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THE EFFECT OF COMBINING ASTAXANTHIN AND VITAMIN E ON IL-1, IL-6, AND CRP LEVELS

Sampurna[1], Rita Kartika Sari[2]*, Mutiara Hanif Syafitri[3], Nafla Aqilah[3], Saskia Febrian Dwi[3]
[1]Department of Clinical Pathology, Faculty of Medicine, Universitas Islam Sultan Agung, Jl. Kaligawe Raya No.Km.4, Terboyo Kulon, Genuk, Semarang, Jawa Tengah 50112, Indonesia
[2]Department of Public Health, Faculty of Medicine, Universitas Islam Sultan Agung, Jl. Kaligawe Raya No.Km.4, Terboyo Kulon, Genuk, Semarang, Jawa Tengah 50112, Indonesia
[3]Faculty of Medicine, Universitas Islam Sultan Agung, Jl. Kaligawe Raya No.Km.4, Terboyo Kulon, Genuk, Semarang, Jawa Tengah 50112, Indonesia
*rita.kartika@unissula.ac.id

ABSTRACT
Carrageenan-induced inflammation binds to TLR-4, activating the NF-kβ pathway, which attracts macrophages to release proinflammatory cytokines, Interleukin-1 and Interleukin-6, leading to the production of CRP. Astaxanthin and vitamin E have anti-inflammatory effects, but their combined effects are poorly studied. This study examines whether astaxanthin combined with vitamin E reduces IL-6, IL-1, and CRP levels in male Wistar rats induced by carrageenan. This experiment used a post-test-only control-group design with groups: KN (standard feed), KS (1% carrageenan induction), and KP (combination of 0.72 mg/kgBW astaxanthin and 24.1 mg/kgBW vitamin E). ELISA was performed 24 hours after carrageenan induction. Parametric data analysis was performed, followed by a post hoc test. The results showed that IL-1 levels were highest in KS (1.61 pg/mL), followed by KP (0.42 pg/mL) and KN (0.28 pg/mL). Statistical analysis (one-way ANOVA and post hoc tests) identified significant differences among all groups ($p<0.05$). IL-6 levels decreased in KP (58.67 pg/mL) compared to KS (98.83 pg/mL). CRP levels were highest in KS (2.35 ng/mL), followed by KP (1.01 ng/mL) and KN (0.75 ng/mL), with KS showing a significant increase compared to KN ($p<0.05$). From these results, it can be concluded that the combination of astaxanthin and vitamin E has an anti-inflammatory effect on IL-6, IL-1, and CRP levels in male Wistar rats induced by carrageenan.

Keywords: astaxanthin; IL-1; IL-6; CRP; vitamin E

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INTRODUCTION

Inflammation is the body's reaction to tissue in response to stimuli that cause local injury such as bacterial infection, chemical injury, or mechanical trauma (Mamarimbing et al., 2020; Novika et al., 2021). Carrageenan-induced inflammation starts when carrageenan binds to the Toll-like Receptor-4 (TLR-4) on the cell membrane. This activates the Nuclear Factor Kappa-β (NF-κB) pathway, leading to the release of chemokines. Chemokines attract inflammatory cells, such as macrophages and lymphocytes. These cells secrete pro-inflammatory cytokines, such as Interleukin-1 (IL-1) and Interleukin-6 (IL-6), which then induce the release of C-Reactive Protein (CRP) (Hormozi, 2019; Coss et al., 2023).

CRP is a serum glycoprotein made by the liver and marked in acute or chronic inflammation. It is linked to diseases such as CHD, rheumatoid arthritis, and obesity (Yao et al., 2019; Myers et al., 2019). The WHO (2020) reports that Indonesia ranks 3rd in cardiovascular disease prevalence, with a 1.5% increase in 2024. CHD will cause 23.3 million deaths in 2030 and accounts for 32% of global deaths (Myers et al., 2019). People in developing countries account for 75% of these deaths (Fahriza and Siregar, 2024; Ni Luh Putu et al., 2024). Untreated inflammation, shown by higher CRP in heart patients, can lead to myocardial infarction and sudden cardiac death (Pokhrel, 2024). Astaxanthin is a reddish carotenoid pigment found abundantly in salmon, shrimp, crab, and

