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Literature Review: The Effect of Zeaxanthin Carotenoid Supplementation on the Prevention of Age-Related Macular Degeneration (AMD)

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ABSTRACT

Introduction: *Age-Related Macular Degeneration (AMD) is a condition that harms the retina and primarily affects those who are 60 years old or older, leading to significant vision loss. In the United States, the count of individuals affected is projected to rise from 9.1 million in 2010 to approximately 17.8 million by the year 2050. The progression of AMD can be prevented by consuming sources of antioxidants which have been proven to inhibit the development of this disease. One type of antioxidant that is easy to find and abundant in nature is the carotenoid zeaxanthin. Given the anticipated close multiplying of AMD cases by 2050, there's an pressing require for more compelling and open preventive techniques. Appropriately, examining the part of characteristic cancer prevention agents such as zeaxanthin in deferring or avoiding AMD movement is fundamental to moderating future open wellbeing burdens.*
Objectives: *This study aimed explore the connection between the administration of carotenoid zeaxanthin and the prevention of Age-Related Macular Degeneration (AMD).*
Methods: *This study about utilized a writing survey strategy by analyzing already distributed inquire about articles. Significant considers were distinguished through online databases, counting PubMed and ScienceDirect, utilizing particular watchwords related to Age-Related Macular Degeneration (AMD) and zeaxanthin. Article selection was guided by the PICOT framework: Population (P) – individuals aged 60 years or older with or at risk of AMD; Intervention (I) – zeaxanthin intake; Comparison (C) – individuals without zeaxanthin intake or taking other antioxidants; Outcome (O) – prevention or delay of AMD progression; Time (T) – based on the duration reported in each study. Inclusion criteria were limited to peer-reviewed journals published within the last five years. A total of five articles were included in this review..*
Results: *The use of the carotenoid zeaxanthin showed a positive effect on preventing the development of Age-Related Macular Degeneration (AMD), yielding significant outcomes ($p<0.05$).*
Conclusions: *Administration of zeaxanthin supplementation has an effect on inhibiting the occurrence of Age-Related Macular Degeneration (AMD)*

Introduction

As we age, the function of the organs in the body gradually experiences a significant decline. Organs whose function is weakened will affect their performance and if their function decreases, it will often cause disease that can attack these organs and other organs that function in the body. One of the organs that experiences decline related to age is the eyes. Diseases related to the retina of the eye are one of the treatments to prevent blindness (Budiono, 2019). One of the diseases of the retina that can occur in old age is: Age-Related Macular Degeneration (AMD). Age-Related Macular Degeneration (AMD) is a retinal damage disease that attacks individuals aged 60 years

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and over and is the main cause of blindness in this age group (Camelo et al., 2020). AMD is a type of degenerative disease of the macula which causes central vision problems in older people (Gheorghe et al., 2015). AMD is a leading cause of blindness among older adults, accounting for approximately 6–9% of all cases of blindness worldwide (Jonas et al., 2017) (Wong et al., 2014). In 2010, the number of AMD patients in the United States increased from 9.1 million individuals, which is predicted to reach 17.8 million individuals by 2050. At the end of 2020, the situation in Europe was worse with the number of patients reaching 59 million individuals (Rupert, 2020). One of the main risk factors for AMD is age, with increasing age in individuals the prevalence and severity of AMD also increases (Salimiaghdam et al., 2019).

