for significantly increasing tear fluid volume and decreasing dry eye symptoms after two months of treatment [16]. This pilot, clinical study investigates the efficacy of standardized MBE supplements in combination with a re-esterified triglyceride form of omega-3 fish oil compared to the efficacy of omega-3 fish oil alone for the treatment of dry eye disease.

Study Design and Methods

This was an institutional review board-approved, single-site, randomized, interventional, placebo-controlled, comparative, pilot clinical study. Written informed consent was obtained from all study participants. The study was conducted in accordance with the Declaration of Helsinki and was HIPAA-compliant with the protection of individually identifiable health information.

Male or female subjects, 18 years or older with mild to moderate DED (tear break-up time; TBUT ≤ 10mm) were enrolled. Patients were divided into four study groups as follows: Group 1 (O3M) received dietary supplements of a re-esterified triglyceride form of omega-3 fish oil (O3) and a standardized maqui berry extract (M); group 2 (O3) received only the omega-3 supplements; group 3 (M) received only the maqui berry extract supplements; and group 4 received placebo capsules. Details of supplements used and dosing schedule are outlined below (Table 1).

Dietary supplement	Brand	Key dietary ingredient (daily intake)	Dose
Omega-3 fatty acid	Atlantic Nutraceuticals™ Omega 1500	EPA[1]-816 mg; DHA[2]-544 mg	3 times daily or as directed by PI
Maqui Berry Extract	Tear Support with MaquiBright® by Life Extensions	60 mg	Once daily or as directed by PI
Placebo	Honest Placebo Pills-Zeebo®	-	Once daily or as directed by PI

Table 1: List of dietary supplements and dosage used in the study.

Efficacy endpoints included: Corneal staining with 2% fluorescein sodium using the Oxford staining scale of 0 to 5 (0: no staining; 5: severe staining); changes in tear osmolarity values using TearLab® Osmolarity System; matrix metalloproteinase-9 (MMP-9) level assessment using the InflammaDry test, Schirmer's test 17, and TBUT testing [17]. Assessments were performed at baseline, week 2, week 4, week 8, and a final assessment at week 12. In addition, at each visit patients were given the Ocular Surface Disease Index (OSDI) questionnaire [18] and the Dry Eye questionnaire (see supplementary materials) to complete in order to assess their level of DED. Adverse events (AEs) were recorded on AE forms at each patient visit, and any serious AEs were to be reported to the sponsor within 24 hours *via* telephone.

Results

A total of 13 patients participated in the study ranging in age from 26 to 78 with an average age of 55 years. The majority of subjects were female (77%) and the majority were Caucasian (92%). Demographics for the study are shown in Table 2. The average tear break-up time (TBUT) notably improved in the O3M group, from baseline to 3 months it went up by ~3.2 seconds (OD) and 2.8 seconds (OS), while for the O3 group the average TBUT values went up by ~1.66 seconds (OD) and 2.0 seconds (OS). The patients who received only the MBE supplements also reported a significant higher average increase in TBUT values of 3.7 seconds (OD) and 3.6 seconds (OS) compared to the O3 and placebo groups (Figure 1).

Study group/parameter	O3M (n=5)	O3 (n=3)	M (n=3)	Placebo (n=2)	Total study (N=13)
Mean age	46.8 20.22	59.00 13.45	58.00 13.00	65.00 1.41	55 15.7 years
Gender	80% Female, 20% Male	100% female	67% Female, 33% Male	50% Female, 50% Male	77% Female, 23% Male
Ethnicity	100% Caucasian	67% Caucasian, 33% Asian	100% Caucasian	100% Caucasian	92% Caucasian, 8% Asian

Table 2: Study demographics. Note: O3M=re-esterified triglyceride form of omega-3 fish oil and a standardized maqui berry extract; O3=re-esterified triglyceride form of omega-3 fish oil; M: standardized maqui berry extract.