microalgae. This compound has potent antioxidant activity and has been shown to suppress inflammation by inhibiting NF-κB activation, reducing COX-2 expression, and suppressing IL-1, IL-6, and CRP production (Liu et al., 2023). Vitamin E also demonstrates potent antioxidant and anti-inflammatory properties. As a fat-soluble compound, it converts peroxyl radicals into lipid hydroperoxides within cell membranes, thereby preventing cellular damage (Putri et al., 2024). Studies evaluating the combined effect of astaxanthin and vitamin E on pro-inflammatory biomarkers such as IL-1, IL-6, and CRP in carrageenan-induced inflammation models remain limited. Considering the role of these biomarkers in the progression of chronic inflammatory conditions, particularly cardiovascular diseases, investigation of the potential synergistic anti-inflammatory effects of these antioxidant compounds is essential. This study aims to determine the anti-inflammatory effects of the combination of astaxanthin and vitamin E on IL-1, IL-6, and C-reactive protein (CRP) levels in male wistar rats induced with carrageenan.

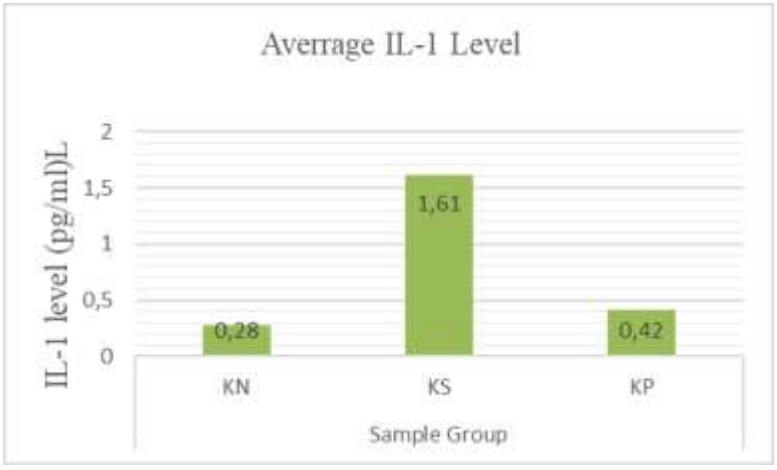
METHOD

This study used a laboratory experiment and a post-test only control group design. This study will examine the anti-inflammatory effects of a combination of astaxanthin and vitamin E on IL-6, IL-1, and CRP levels in male Wistar rats induced by carrageenan. Data for this study were collected simultaneously from 30 samples selected using a consecutive sampling technique based on predefined inclusion and exclusion criteria. After selection, the animals were randomly allocated into three groups using simple random sampling (lottery method). The subjects were male white Wistar rats (Rattus novergicus) kept in the Nutrition Laboratory of the Center for Food and Nutrition Studies (PSPG) at Gadjah Mada University, aged 2 months and weighing 175-200 grams. The sample size was obtained using the formula(Federer, 1956); 9 mice were obtained in each group, and the formula 1/(1-f) was used to anticipate the presence of samples that died or dropped out, where f is the percentage of test samples that died or dropped out (10%) (Lala & Sari, 2023). A total of 30 rats were adapted to the same food and water for 7 days, then divided into normal (n = 10), diseased (n = 10), and treatment (n = 10) groups. The treatment group received a combination of astaxanthin (0.72 mg/kg BW) and vitamin E (24.1 mg/kg BW). One hour later, the diseased and treatment groups were injected with 0.1 mL of 1% carrageenan, and the normal group was given only standard feed. All groups were observed for 24 hours. To prepare the astaxanthin and vitamin E solution, dissolve 0.72 mg/kg bw of Natural MPL brand astaxanthin powder (from Haematococcus pluvialis microalgae) and 24.1 mg/kg bw of IPI brand vitamin E in distilled water at a 1:1 ratio. To make 1% carrageenan, dissolve 100 mg of carrageenan in 10 mL of 0.9% physiological NaCl. Collect blood from the orbital sinus for measurement with the ELISA method. Data analysis in this study used IBM SPSS Statistics 23. It began with the Shapiro-Wilk normality test and Levene's test for homogeneity of variances. The Shapiro-Wilk and Levene tests were both performed.

