

absorption spectrum of macular pigment [41] which consists mainly of L and Z. Secondly, they are able to quench oxidising agents such as free radicals [42].

A study of retinal levels of L and Z in donor eyes found an 82% lower risk of age-related macular degeneration (AMD) in retinae among the 25% with highest L and Z levels compared to the 25% with the lowest levels [43]. A 70% reduced risk of AMD has been demonstrated with high (>0.67µmol/L) versus low (0.25µmol/L) L/Z plasma levels [44]. Measurement of macular pigment optical density (MPOD) in healthy eyes showed an age-related decline, and healthy eyes considered to be at risk for AMD had significantly less MP than healthy eyes not at risk [45].

The Lutein Antioxidant Supplementation Trial (LAST) [46] investigated the effect of L and antioxidant supplementation on visual function in people with dry AMD. Participants were randomised into three treatment groups; 1) 10mg L, 2) 10mg L/antioxidants, 3) placebo. Investigators found a statistically significant concurrent improvement in glare recovery, contrast sensitivity, and distance/near VA in both treatment groups. Combining L with other antioxidants appears to provide added improvement to contrast sensitivity. The 10 mg dose of L in Nutrofol Total was informed by this trial.

Essential fatty acids

Essential fatty acids (EFA) are fatty acids which cannot be produced within the body while saturated and monounsaturated fatty acids are synthesised by the body from carbohydrate and protein. EFA include those in the linoleic acid (omega-6) and alpha-linolenic acid (omega-3) groups. EFA are natural constituents of cell membranes and have a role in the maintenance of fluidity, flexibility, and permeability [47]. Linoleic acid and alpha-linolenic acid are also precursors to a group of hormone-like eicosanoid compounds, prostaglandins, and leukotrienes. Linoleic acid (LA) is converted to arachidonic acid (AA); alpha-linolenic acid (ALA) is converted to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA); the latter is found in the retinal photoreceptors.

Eicosanoids are produced in almost all the cells of the body and have a role in the modulation of many physiological processes including reproduction, inflammation, and blood pressure. They are oxygenated metabolites of arachidonic acid, eicosapentaenoic acid (EPA), and dihomo-gamma-linolenic acid (DGLA). Eicosanoids are converted via the cyclooxygenase pathway to prostaglandins and thromboxanes, and via the lipoxygenase pathway to leukotrienes.

The recommended ratio of omega-3 EFA to omega-6 EFA is 1:2.3, however actual ratios of consumption have been estimated at 1:10 [48].

DHA is a major omega-3 essential fatty acid (EFA) in the membranes of photoreceptor outer segments [49] and plays a part in protecting the retina against oxidative stress [50]. Several studies have highlighted a relationship between high dietary intake of EFA and fish and a reduced risk of AMD [51, 52] [53].

Resveratrol

Resveratrol is a phytoalexin, which is a type of antibiotic produced by plants when they are under attack by bacteria. Resveratrol has been shown to reduce oxidative stress in the retinal pigment epithelium [54]. Resveratrol is derived from red wine and nuts.

Bioavailability

A significantly higher serum response following supplementation with L-enriched eggs has been reported compared to that found following consumption of spinach, L supplements, or L esters supplements [55]. Investigators concluded that the bioavailability of L from eggs is higher than that from other sources, and that this may be related to the fact that within eggs, lutein is located in the highly digestible lipid matrix. It should be noted that the eggs used in this study contained approximately five times the amount of L found in conventional eggs. Nevertheless, the results provide useful information about the bioavailability of different sources, suggesting that a lipid base may be optimum for ocular supplements. Spectrum Théa Pharmaceuticals have taken this one step further by combining L with fish oil, which is also thought to have benefits for retinal health. A combination of L and fish oil is currently under investigation as part of the AREDS II clinical trial.

Summary

Nutrofol Total is an informed formulation that contains nutrients in a form that promotes good bioavailability. It does not contain beta-carotene and so is suitable for use by people who smoke. This is a formulation that people with early stages of AMD, or people who are concerned about their risk of the developing the condition might consider taking. It is

advisable to recommend that patients who are taking prescribed medication discuss nutritional supplementation with their GP.

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NUTROF TOTAL

Age-related macular degeneration (AMD) is the leading cause of irreversible visual loss in the developed world [1-6]. In the UK, half of those registered as blind or partially sighted every year (approximately 30,000) have the condition [7]. This pattern in the registered population is reflected in the rest of Europe, North America and Australia [2, 8-12].



There are estimated to be nearly one million visually impaired people in Britain, 90% of whom are over 65 years of age [13]. Age-related macular disease is the most frequently occurring condition that results in permanent vision loss in this age group [3, 14]. The proportion of blindness attributable to the disease is expected to increase during the 21st century as a result of the aging population [13, 15]. People over the age of 65 represent the fastest growing segment of the US population, and between 2000 and 2020 this group is expected to increase by 53%. This age group will then make up 16.5% of the entire US population [16].