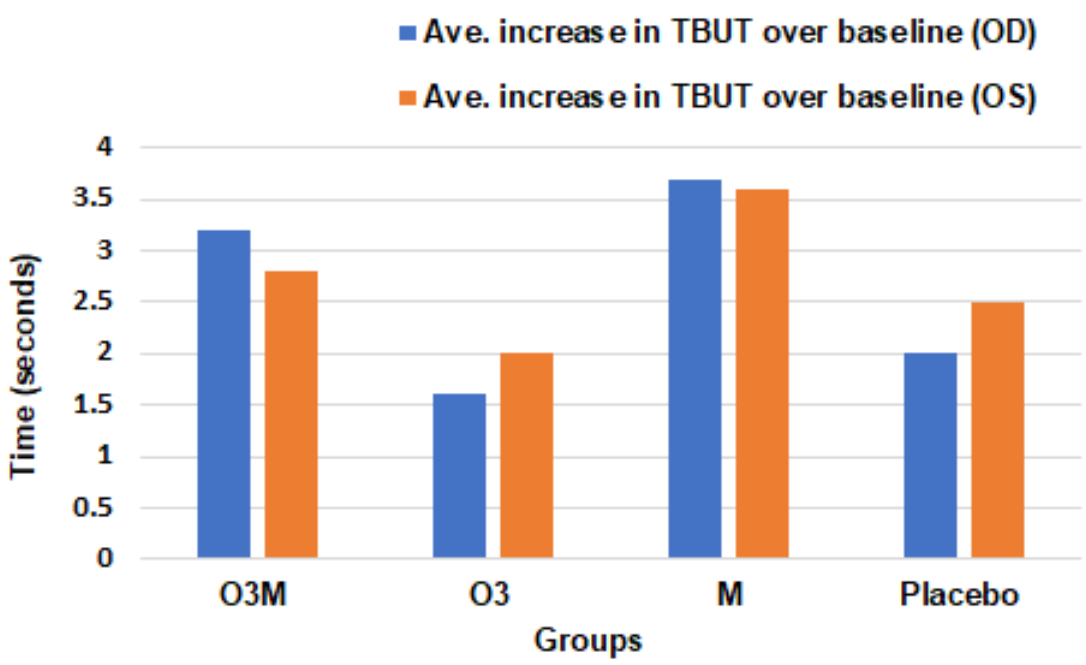

Figure 1: Average increase in tear break-up time (TBUT) in seconds from baseline to 12 weeks for (OD&OS) Note: OD=Oculus Dexter (right eye); OS=Oculus Sinister (left eye); O3M=re-esterified triglyceride form of omega-3 fish oil and a standardized maqui berry extract; O3=re-esterified triglyceride form of omega-3 fish oil; M: standardized maqui berry extract.

Schirmer's tests demonstrated an average increase in tear production over baseline of ~3.4 mm in OD and ~0.8 mm in OS after 3 months for the O3M group. In comparison, for the O3 group, the tear production decreased by ~0.6 mm in OD and increased by ~1.67 mm in OS from baseline to 3 months. The corneal staining assessments improved from mild to minimal in both the O3 and O3M groups, while remaining minimal for the M and placebo groups. An overall decrease in the number of positive InflammaDry test results was seen in the O3M group after 12 weeks of treatment, while in the O3 group the number of positive remained constant throughout the study. In addition, the average tear osmolarity (TO) in the O3M group decreased after 12 weeks compared to an increase in TO for the O3 group. A comparison of the efficacy endpoint results in the O3M and O3 groups are summarized in Table 3.

Study Assessments/ (Group)	Summary of results (Baseline *vs.* Week 12)
Schirmer's test/ (O3M)	Tear production increased by ~3.4 mm in OD and ~0.8 mm in OS
Schirmer's test/ (O3)	Tear production decreased by ~0.6 mm in OD and increased by ~1.67 mm in OS
Corneal staining/ (O3M)	Improved from mild to minimal as per the grading system
Corneal staining/ (O3)	Improved from mild to minimal as per the grading system
InflammaDry test/ (O3M)	40% turned -ve at the end of the study and 60% remained +VE
InflammaDry test/ (O3)	There was no change from baseline, 66.67% tested +VE and 33.43% were tested -ve
Tear osmolarity/ (O3M)	There was a decrease in tear osmolarity by 4.85 mOsm/L units
Tear osmolarity/ (O3)	There was an increase in tear osmolarity by 11.33 mOsm/L units

Table 3: Comparison of the efficacy endpoint results in the O3M and O3 groups.