AMD is characterized by accumulation of extracellular deposits, namely drusen, along with progressive degeneration of photoreceptors and adjacent tissues. AMD is regarded as a multifactorial disease comprising a complex interplay between ageing, genetic susceptibility and environmental risk factors. Not only due to the main risk of AMD, there was increasing age, but there are several environmental factors that also cause an increase in the incidence of AMD in a person (Fleckenstein et al., 2021). The first other environmental factor is smoking, smoking can increase the risk of AMD two to four times by affecting blood flow, reducing high-density lipoprotein levels, increasing fibrinogen, platelet aggregation, oxidative stress and lipid peroxidation, reducing plasma antioxidant levels, and increasing levels of inflammation and inflammatory cytokines (Sobrin & Seddon, 2014). In addition to smoking, daily food consumption patterns can also affect the risk of AMD. Several studies have stated that consumption of lutein and zeaxanthin can reduce the risk of AMD such as in spinach, mustard greens, and kale, as well as increasing consumption of fish oil or polyunsaturated fatty acids, namely docosahexaenoic acid and eicosapentaenoic acid (Merle et al., 2014). Physical activity is also said to be a risk factor for AMD. Low to moderate intensity physical activity for 3 hours per week is classified as an active lifestyle, indicating that small amounts of physical activity may be sufficient to provide beneficial effects on the body (McGuinness et al., 2017).

AMD disease develops in three stages starting from the initial stage (early AMD) to the intermediate stage (intermediate AMD), then referred to late AMD which is an advanced stage of AMD. Age Related Eye Disease Study or called AREDS groups AMD based on the presence or absence of drusen, atrophy, and fundus neovascularization in the photograph. In the AREDS guidelines, AMD is divided into early stages (early) characterized by multiple medium-sized drusen (63-124 µm) or pigment changes in the macula, intermediate stage (intermediate) defined by the presence of at least one large drusen (≥125 µm) as well as many medium-sized drusen or geographic atrophy not involving the fovea centralis, and advanced stage (advanced) which indicates geographic atrophy involving the fovea centralis or neovascularization in the choroid (Al-Zamil & Yassin, 2017). Clinically, AMD can be classified into two types: neovascular (wet) and non-neovascular (dry) AMD (Thomas et al., 2021).

Patients with AMD have clinical characteristics, including often experiencing a sharp decline in vision that gets worse in one or both eyes. Patients will also feel distortions in vision or metamorphopsia, especially when looking at lines or patterns on ceramic tiles. They also complained about difficulty in identifying someone's face. Initial phase (early AMD), in AMD patients may not show any indication or be in a subclinical state. In the advanced phase (late AMD), the decline in vision occurs quickly and continues, which is characterized by a very rapid decline in reading ability within a matter of days. (Johra et al., 2020).

The progression of AMD can be prevented by consuming sources of antioxidants which have been proven to be able to inhibit the development of AMD. One type of antioxidant that is easy to find and abundant in nature is carotenoids (Putri et al., 2022). Carotenoids have been shown to

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inhibit the development of macular degeneration. Carotenoids are divided into a number of categories, one of which is xanthophyll. This xanthophyll is a category that contains the compounds lutein and zeaxanthin. Consuming foods and drinks with high xanthophyll content can increase plasma levels of lutein and zeaxanthin. Plasma in the body with high levels of lutein and zeaxanthin has been proven to reduce the risk of macular diseases such as AMD. Therefore, the levels of lutein and zeaxanthin in plasma need to be increased which can then play a role in preventing AMD. (Eisenhauer et al., 2017).

One of the main factors that accelerated the development of AMD is oxidative stress in retinal cells, which damages macular photoreceptors and accelerates degeneration (Kvansakul et al., 2006). Therefore, preventive approaches through antioxidants have become the focus of attention in recent years. Zeaxanthin, a type of carotenoid found in abundance in green vegetables and yellow-orange fruits, is known to accumulate in the macular part of the retina and plays a role in protecting the eyes by filtering blue light and neutralizing free radicals. Several studies have shown that zeaxanthin supplementation can increase macular pigment density (MPOD) and improve visual function in healthy individuals and AMD patients (Majeed et al., 2021; Li et al., 2021) (Loughman et al., 2012).

However, although the results of previous research are quite promising, there is no agreement regarding this.optimal dose, duration of administration, and effectiveness of zeaxanthinin preventing the development of AMD. Variations in study design, sample characteristics, and outcome parameters have led to mixed conclusions. In addition, most studies have focused more on improving visual function, while the role of zeaxanthin in early prevention of AMD is still not widely explored.