RESULT

This research was conducted at the Faculty of Medicine, Sultan Agung Islamic University, in compiling proposals, preparing research materials, and data analysis, the research was continued at the Center for Food and Nutrition Studies (PSPG) at Gadjah Mada University, using 30 male white rats of the Wistar strain adapted for 7 days and randomly divided into 3 groups.

IL-1



Picture 1. Average Results of IL-1 Levels in Each Research Group

The results showed differences in IL-1 levels between groups, with the lowest mean in the normal group (0.28 pg/mL), a significant increase in the diseased group (1.61 pg/mL), and a decrease again in the treatment group (0.42 pg/mL). These findings demonstrate that carrageenan induction increases IL-1 levels, whereas the combination of astaxanthin and vitamin E reduces IL-1 levels to near-normal levels. Statistical analysis began with the Shapiro-Wilk normality test and Levene's test for homogeneity of variances. The results showed that the data were normally distributed ($p>0.05$) but not homogeneous ($p<0.05$), so a one-way ANOVA was used. The One-Way ANOVA test showed a significant difference in IL-1 levels between groups ($p=0.000$; $p<0.05$). The results of the analysis are shown in Table 1. Further analysis used Post Hoc Tamhane's test to determine differences between groups, specifically as shown in Table 2.

Table 1.
Results of Normality, Homogeneity, and One-Way ANOVA Test Analysis

	p-value		
Group	*Shapiro Wilk*	*Levene*	*One Way Anova*
KN	0,938*	0,001	0,000
KS	0,882*		
KP	0,838*		

Description: * = normal data distribution

Table 2.
Results of Tamhanes Post Hoc Test Analysis

Group		*P value* *Pos Hoc Tamhanes*
Normal (KN)	Sakit (KS)	0,000*
	Treatment (KP)	0,000*
Sick (KS)	Treatment (KP)	0,000*

Description: * = There are significant differences in all pairs of groups

The results of the Tamhanes Post Hoc Test in Table 1.2 indicate a significant difference between the three groups studied. The test results show that the IL-1 levels in the Normal Group (KN), the Diseased Group (KS), and the Treatment Group (KP) differ significantly p-value <0,05 indicating a significant difference in the means.

IL-6

Figure 2 shows the differences in IL-6 levels. The IL-6 level in the diseased group (KS) was 98.83 pg/mL, significantly higher than the normal group (KN) at 38.67 pg/mL ($p < 0.05$). This indicates that 1% carrageenan induction successfully triggered an increase in IL-6 levels in the test animals through an inflammatory process.which occurs due to stimulation of the innate immune systemThis finding is in line with research conducted by(Rabou et al., 2025)that carrageenan activates TLR-4

and the NF-kB signaling pathway, which plays a role in increasing the expression of proinflammatory cytokines such as IL-6.

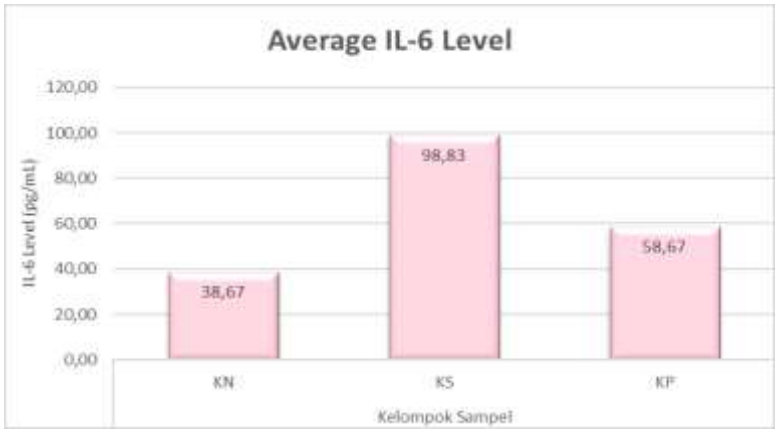


Figure 2. Bar Chart of Mean IL-6 Level Data (pg/mL)

