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THERAPEUTIC POTENTIAL OF NATURAL PRODUCTS ON AGE-RELATED MACULAR DEGENERATION

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Abstract

There is an increasing value of natural products in age-related macular degeneration (AMD). This study evaluates the association of different Natural products and development of AMD. online medical data bases like PubMed, web of science and Google Scholar with keywords as "AMD", "Age-related Macular Degeneration", "Natural Products", "food supplements", "traditional herbal medicine", "health supplements", literature from 2000 to March 2020 were searched. Limited case sets, commentaries, Abstracts of cases or individual opinions are omitted, although case-controlled experiments, population-based analyses, and meta-analysis were reviewed. Often subject to strong research concerns is vitamin B and extractions of wolfberry, gingko biloba, and berry anthocyanins, but no study with statistical confirmation has been found in this study to suggest yet. The first large-scale randomised controlled scientific trial named "Age-related Eye diseases Study" (AREDS) shows benefits of AREDS vitamin "C, E, beta-carotene" and "copper zinc" in minimizing possible advancement to severe AMD in patients with moderate AMD or severe AMD in one eye.

INTRODUCTION

According to the Global Burden of Disease Study (2010) the ever-growing world population, a noticeable increase in the life expectancy, and declining deaths ratio has assisted change in nature of the illness into disorders that causes infirmity rather than deaths (Jonas, 2014). AMD is among those disabling conditions, attacking mainly the old age group. In the USA there is a high number of old people, as people are living longer and has an incidence of 2 million of visually impaired people due to AMD alone and this number is going to rise to 5 million in a couple of decades when the old population is expected to double in the coming 3 decades, as a result, exposing more people to the disease (Friedman *et al*, 2004). In Europe early AMD is expected to be incident between 14.9 to 21.5 million and the late AMD is expected to rise to be between 3.9 to 4.8 million cases by the year 2040

(Colijn *et al*, 2017). In the years between 1990 and 2010 AMD was the third major reason for blindness (Bourne *et al*, 2013) that accounted for 6.6% of all blindness cases then. Recently, a study by Seddon (2017) estimated the total number of AMD cases to be 196million and this number will go as high as 288million, with a 40% increase in 2040.

Physiologically, the retina is the location for conversion of incident light into neural impulses, which are then taken in to the visual cortex of the occipital lobe. Retina is made up of several layers. The middle layer is composed of single cell thick sheet known as Retinal Pigment Epithelium (RPE). It serves to provide metabolic support to the photoreceptor cells, as well as manages the draining out of cellular debris which is produced during the renewal of the photoreceptor cells. RPE lays on Bruch's membrane and inner sensory neural layer containing the photoreceptors, passing on the electrical impulse to nerve fiber layers of the optical nerve (Aaberg, 2003). The macula is the central part of the retina, providing the finest visual acuity and central vision due to the occurrence of large number of photoreceptors cells. The remaining retina helps in providing peripheral and night vision.

2.1 Methodology

The technique followed is a review of peer reviewed papers and other grey/unpublished works related to the topic. For peer reviewed papers 2 main databases of published papers, PubMed and Web of Science, were selected and peer reviewed papers were selected based on their relevance.

For grey literature and other reviewed papers Google Scholar and other relevant websites and research institutes whom are focusing on eye health care, along with other well-known eye care/health care organisations were reached online. Relevant peer reviewed papers and/or grey literature were searched with the help of key words for this study, "AMD", "Age-related Macular Degeneration", "Dry AMD", "Wet AMD/nAMD", "Natural Products", "food supplements", "traditional herbal medicine", "health supplements" and following the use of relevant Boolean operators. All the relevant articles with this study were collected and any repeating study was excluded from the articles collection.

These organised articles with their titles and abstracts were then studied and those papers not related to this study "therapeutic effect of Natural products on Age-related Macular Degeneration" were excluded again. The full text form of the remaining chosen papers were then studied to know which of the different natural products contributes prevention, inhibition or delaying, and treatment of the age-related macular degeneration.

After studying the full texts of these remaining papers they were then grouped on the basis of the main natural product discussed in the study. These articles were then noted and referenced under the discussion of the each relevant natural product in this study.

The restriction in searching for the papers in relevance to this study was English language only, being easy to for the reviewers to understand. Nevertheless, papers selection was restricted to published from January 1st 2000 and onward till date.

Results:

Different experimental (longitudinal and clinical trials) studies (Falsini *et al.*, 2010; LASHAY *et al.*, 2016; Di Marco *et al.*, 2019) have evaluated and confirmed that saffron supplements consumption has improved visual parameters, both objective and subjective. Nonetheless, these cannot be compered directly because the dosage amount, ingredients of the formula, time taken for intervention, study technique and outcome variables were are different in each one. Although, saffron consumption is considered safe with a daily dose of 30 mg is safe for consumption and effective against AMD, while a daily dose of 5 g or above is considered harmful whereas, it can be lethal if consumed 20 g (Mohamad pour *et al.*, 2013; (Christodoulou *et al.*, 2015). Along with studies on rodents/animal models, proving saffron and its constituent elements as protective to ocular health, other helpful results can be seen in Table 1.