Based on this, this study aims to review and analyze the latest evidence regarding the role of zeaxanthin supplementation in the prevention and development of Age-Related Macular Degeneration (AMD), and identify research gaps to be used as a reference in further research.

Methods

The method applied in this study is literature review with articles that are previous experimental articles. The experimental article used is an article that discusses the administration of the carotenoid zeaxanthin with events Age-Related Macular Degeneration (AMD) for the last five years, namely between 2020 and 2024. The selection of articles used in this study was carried out using the PRISMA method (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The databases used by researchers in this research are Pubmed NCBI and Sciencedirect with the keyword carotenoid, zeaxanthin, and Age-Related Macular Degeneration (AMD). There are several criteria determined in selecting articles. Some of the criteria chosen for use in this research include experimental research design, English language articles, and whether they are articles full-access. Based on these criteria, five international journals were obtained. Literature searches were conducted using the Boolean operator "AND" to identify relevant journal articles. The list of journals found in the literature search is presented in the table below.

Table 1 Literature search on the website

Jurnal Website	Keyword	Result
Pubmed NCBI	Carotenoid	112.833
	Zeaxanthin	4.570

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	Age-Related Macular Degeneration (AMD)	14.101
	Carotenoid, Zeaxanthin, and Age-Related Macular Degeneration (AMD)	241
ScienceDirect	Carotenoid	109.480
	Zeaxanthin	5.926
	Age-Related Macular Degeneration (AMD)	13.641
	Carotenoid, Zeaxanthin, and Age-Related Macular Degeneration (AMD)	794

Source: Primary Data, 2024

The table above shows the literature search conducted on journal websites, namely PubMed NCBI, which can be accessed at https://pubmed.ncbi.nlm.nih.gov/ .The search results using the keyword "carotenoid" yielded 112,833 results, "zeaxanthin" yielded 4,570 results, and "Age-Related Macular Degeneration (AMD)" yielded 14,101 results. Meanwhile, when using the combined keywords "Carotenoid, Zeaxanthin, and Age-Related Macular Degeneration (AMD)," a total of 241 results were obtained. A similar search was conducted on the ScienceDirect website, accessible at https://www.sciencedirect.com/. The keyword "carotenoid" resulted in 109,480 findings, "zeaxanthin" yielded 5,926 results, and "Age-Related Macular Degeneration (AMD)" provided 13,641 results. When the combined keywords "Carotenoid, Zeaxanthin, and Age-Related Macular Degeneration (AMD)" were used, a total of 794 results were found.

The search results based on the specified keywords were further screened according to the predetermined inclusion criteria. A total of 1,030 journals did not pass the selection process and were therefore excluded. The article selection process is illustrated in Figure 1.