The treatment group (KP), given a combination of astaxanthin and vitamin E, showed lower IL-6 levels than the disease group (KS), with a significant difference ($p < 0.05$). This indicates that the combination of astaxanthin and vitamin E has an Sample Group otential, with the mechanism of action involving inhibition of inflammatory signal transduction pathways and suppression of free radical production (Najoan et al., 2021). The IL-6 level data in each group were tested for normality using the Shapiro-Wilk test and homogeneity using the Levene test. The results of the normality test indicated a normal data distribution ($p>0.05$). The results of the homogeneity test obtained a p value = 0.446 ($p>0.05$) which indicates that the IL-6 level data between the three groups are homogeneous, so that the three groups meet the requirements for hypothesis testing using the One Way Anova parametric test which obtained p = <0.001 ($p<0.05$), so this study can be concluded that there are significant differences in IL-6 levels between the three research groups.

Table 3.
Results of the analysis of the Normality, Homogeneity, and One-Way ANOVA tests

Group	*p-value*	*p-value*	*p-value*
Group	Normality	Homogeneity	*One Way Anova*
KN	0.451*	0.446**	<0.001
KS	0.669*		
KP	0.970*		

Description: * = normal data distribution; ** = homogeneous data variance.

The analysis was continued with the Post Hoc LSD test to determine which pairs of groups had significant differences, as shown in Table 4.2. The results of the Post Hoc test in Table 4.2 show that between the normal group (KN) and the diseased group (KS), there was a significant difference ($p<0.05$), where the average IL-6 level in the diseased group was higher, with an average of 98.83 pg/mL. The difference between the diseased group (KS) and the treatment group (KP) was significant ($p<0.05$). Clinically, the average IL-6 level in the treatment group was lower, at 58.67 pg/mL. A significant difference was also found between the treatment group (KP) and the normal group (KN) ($p<0.05$), indicating that, clinically, the treatment did not fully restore IL-6 levels to normal, although it significantly reduced IL-6 levels compared to the diseased group.

Table 4.
Results of Analysis of Differences in IL-6 Levels between Test Groups

Group		*Post Hoc LSD*
KN	KS	<0.001*
KN	KP	<0.001*
KS	KN	<0.001*
KS	KP	<0.001*
KP	KN	<0.001*
KP	KS	<0.001*

Description: * = There is a significant difference in mean IL-6 levels (p<0.05) between research groups.

C-Reactive Protein (CRP)