Improvements in the objective signs of DED were demonstrated in this study, the highest average percent improvement in OSDI & DED scores from baseline through week 12 of study treatment was seen in the O3M group (77.6% and 70.5% respectively), compared to 39.2%

improvement in OSDI assessment and 44.9% in DED score for the O3 group (Table 4). Notably, there were no adverse events reported due to dietary supplement usage during the study.

Study Group	O3M (%)	O3 (%)	M (%)	Placebo (%)
OSDI Assessment	77.61	39.22	46.15	30.31
DED Assessment	70.54	44.91	25.74	11.15

Table 4: Average % Improvement in OSDI & DED Score from Baseline through week 12 of Study Treatment. Note: O3M=re-esterified triglyceride form of omega-3 fish oil and a standardized maqui berry extract; O3=re-esterified triglyceride form of omega-3 fish oil; M: standardized maqui berry extract; OSDI=Ocular Surface Disease Index.

Discussion and Conclusion

By using a sequence of clinical tests and objective assessments we demonstrated that a combination of standardized dietary supplements of maqui berry extracts and re-esterified triglyceride form of omega-3 fish oil is a safe and promising treatment for dry eye disease. The potential of standardized supplements of maqui berry extracts and re-esterified triglyceride form of omega-3 fish oil in treating DED has been demonstrated independently by other studies. To the best of our knowledge we describe herein the first clinical study to investigate using this combination of supplements to treat patients with DED.

The multifactorial nature of dry eye disease makes it difficult to treat. However, one consistent factor that contributes to DED pathology is an increase of reactive oxygen species (ROS) in lacrimal gland (LG) which leads to decreased tear production. In a pre-clinical study, a major anthocyanins constituent of MBE (D3G5G) suppressed the formation of ROS from LG tissue, and the resulting restoration of tear secretion was more potent for D3G5G than other anthocyanins naturally contained in MBE [15]. This highlights the therapeutic potential of MBE for treating DED, and as predicted, this study demonstrated an increase in tear production (Schirmer's test) in patients receiving MBE supplements.

Other clinical tests indicative of DED such as TBUT and tear osmolarity showed improved assessments in the O3M group compared to the O3 group. Specifically, an increase in TBUT was reported in the O3M group which is indicative of decreased DED severity, and a decrease in the tear osmolarity was demonstrated in the O3M group which points also to reduce DED severity. Whereas, test results for corneal staining and inflammatory MMP-9 status were not as indicative of the effect of MBE and omega-3 fish oil supplements on DED status in this study. Conversely, the DED questionnaires for objective assessment strongly indicated that the combination dietary supplements of MBE and omega-3 fish oils had the most beneficial effects on treating DED symptoms than any other treatment group.

A recent study confirmed the bioavailability of maqui berry extracts and its specific anthocyanin compounds when taken orally in healthy subjects [19], in addition the increased bioavailability of the re-esterified form of omega-3 fish oils compared to the ethyl ester form has been previously established [10]. The beneficial effects of these two supplements were rapidly seen in treating some DED signs and symptoms, some effects apparent even after only six weeks of treatment. The combination of MBE and omega-3 fish oil outperformed omega-3 fish oil alone for the treatment of DED in this pilot study, and suggests that dietary supplements of MBE in combination with re-esterified omega-3 fatty acids should be included as a standard therapy for dry eyes.

Disclosure

The authors of this publication received research funding from Focus Laboratories, Inc. which is developing products related to research described in this publication. In addition, the primary author serves on the scientific advisory board Paragon BioTeck, Inc.

Acknowledgements

The authors would like to acknowledge Nicola Donelan for her scientific/medical writing and editorial support.