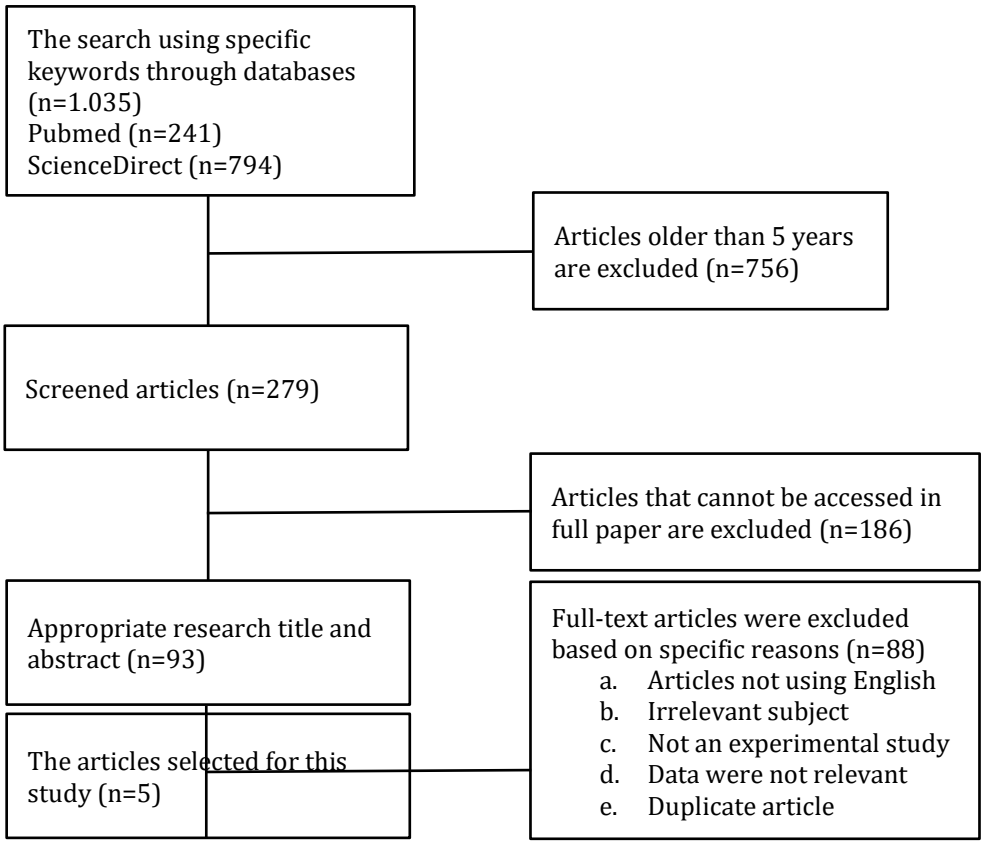

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Figure 1 PRISMA Diagram of the article selection process used in the literature review

Results

This study includes five journals that will be analyzed to examine the effect of carotenoid zeaxanthin supplementation on the prevention of Age-Related Macular Degeneration (AMD). The literature used has different characteristics, including the year of publication, research respondents, and analytical methods. The respondents in the selected literature consist of individuals aged over 45 years, with some studies also involving animal models. However, all studies conducted interventions by providing carotenoid zeaxanthin supplementation to the subjects. The characteristics and results of the literature review are presented in the following table.

Table 2 Journal characteristics and literature review results

Study Design	Method	Dose	Duration	Result	Reference
Pilot study open-label. Subjects: (n=40) aged ≥ 50 years with a diagnosis of early-stage dry-type Age-Related Macular Degeneration (AMD).	All subjects received the Macumax supplement intervention, which contained ZeaLutein (comprising lutein, zeaxanthin, and piperine), bilberry extract, saffron extract, and zinc monomethionine, for 90 days. The analysis was conducted using Statistical Analysis Software (SAS) version 9.1.3 from the statistical package software (Cary, NC, USA) and an ANOVA t-test. The analysis also utilized the Amsler grid aberration score to assess visual acuity.	Twice in a day, one capsule of the Macumax supplement was administered, containing ZeaLutein (comprising lutein: 5 mg, zeaxanthin: 1 mg, and piperine: 2 mg) 100 mg, bilberry extract 20 mg, saffron extract 5 mg, and zinc monomethionine 7.5 mg.	90 days	The intervention administered over 30, 60, and 90 days of observation showed a significant improvement ($p<0.05$) compared to baseline values. In 60% of subjects, a significant reduction ($p<0.05$) in Amsler grid aberration scores was observed on days 60 and 90 of treatment.	Majeed *et al.*, (2021). *Journal of Medicinal Food*, 24(5), 551–557. https://doi.org/10.1089/jmf.2020.0097 **Accreditation:** Q3 – JIF 2.0 (2023) **Indexing:** Scopus, SCIE, PubMed
Prospective, single-center, open-label cohort study. Subjects:	Subjects were given lutein and zeaxanthin supplementation for 3 months, followed by a 3-month observation	Orally administered once daily at a dose of 2	3 months	A significant increase in serum lutein and zeaxanthin levels from	Jaggi *et al.*, (2023). *Clinical Nutrition ESPEN*, 56,