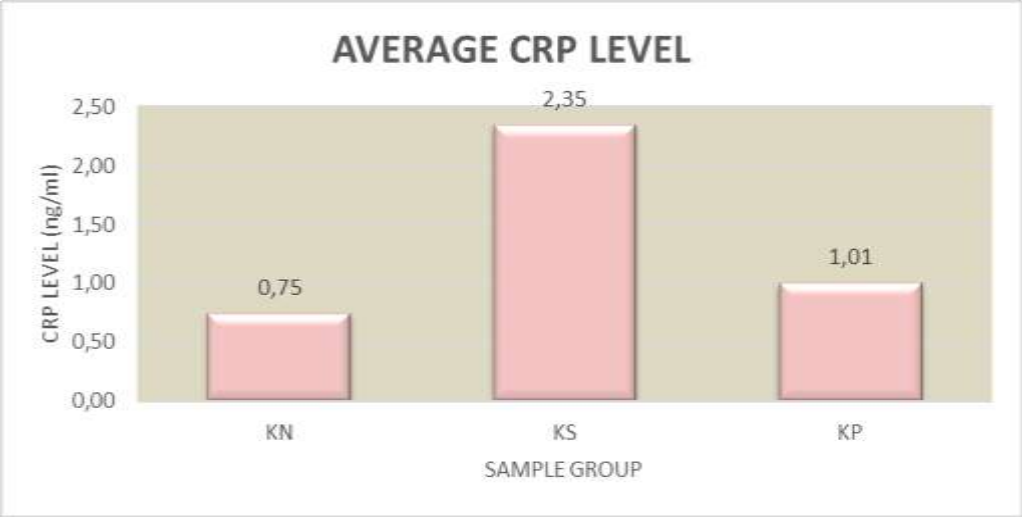


Figure 1.1Mean CRP Levels Between Groups

Based on Table 1.1, each group's results were tested for normality using Shapiro-Wilk (p > 0.05) and for homogeneity using Levene's test (p > 0.05). All three groups satisfied the parametric test requirements. One-way ANOVA showed p = 0.001 (p < 0.05), indicating significant differences in CRP levels between groups. Post Hoc LSD was then used to determine which groups differed significantly. The highest CRP levels were in KS with an average of 2.35 ng/mL and the lowest in KN with an average of 0.75 ng/mL, while the reference normal CRP value in male white rats of the Wistar strain is around 0.70 – 1.11 ng/mL. The treatment group had an average CRP of 1.01 ng/mL so it can be concluded that KP was lower than the KS group. The average CRP level in KS compared to KP decreased by 1.34 ng/mL.

Table 5.
Results of Normality Test Analysis,

Group	*p-value*	*p-value*	*p-value*
Group	Normality	Homogeneity	*One Way Anova*
KN	0.970*	0.148**	0.000
KS	0.150*		
KP	0.648*		

Description: * = normal data distribution; ** = homogeneous data variance

Table 6.
Results of Statistical Analysis of CRP Levels Between Test Groups

Group	Group	*P-Value* LSD Post Hoc Test
KN	KS	0,000*
KN	KP	0,000*
KS	KN	0,000*
KS	KP	0,000*
KP	KN	0,000*
KP	KS	0,000*

Description: * = There is a significant difference in mean CRP levels (p<0.05) between research groups.

The results of the LSD post hoc test in Table 1.2 indicate a significant difference between the three groups studied. The test results show that the CRP levels between the Normal Group (KN), the Diseased Group (KS), and the Treatment Group (KP) have a p-value <0.05, indicating a significant difference in the mean.

DISCUSSION

IL-1

The results of the study showed that the average IL-1 level in KS (1.61 pg/mL) was higher than that in KN (0.28 pg/mL) with a statistically significant difference ($p<0.05$), so it can be concluded that 1% carrageenan induction is effective in increasing IL-1 levels in KS test animals. The increase in IL-1 indicates the activation of an acute inflammatory response, which generally occurs as a defense mechanism of the body against pro-inflammatory stimuli. (Maghfirah *et al*., 2023). This is in line with research Liu *et al*., (2023) and Xiang *et al*., (2023) carrageenan administration causes inflammation by binding to TLR-4, activating the NF-kB pathway, which results in the polarization of inflammatory macrophage cells. Macrophage polarization can directly produce IL-1 and activate the arachidonic acid pathway. The arachidonic acid pathway induces cyclooxygenase and lipoxygenase enzymes. Cyclooxygenase produces prostaglandins and prostacyclins, which trigger leukocyte aggregation and stimulate IL-1 production.