References

1. Goto E, Yagi Y, Matsumoto Y, Tsubota K (2002) Impaired functional visual acuity of dry eye patients. Am J Ophthalmol 133: 181-186.
2. Koh S, Maeda N, Hirohara Y, Mihashi T, Bessho K, et al. (2008) Serial measurements of higher-order aberrations after blinking in patients with dry eye. Invest Ophthalmol Vis Sci. 49: 133-138.
3. Gayton J (2009) Etiology, prevalence, and treatment of dry eye disease. Clin Ophthalmol. 3: 405-412.
4. Uchino M, Yokoi N, Uchino Y, Dogru M, Kawashima M, et al. (2013) Prevalence of dry eye disease and its risk factors in visual display terminal users: the Osaka study. Am J Ophthalmol 156: 759-766.
5. Kawashima M, Uchino M, Kawazoe T, Kamiyashiki M, Sano K, et al. (2013) A field test of Web-based screening for dry eye disease to enhance awareness of eye problems among general Internet users: a latent strategy to promote health. J Med Internet Res 15: e209.
6. Deinema LA, Vingrys AJ, Wong CY, Jackson DC, Chinnery HR, et al. (2017) A Randomized, Double-Masked, Placebo-Controlled Clinical Trial of Two Forms of Omega-3 Supplements for Treating Dry Eye Disease. Ophthalmology 124: 43-52.
7. Chinnery HR, Naranjo Golborne C, Downie LE (2017) Omega-3 supplementation is neuroprotective to corneal nerves in dry eye disease: a pilot study. Ophthalmic Physiol Opt. 37: 473-481.
8. Epitropoulos AT, Donnenfeld ED, Shah ZA, Holland EJ, Gross M, et al. (2016) Effect of Oral Re-esterified Omega-3 Nutritional Supplementation on Dry Eyes. Cornea 35: 1185-1191.
9. Wojtowicz JC, Butovich I, Uchiyama E, Aronowicz J, Agee S, et al. (2011) Pilot, prospective, randomized, double-masked, placebo-controlled clinical trial of an omega-3 supplement for dry eye. Cornea. 303: 308-314.
10. Dyerberg J, Madsen P, Møller JM, Aardestrup I, Schmidt EB (2010) Bioavailability of marine n-3 fatty acid formulations. Prostaglandins Leukot Essent Fatty Acids. 833: 137-141.
11. Misle E, Garrido E, Contardo H, González W (2011) Maqui Aristotelia chilensis (Mol.) Stuntz the amazing Chilean tree: A review. J Agric Sci Technol 1:1.
12. Escribano-Bailon MT, Alcalde-Eon C, Munoz O, Rivas-Gonzalo JC, Santos-Buelga C (2006) Anthocyanins in berries of Maqui (Aristotelia chilensis (Mol.) Stuntz). Phytochem Anal 171: 8-14.
13. Romanucci V, D'Alonzo D, Guaragna A, (2016) Bioactive Compounds of Aristotelia chilensis Stuntz and their Pharmacological Effects. Curr Pharm Biotechnol. 176: 513-523.
14. Tanaka J, Kadekaru T, Ogawa K, Hitoe S, Shimoda H, et al. (2013) Maqui berry (Aristotelia chilensis) and the constituent delphinidin glycoside inhibit photoreceptor cell death induced by visible light. Food Chemistry 139: 129-137.
15. Nakamura S, Tanaka J, Imada T, Shimoda H, Tsubota K (2014) Delphinidin 3,5-O-diglucoside, a constituent of the maqui berry (Aristotelia chilensis) anthocyanin, restores tear secretion in a rat dry eye model. J Functional Foods 10: 346-354.

16. Hitoe S, Tanaka J, Shimoda H (2014) MaquiBright standardized maqui berry extract significantly increases tear fluid production and ameliorates dry eye-related symptoms in a clinical pilot trial. Panminerva Med 56: 1-6.
17. Messmer EM (2015) The pathophysiology, diagnosis, and treatment of dry eye disease. Dtsch Arztebl Int 112: 71-81.
18. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL (2000) Reliability and validity of the Ocular Surface Disease Index. Arch Ophthalmol 118: 615-621.
19. Schon C, Wacker R, Micka A, Steudle J, Lang S, et al. (2018) Bioavailability Study of Maqui Berry Extract in Healthy Subjects. Nutrients 10: 1720.