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(n=21) aged between 50 and 87 years with a diagnosis of nonexudative, early, or intermediate Age-Related Macular Degeneration (AMD).	period. Measurements were conducted on lutein and zeaxanthin concentration, Macular Pigment Optical Density (MPOD), and Fluorescence Lifetime Imaging Ophthalmoscopy (FLIO) to evaluate the effects of L and Z supplementation on serum concentration, MPOD, and retinal autofluorescence parameters in patients with nonexudative, early, or intermediate Age-Related Macular Degeneration (AMD).	mg zeaxanthin.		185.5 ng/ml to 430.3 ng/ml was observed. A significant increase in MPOD was also noted. Additionally, a significant reduction in the median FLIO lifetime in the central fovea was recorded during the supplementation period.	127–134. https://doi.org/10.1016/j.clnesp.2023.05.009 **Accreditation:** Q2 – JIF 2.6 (ESCI) **Indexing:** Scopus, ESCI, PubMed
Experimental study. Subjects: (n=20) transgenic mice with ApoA-I and/or BCO2 gene deletion in a healthy condition.	The study subjects were divided into two groups: ApoA-I−/−/Bco2−/− mice were treated with carotenoids, while Bco2−/− mice served as the control group to compare carotenoid levels in mice and examine the role of ApoA-I in influencing carotenoid metabolism and transport to the retina in relation to Age-Related Macular Degeneration (AMD).	There was 1–2.6 g/kg of food. The total carotenoid intake was 12 mg/day.	1 month	After carotenoid administration, HPLC data showed that total carotenoids increased in the liver but decreased in the serum, retinal pigment epithelium (RPE)/choroid, and retina of ApoA-I−/−/Bco2−/− mice compared to Bco2−/− mice. Supplementation with antioxidant carotenoids is a therapeutic strategy to protect against Age-Related Macular Degeneration (AMD);	Li *et al.*, (2022). *Archives of Biochemistry and Biophysics*, 716, 109111. https://doi.org/10.1016/j.abb.2021.109111 **Accreditation:** Q1 – JIF 3.0 **Indexing:** Scopus, SCIE, PubMed

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				however, the mechanism of carotenoid transport from the liver to the retina is still not fully understood.	
Experimental study. Subjects: (n=30) double knockout mice Abca4−/−/Bco 2−/− and Abca4−/− mice.	Subjects were divided into three groups. Double knockout mice Abca4−/−/Bco2−/− were assigned to the treatment group and received lutein and zeaxanthin supplementation, while Abca4−/− mice served as the control group and were given a placebo.	Administr ation of 2.6 mg/day per mice.	3 months	Supplementatio n with lutein and zeaxanthin significantly reduced the accumulation of A2E and iso-A2E in the retinal pigment epithelium (RPE) of Abca4−/−/Bco 2−/− mice by 63.2% and 71.3%, respectively. There was a strong correlation between increased retinal carotenoid levels and decreased bisretinoid levels in the RPE/choroid, helping to prevent AMD-related retinal damage.	Arunkumar *et al.*, (2021). *Experimental Eye Research*, 209, 108680. https://doi.org/10.1016/j.exer.2021.108680 **Accreditation:** Q1 – JIF 2.7 **Indexing:** Scopus, SCIE, PubMed
Randomized pilot trial with a parallel-arm design. Subjects: (n=27) healthy individuals aged 45–65 years.	In this study, subjects were divided into two groups: the treatment group, which consumed goji berries, and the control group, which received a supplement containing lutein and zeaxanthin.	The treatment group was given 28 g of goji berries five times per week, while the	90 days	MPOD significantly increased in the goji berry group at retinal eccentricities of 0.25 and 1.75 ($p = 0.029$ and $p = 0.044$),	Li *et al.*, (2021). *Nutrients*, 13(12), 4409. https://doi.org/10.3390/nu13124409 **Accreditation:** Q1 – JIF 5.0