Pathogenesis of age-related macular disease

It is generally thought that oxidative damage is responsible for aging and that this process has an important role in the pathogenesis of age-related conditions such as AMD [17]. Oxidation refers to the removal of electrons. Reactive oxygen intermediates (ROI) is a term used to describe free radicals, hydrogen peroxide, or singlet oxygen. Free radicals are molecules that contain one or more unpaired electrons in their outer orbits [18]. Free radicals extract electrons from other molecules in order to achieve stability. These molecules are rendered unstable by this interaction, and a cytotoxic oxidative chain results. Carbohydrates, membrane lipids, proteins, and nucleic acids may all be damaged by ROI. This damage is believed to contribute to the pathogenesis of many diseases such as diabetes, chronic obstructive airway disease, Parkinson's disease, and cervical cancer [19, 20].

The oxidative stress hypothesis for the pathogenesis of AMD is a popular one, mainly due to the fact that it is biologically plausible. Other factors have been proposed, such as the age-related deterioration of Bruch's membrane, vascular insufficiency, and genetic predisposition.

The eye is particularly prone to ROS damage. The transparency of the cornea, aqueous humour, lens and retina allow continuous exposure to light, which along with aging, inflammation, air pollutants, and cigarette smoke, has been shown to increase production of ROS [21, 22]. Polyunsaturated fatty acids are abundant in the retina, predominantly found in photoreceptor outer membranes, and are readily oxidised [21, 23, 24]. In addition, phagocytosis, a process that produces ROS, occurs within the retinal pigment epithelium.

Terminology and presentation of dry age-related macular degeneration
Classification of age-related macular degeneration is required for studies investigating the condition in order to make reliable comparisons between findings. For this reason, the International Classification and Grading System for Age-Related Maculopathy (ARM), and Age-Related Macular Degeneration (AMD) has been developed in an attempt to standardise terminology. ARM refers to large soft drusen and pigmentary abnormalities of the retinal pigment epithelium (RPE) and the retina, and AMD refers to later stages of the disease such as geographic atrophy (GA), choroidal neovascularisation (CNV), pigment epithelium detachment and fibrous scarring of the macula [25]. This review will use the terms ARM and AMD according to this classification. The term age-related macular disease will be used to encompass ARM and AMD.

Nutrof® Total

Spectrum Théa Pharmaceuticals have recently released a new nutritional supplement called Nutrof® Total specially formulated for people with age-related macular disease (ARMD) and based upon the most up-to-date evidence for ARMD. Most practitioners are familiar with the Age-Related Eye Disease Study (AREDS) [26], which determined that a combination of high dose vitamin C, vitamin E, beta-carotene and zinc was moderately effective in preventing progression to advanced AMD. This effect was only seen in those subjects with extreme intermediate drusen, large drusen or non-central GA without advanced AMD [26]. Since then there have been

new studies and evidence and the role of nutritionals in eye health is becoming more and more debated. There are now numerous publications showing the benefits of antioxidants, macular pigments and omega 3 for ARMD.

Nutrof® Total is a complete and well balanced unique formulation that could be recommended to all patients with ARMD. The paucity of data from large scale randomised controlled trials means that formulation design is largely based on epidemiological and bioavailability research, as well as on the results of intervention studies. This article will give an overview of the scientific basis for the Nutrof® Total formulation. The formulation details are shown in table 1; the dose is one soft-gel capsule per day.

Nutrient	Daily dose
Vitamin C	60 mg
Zinc	10 mg
Selenium	25 ug
Vitamin E	10 mg
Copper	500 ug
Glutathione	1 mg
Essential fatty acids	280 mg (50 % DHA)
Lutein	10 mg
Zeaxanthin	2 mg
Resveratrol	0.25 mg

Table 1: Nutrof® Total formulation

Antioxidant vitamins and minerals

The role of individual antioxidants in the prevention of ocular disease has been reviewed by Bartlett and Eperjesi [27]. A brief overview follows.

Vitamin C (ascorbic acid) is water-soluble and is involved with several biological processes. It protects LDL (low density lipoprotein) cholesterol from oxidative damage and reduces platelet aggregation [28]. Vitamin E protects cell membranes and low density lipoprotein (LDL) cholesterol [29]. Zinc is an essential component of over 200 enzymes, including antioxidant enzymes such as superoxide dismutases [21]. Zinc interacts with copper, leading to copper deficiency anaemia, since copper is required for production of erythrocytes [30-32]. For this reason, copper is added to all supplements containing zinc. Selenium activates the antioxidant enzyme, glutathione peroxidase, which protects cell membranes from oxidative damage [33].

The epidemiological clinical data pertaining to these nutrients is conflicting; however, the general cellular functions are well-documented.

Lutein and zeaxanthin

Although yellow pigmentation of the macular region was first documented in 1782, it was attributed to the xanthophyll group of carotenoids much later in 1945 [34]. It wasn't until 1985, that the retinal carotenoids were separated using high-performance liquid chromatography [35]. Two slightly different chemical structures were found, and were termed lutein (L) and zeaxanthin (Z). Lutein and Z are the only carotenoids found in human serum that are also found in the retina and macula [35-37] prompting them to be termed the macular pigment (MP). Dissection of human retinae has demonstrated that Z dominates in the macula, centre whereas L is more abundant in the medial and peripheral macula [38]. This suggests a possible protective role of L for rod photoreceptors [39] and of Z for the central cone photoreceptors [40].

Lutein and Z are believed to protect the retina in two ways. Firstly, they act as blue-light filters. Action spectrum for blue-light induced damage shows a maximum at 400nm and 450nm, and this is consistent with the