The effect of the combination of astaxanthin and vitamThe combination of astaxanthin and vitamin E showed an effect in the treatment group (KP), which had a lower mean IL-1 level than the disease group (KS), with a statistically significant difference ($p < 0.05$). Vitamin E in this study has potential as an anti-inflammatory and antioxidant, consistent with the literature. Research (Rahmalia *et al*., 2024) shows that astaxanthin, which comes from carotenoids, acts as an antioxidant by donating electrons from the hydroxyl (OH) group on its ionone ring. This group can react with free radicals and then be converted into more stable products, thus preventing the formation of free radicals. Astaxanthin activity is not limited to neutralizing ROS, it also regulates inflammatory signals. Astaxanthin inhibits the inflammatory process by inactivating NF-κB, the main regulator of proinflammatory gene expression, thereby inhibiting COX-2 expression, which produces prostaglandins and prostacyclin, and suppressing Interleukin-1 (Guo *et al*., 2021; Nair *et al*., 2023). The same thing happens with vitamin E, which has an antioxidant function: it reduces ROS by donating a hydrogen atom from the hydroxyl group (-OH) on the phenolic ring to ROS free radicals, thereby reducing or preventing oxidative damage and making free radicals non-reactive and unable to damage cells. (Devitasari, 2022).Vitamin E in the inflammatory process is able to suppress pro-inflammatory signaling pathways, such as the NF-kB pathway which can suppress COX-2 expression in the cyclooxygenase pathway which produces prostaglandins and suppresses IL-1 (Gardaneh *et al*., 2020; Nair *et al*., 2023). Research Li *et al*., (2019) study in animal models showed that the combination of astaxanthin and α-tocopherol was more effective than single administration in reducing TNF-α, IL-6, and IL-1 levels and increasing the activity of antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase (GPx). The IL-1 levels in this study showed a significant difference between KN and KP. However, administering a combination suspension of astaxanthin (0.72 mg/kgBW) and vitamin E (24.1 mg/kgBW) was unable to restore normal IL-1 levels prior to inflammation.

IL-6

The results of this study showed that the mean IL-6 level in the disease group (KS) (98.83 pg/mL) was significantly higher than that in the normal group (KN) (38.67 pg/mL) ($p < 0.05$). This finding demonstrates that 1% carrageenan induction effectively increases IL-6 levels in the test animals, indicating the activation of an inflammatory response mediated by the innate immune system. This result is consistent with previous studies reporting that carrageenan activates TLR-4 and the NF-κB signaling pathway, leading to an upregulation of pro-inflammatory cytokines such as IL-6. The treatment group (KP), which received a combination of astaxanthin and vitamin E, showed a significantly lower IL-6 level compared with the disease group (KS) ($p < 0.05$), indicating the anti-inflammatory potential of this combination. The mechanism is likely related to the inhibition of inflammatory signal transduction pathways and suppression of free radical formation. This finding aligns with the work of Najoan (2020), who explained that astaxanthin downregulates NF-κB-mediated transcription, thereby inhibiting the arachidonic acid pathway, reducing COX-2

expression, and subsequently lowering IL-6 levels. The NF-κB pathway is a central regulator of inflammatory gene expression, including cytokines, chemokines, and adhesion molecules. Vitamin E also contributes to the anti-inflammatory effect. As reported by Asbaghi (2020), vitamin E acts as an antioxidant by donating electrons to reactive oxygen species (ROS), thereby interrupting free-radical chain reactions. The synergistic antioxidant activities of astaxanthin and vitamin E likely explain the reduction in IL-6 documented in the KP group. Although IL-6 levels in KP were significantly reduced compared with KS, they did not fully return to those of the normal group (KN). This suggests that the current dosage of astaxanthin (0.72 mg/kgBW/day) and vitamin E (24.1 mg/kgBW/day) may not yet be optimal to restore IL-6 to physiological baseline levels. In addition, the use of a single-dose regimen represents a limitation of this study. Overall, this study demonstrates that the combination of astaxanthin and vitamin E exerts a protective anti-inflammatory effect against carrageenan-induced inflammation, as reflected by reduced IL-6 levels. Because IL-6 expression is closely related to NF-κB activation and ROS accumulation, future research should include multiple dose variations and assess NF-κB expression as well as ROS levels to provide a more comprehensive mechanistic understanding.