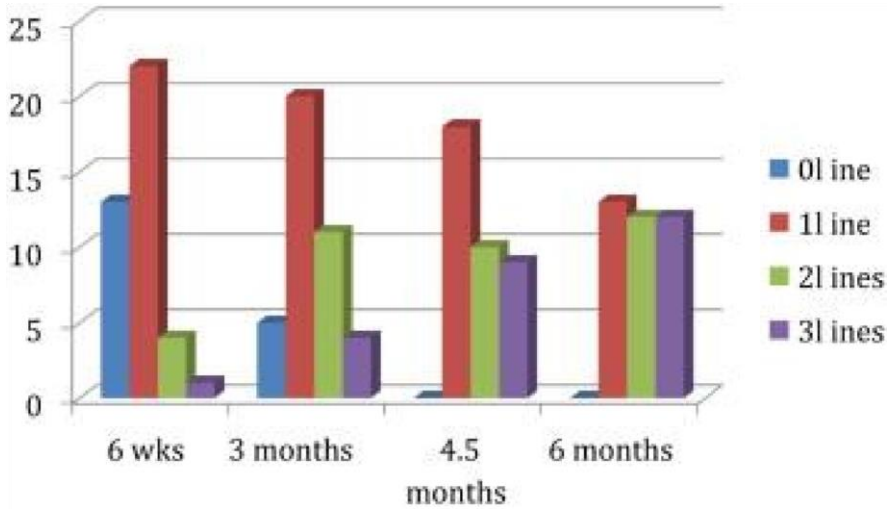
Subjects (n = eyes)	Treatment	Type of study	Visual parameters and results	Reference
Early AMD (n = 25)	20 mg/d	Double-blind, placebo controlled, crossover, RCT 3-month period with cross over for another 3 months	fERG: ↑ in amplitude in patients, but not in placebo group	Falsini et al., 2010
Early AMD (n = 29)	20 mg/d	Longitudinal interventional open-label study 3 monthly follow-ups over a 15-month period of treatment	Mean VA: ↑ 2 lines fERG: ↑ 0.3 log units	Piccardi et al., 2012
Early AMD (n = 33) Presence of known AMD risk genotypes	20 mg/d	Longitudinal 3 monthly follow-ups over a 12-month period	fERG: ↑ amplitude and sensitivity amplitude that stabilized after 3 months independent of genotype	Marangoni et al., 2013
Dry and wet AMD (n = 40)	15 mg, twice a day	Placebo-controlled, RCT 6-month period with follow-ups at 3 and 6 months	CMT: ↓ in saffron and placebo groups in wet AMD, but not in dry AMD ERG: ↑ amplitude in the saffron group (dry and wet AMD) compared to placebo after 3 months, but not 6 months	Lashay et al., 2016
Mild/moderate dry AMD (n = 54)	50 mg/d	Placebo-controlled, RCT three months	CMT: unchanged BCVA: ↑ in saffron, but not in placebo group CS: ↑ in saffron, but not in placebo group	Riazi et al., 2017
Mild/moderate AMD (n = 96) 73.2% consuming AREDS supplements	20 mg/d	Double-blind, placebo-controlled, crossover, RCT 3 months followed by crossover for 3 months	BCVA: ↑ in saffron group and AREDS + saffron, but not in placebo mfERG response density: ↑ in AREDS+saffron, but not in the saffron or placebo group mfERG latency: ↓ in saffron group, but not in placebo group	Broadhead et al., 2019
Intermediate AMD (n = 42) Two groups (n = 19) lutein/zeaxanthin n = 23 saffron	–	Longitudinal open-label study 8 monthly follow-ups over a 29 (±5)-month period	fERG Saffron treated AMD patients: Visual function remains stable Lutein/zeaxanthin treated patients: Deterioration of retinal functions	Di Marco et al., 2019

AREDS: Age-related eye disease study; BCVA: best-corrected visual acuity; CMT: central macular thickness; CS: contrast sensitivity; ERG: electroretinography; fERG: focal electroretinography; mfERG: multifocal electroretinography; RCT: randomized clinical trial.

Fig 1:

patients. Image retrieved from (*et al.,*2014).

Bar graph representing the effect of omega3 supplement on visual acuity in AMD



Discussion and Conclusion

One of the focuses, in treating AMD is reducing the harmful consequences of oxidative stress and anti VEGF materials to overcome new vessels formation in the retina. In light of this study different natural products may prove helpful as valuable treatment supplementation against a specific type/stage of AMD. According to the literature AMD comes with age

(Jager, et. al., 2008) and is linked with imbalance of free radicals and antioxidant (oxidative stress), while the known main factor for the advanced forms of AMD is the formation of new blood vessels in the choroid region (Mitchell *et al.*, 2018). The possible natural products with possible therapeutic effect against AMD according to the literature are crocus sativus, ginkgo biloba, and blue berries. According to the researchers (Rahaiee *et al.*, 2014; Di Marco et al., 2019; Falsini *et al.*, 2010;Tamaddonfard *et al.*, 2013; LASHAY *et a.*, 2016) the antioxidant properties of saffron can help restore visual acuity if consumed within safe dose limits. Blueberries have the same antioxidative ability with an additional ability to increase ocular blood flow (Huang *et al.*, 2018). Though saffron and blueberries show similar properties the main constituent elements in both of them are different from each other, as the saffron is composed of carotenoids and blueberry contains polyphenols. The better option for the late stage AMD/nAMD is ginkgo biloba due to anti-oxidative and antiangiogenic properties. Both Carotenoids and polylhenol (natural product) are proven protective against AMD. The AREDS (2014) recommends lutein and zeaxanthin to prevent the chances of AMD progression. As no harmful side effects, with the use of lutein and zeaxanthin have been reported. Other micronutrients like Vit. "C" and "E" shows no highlighted association with AMD,though, some results pointing in the positive direction were obtained, however further experiments and studies are needed to understand the action course and average safe dosage. Therefore, from this review we can propose that by using natural products with antiVEGF effects and antioxidant properties, production of a single product is possible to be used for age-related macular degeneration prevention and/or treatment. Natural elements like Corcus sativa, Ginkgo biloba and Blueberries and lutein and zeaxanthin might be a good option, if proves helpful after further scientific researches and clinical trials.

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