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	Measurements were taken for macular pigment optical density (MPOD) on days 0 and 90, and for skin carotenoids on days 0, 45, and 90. Analysis was conducted to evaluate changes in MPOD and skin carotenoids between the two groups	control group received a supplement containing 6 mg of lutein and 4 mg of zeaxanthin five times per week.	whereas no significant changes were observed in the lutein-zeaxanthin supplement group. Goji berries are rich in zeaxanthin, which may enhance MPOD and help prevent or delay the progression of age-related macular degeneration (AMD).	**Indexing:** Scopus, SCIE, PubMed, CINAHL, Embase

Based on the five journals presented , each study utilized an experimental study design with interventions applied to the research subjects. Each study involved different subjects; two journals used animal models (mice), while three journals involved human participants aged over 45 years. The dosage of supplementation varied across studies, including administration twice daily with 1 mg of zeaxanthin in capsule form, 2 mg of zeaxanthin per day orally, 12 mg of carotenoids per day, 2.6 mg per day, and 4 mg of zeaxanthin five times per week. Apart from that, in each study it is known that intervention was carried out in the form of giving supplementation containing zeaxanthin to respondents, for the time used in each study was different. There were four studies with a period of 90 days or 3 months and there was 1 study with a period of 1 month. The results of the analysis of 5 journals from literature studies show that there is a significant impact of administering the carotenoid zeaxanthin in preventing the occurrence of age-related macular degeneration (AMD).

Discussion

Macular degeneration or commonly called macular degeneration is a degenerative disease that attacks the organs of vision. Factors that contribute to the emergence of this disease vary, such as age, inflammation in the body, exposure to ultraviolet rays, and smoking habits. These factors can increase the formation of ROS (reactive oxygen species) in the retina which, if accumulated over the long term, will trigger lipid peroxidation in the retina, which in turn leads to cellular damage that causes macular degeneration. (Johra et al., 2020).

Inflammatory factors also play a major role in the occurrence of macular degeneration. Oxidative damage will cause inflammation and trigger the formation of lesions that resemble AMD, this includes the buildup of drusen in the RPE stratum (Retinal Pigment Epithelial) and the development of lesions that resemble geographic atrophy. Furthermore, the RPE will release various mediators of inflammation. If this condition persists for a long time, a disproportion will occur in the intermediaries pro-inflammatory as well as anti-inflammatory, which will further give rise to the development of AMD. (Tan et al., 2020).

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Oxidative damage that arises due to inflammation can be inhibited by consuming high levels of antioxidants so that the development of macular degeneration can be hampered. Carotenoids can be an alternative source of high oxidants. One type of carotenoid is zeaxanthin. Zeaxanthin is a form of xanthophyll found in the retina, especially in the macula, which also contains lutein and meso-zeaxanthin. Various studies conducted previously have indicated that zeaxanthin and lutein contribute to protecting the eyes from diseases that can occur, one of which is late AMD. (Estrada et al., 2018).

Zeaxanthin can activate its antioxidant properties by directly inactivating ROS. Zeaxanthin contains a chain of isoprene residues containing conjugated double bonds. Additionally, zeaxanthin enhances its antioxidant function by stimulating glutathione (GSH) synthesis in human retinal pigment epithelial (RPE) cells (Hirdyani & Sheth, 2017). Increased levels of VEGF in the retina can be prevented by compounds contained in lutein and zeaxanthin, this content can avoid the thickening of Bruch's membrane which usually occurs in AMD. L/Zi (lutein zeaxanthin) supplementation has the potential to help improve retinal degradation in the oxidative stress process, namely by modulating the genes involved in this process.