C-Reactive Protein(CRP)

The results of the average comparison of CRP levels of KN (0.75 ng/mL) and KS (2.35 ng/mL) induced by 1% carrageenan showed a significant difference ($p<0.05$), so this study successfully proved the occurrence of a systemic inflammatory process in male white rats of the Wistar strain after being induced by 1% carrageenan. This increase in CRP levels is in line with the theory in Borsani's (2021) study that carrageenan induction triggers inflammation because it binds to TLR-4, thereby triggering the interaction of BCL-10 and Inhibitor κB kinase gamma (IKKγ), which modulates the activation of the NF-κB pathway, thereby attracting inflammatory cells such as macrophages, lymphocytes, and dendritic cells. These inflammatory cells release pro-inflammatory cytokines and modulate hepatic CRP production. Other studies have also shown that carrageenan damages endothelial cell membranes, thereby activating phospholipase enzymes that convert phospholipids into arachidonic acid, which in turn activates COX-2 and LOX. LOX can induce ROS production. Furthermore, leukotrienes produced by LOX activate NADPH oxidase, leading to ROS production. ROS can activate the NF-κB pathway, resulting in the release of pro-inflammatory cytokines and increased CRP levels (Lee *et al*., 2023; Liu *et al*., 2023).

The effect of the combination of astaxanthin with vitamin E can be seen from the comparison of the treatment group (KP) and the disease group (KS); the average CRP level in KP was 1.01 ng/mL, and in KS, it was 2.35 ng/mL, so that it was significantly different ($p<0.05$). This indicates that the combination of astaxanthin with vitamin E has an anti-inflammatory effect and is in line with research by Nair *et al*., (2023) and EKPE *et al*., (2018) which proves that astaxanthin is able to protect from oxidative damage through its conjugated double bonded polyene structure capable of capturing ROS free radicals on the cell membrane while the terminal ring of astaxanthin can capture radicals on the surface and on the inside of the phospholipid membrane. Astaxanthin reduces inflammation by suppressing the NF-κB pathway, which promotes the transcription of pro-inflammatory genes such as TNF-α, IL-1, IL-6, and IL-12 in macrophages, and activating the IRF-3 pathway, which suppresses NF-κB p65. The same thing happens to vitamin E, with alpha-tocopherol as the most potent antioxidant, as it reacts with peroxyl radicals on cell membrane lipids to form α-tocopheroxyl free radicals, thereby stabilizing ROS and suppressing pro-inflammatory NF-κB signals (Martha, 2018). Astaxanthin inhibits NF-κB activation and nuclear translocation, thereby reducing the transcription of COX-2 and iNOS genes and decreasing the secretion of PGE2 and NO as inflammatory mediators. Astaxanthin activates Nrf2 target proteins that increase antioxidant enzymes (SOD, catalase, GPx), thereby reducing oxidative stress and free radicals (ROS) and suppressing inflammatory stimuli that trigger COX-2 and iNOS (Muhammad *et al*., 2022; Sheng *et al*., 2023). Tocopherol can protect various cellular components by neutralizing ROS before lipid oxidation or DNA damage occurs, breaking the lipid peroxidation chain reaction, and

maintaining cell membrane integrity through lipid repair and replacement. Vitamin E directly suppresses pro-inflammatory NF-κB signals that occur through A20 activation in the ubiquitin pathway that blocks TNF-α and IL-1 receptor signaling, such as Neurotrophic Tyrosine Receptor Kinase 1 (NTRK1) (Birringer *et al*., 2019; Jiang, 2019). In Jiang's research (2022), vitamin E is metabolized by CYP4F2 (an omega-hydroxylase) in the liver, producing bioactive metabolites such as 13'-carboxychromanol (13'-COOH) and carboxyethyl-hydroxychroman (CEHC). 13'-COOH binds strongly to the COX-2 and LOX enzymes using the carboxyl group (-COOH) thereby inhibiting the conversion of COX to prostaglandins and LOX to leukotrienes so that vasodilation does not occur, vascular permeability does not increase and the release of chemotactic agents decreases which ultimately reduces inflammation (Jiang, 2022). γ-tocopherol is able to trap membrane-soluble electrophilic nitrogen oxides and electrophilic mutagens that have free rings, thereby inhibiting damage originating from reactive nitrogen species (Miyazawa *et al*., 2019).

CONCLUSION

This study shows that the combination of astaxanthin and vitamin E has an anti-inflammatory effect on interleukin-1 (IL-1), interleukin-6 (IL-6), and CRP levels.

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