In the five articles described in literature review above, shows that supplementation with the carotenoid zeaxanthin has a good impact in inhibiting the occurrence of AMD. Studies conducted by Majeed et al. (2021) and Jaggi et al. (2023), in which zeaxanthin was administered in supplement form to subjects aged ≥50 years diagnosed with Age-Related Macular Degeneration (AMD), showed significant results ($p<0.05$) compared to baseline values. Measurements in the study by Majeed et al., (2021) showed that the Amsler grid aberration score, which is a method for determining changes in central vision, experienced a significant decrease in scores on days 60 and 90 of treatment ($p<0.05$). A decreasing score means there is a decrease in distortion or disturbance in central vision. Research by Jaggi et al., (2023) also obtained results of an increase in MPOD (Macular Pigment Optical Density) namely the optical density of macular pigment, an increase in MPOD means that the amount of carotenoid pigments, such as lutein and zeaxanthin, in the macular layer of the eye increases which can be used as an antioxidant. In addition, there was a decrease in FLIO (fluorescence lifetime imaging ophthalmoscopy) which indicates that lutein and zeaxanthin supplements can increase macular pigment density (MPOD) in the fovea area. In research by Li et al., (2021), the MPOD value also increased in the intervention group with goji berries containing 28 mg of zeaxanthin compared to the group that was only given 4 mg of zeaxanthin supplement.

Research with experimental animals by Li et al., (2022) and Arunkumar et al., (2021) showed an increase in carotenoids. Research by Li et al., (2022), there was an increase in carotenoids in the liver but a decrease in carotenoids in the serum, RPE/choroid, and retina in ApoA-I knockout mice indicating that HDL, with ApoA-I as a key component, is the main transporter that delivers carotenoids from the liver to the retina. In research by Arunkumar et al., (2021), reducing bisretinoids such as A2E and iso-A2E is useful for preventing retinal damage associated with macular degenerative diseases such as AMD (age-related macular degeneration) and Stargardt's disease (STGD1).

Based on the research that has been carried out, there are shortcomings, namely in giving zeaxanthin, the safe dosage for its use is not stated, so the safe limit for giving zeaxanthin is not yet known. In addition, some articles do not mention the side effects that result from administering zeaxanthin. Researchers believe that zeaxanthin supplementation plays an important role in preventing AMD, which of course depends on several factors such as duration of consumption, age, and individual conditions. Consumption of natural food sources such as fruits and vegetables containing zeaxanthin has good benefits even though it requires a high dose

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to achieve the same therapeutic effect as supplementation. Previous studies still lack information regarding the effects of zeaxanthin on preventing AMD. Therefore, additional studies are needed regarding the use of zeaxanthin in preventing its occurrence Age-Related Macular Degeneration (AMD).

Strength

This research uses the method of literature review. By selecting the journal that will be used with a PRISMA diagram, the advantage of using this diagram is that it can provide information on journals found and used by researchers so that the transparency of journals can be seen clearly, such as the type and number. Besides that, this method can reduce research bias because the inclusion and exclusion criteria in journal screening can be clearly known. Research on the carotenoid zeaxanthin with Age-Related Macular Degeneration (AMD) can be said to be quite limited, so this research can add sources regarding the discussion of the carotenoid zeaxanthin.

Weakness

Limitations to this research lie in the research methods used in each study. Several studies use different methods. In addition, there are variations in the duration of each study and the uses of research subjects. So these things cannot be controlled by researchers and there are limitations in this research.

Conclusion

Based on results literature review from the five studies regarding the administration of zeaxanthin, it was found that supplementation with the carotenoid zeaxanthin had a good impact in preventing the occurrence of Age-Related Macular Degeneration (AMD). In addition, administration of zeaxanthin can increase MPOD (Macular Pigment Optical Density) which has a good impact on the macular layer of the eye. So it can be concluded that administration of zeaxanthin has an effect in inhibiting the incidence Age-Related Macular Degeneration (AMD).

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