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| RESEARCH ARTICLE

Effects of Extra Virgin Olive Oil on Changes in CRP Levels in Colorectal Cancer Patients Receiving Capecitabine

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| ABSTRACT
Colorectal cancer has a high incidence, morbidity, and mortality, where the incidence is often associated with inflammation. Extra Virgin Olive Oil (EVOO) has an anti-inflammatory effect that has been widely studied, especially the phenol components in the form of hydroxytyrosol and oleocanthal, which have anti-inflammatory properties. C - reactive protein is an acute inflammatory protein that is expressed in the presence of tissue damage. CRP levels themselves run parallel to the progression of malignancy, and elevated CRP is a predictor of poor prognosis. This study was conducted to determine the effect of EVOO on changes in CRP levels in colorectal cancer patients undergoing capecitabine chemotherapy. This study is a randomized, placebo-controlled, double-blind trial. The subjects of the study were 30 colorectal cancer patients who would undergo capecitabine chemotherapy. They were randomly divided into 2 groups: the group receiving 30 ml of EVOO per day and the group receiving a placebo (corn oil). Plasma CRP levels will be assessed at the start of the study and after two cycles of chemotherapy. The median age in the EVOO group was 45.5 (28-58), and in the placebo group, 55 (26-59). Nineteen samples (33%) were late-stage cancer that had metastasized. The median BMI of research subjects was 19.7 (14.8-31.2), and the mean performance status score was 77.6 ± 5.6. CRP levels after treatment had no significant difference (p=0.218) in the EVOO and placebo groups. In the EVOO group, there was a decrease in serum CRP levels from 19.8 ± 19.4 to 14.8 ± 15, while in the placebo group from 25.8 ± 26 to 22 ± 20.5. EVOO can significantly reduce CRP levels, but in comparison with a placebo did not show a statistically significant difference.

| KEYWORDS
Extra Virgin Olive Oil, CRP, Colorectal Cancer

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1. Introduction

Colorectal cancer is the third most diagnosed cancer in the US, with an estimated total of 151,030 new cases by 2022. In the last decade, the incidence of colorectal cancer has increased in Asian countries, which is often attributed to the adoption of the western lifestyle. There has been a lot of research evidence linking the incidence of colorectal cancer with inflammatory processes such as Chron's Disease and Ulcerative Colitis. Research has also shown that using NSAIDs can reduce the incidence and mortality of colorectal cancer (Laukoetter et al. 2011)

Capecitabine, a fluoropyrimidine and a prodrug of 5-fluorouracil (5-FU), is completely absorbed and is more active in the gastrointestinal tract. The use of capecitabine is starting to increase in colorectal cancer and is preferred by some because it is more easily tolerated and has fewer side effects. One of the side effects of capecitabine is its catabolism product, such as *α-fluoro-β-alanine* (FBAL), which can cause inflammation in the target tissue, which is the cause of Hand-Foot Syndrome. This inflammation occurs in the hand and foot (Milano, 2008).

Olive oil is known as a form of low-fat Mediterranean diet intake, which is believed to cure several diseases. The Food and Drug Administration (FDA) has also recommended using 30-50 ml of extra virgin olive oil (EVOO), equivalent to 23 grams of EVOO per day. The most critical components in EVOO are polyphenols, especially Hydroxytyrosol and Oleocanthal which are minor components of EVOO and have been widely studied for their anti-inflammatory, antioxidant, and neuroprotectant effects. (Slynn, 2010; Massaro, 2020; Maur, 2021)

Oleocanthal is a phenol component responsible for the stinging and irritation sensation in the throat of EVOO and has potent anti-inflammatory properties. Oleocanthal works by inhibiting the COX-2 enzyme; its mechanism of action is similar to ibuprofen, where Oleocanthal at the same concentration as ibuprofen shows a better inhibitory effect of COX-2 activity than ibuprofen. (Parkinson, 2014).

C-reactive protein (CRP) is an acute-phase inflammatory protein widely used to diagnose acute and chronic inflammation. CRP seru is often associated with its clinical use for predicting or diagnosing cardiovascular disease, inflammation, or malignancy. Prospective studies have shown a higher cancer risk in patients with high CRP. CRP levels were also elevated in cancer patients suggesting an association between inflammation and malignancy. Hepatocytes produce CRP in response to inflammatory cytokines, particularly interleukin-6, from the microtumor environment. Elevated CRP alone is a predictor of poor prognosis in patients with malignancy (Ruder et al. 2011). This study aimed to assess the effect of EVOO on changes in CRP levels in colorectal cancer patients receiving capecitabine chemotherapy.

2. Methods

The type of research is a clinical study using a *double-blind, randomized clinical trial* (RCT) method. The study was conducted at the Internal Medicine Hematology Oncology Polyclinic and the inpatient ward of Dr. Mohammad Hoesin Hospital Palembang from December 2021 to June 2022. This study has been approved by the Medical Research Ethics Committee, Faculty of Medicine, Sriwijaya University, RSUP. Dr. Mohammad Hoesin, with no. 144/KEPKRSMH/2021.

The population in this study were all colorectal cancer patients undergoing chemotherapy—research with *a pilot study*. The sample in this study was divided into two groups, namely the treatment group (EVOO) and the placebo group (corn oil). EVOO and corn oil were given as much as 30 ml daily for two cycles of chemotherapy. The sampling method is based on *simple random sampling*; that is, all subjects who come and meet inclusion will be selected randomly until the required number of samples is met—performed *Randomization* to determine which subjects were included in the intervention group or the placebo group.

The inclusion criteria for this study were all patients who had been diagnosed with colorectal cancer, were eligible for chemotherapy, were over 18 years of age, and were willing to participate in the study by signing an *informed consent form*. The exclusion criteria for this study were patients with autoimmune diseases and taking anti-inflammatory drugs, both steroid and non-steroidal.

Data analysis was performed with SPSS 25.0. Data are presented as mean and standard deviation for normal distribution variables or median and range for non-normal distribution variables. A normality test was carried out with Shapiro-Wilk. Mann-Whitney used a test.

3. Results and Discussion

3.1 Results

A total of 30 subjects who received treatment from December 2021 to June 2022 participated in this study. It was divided into 2 groups: the EVOO group and the placebo (corn oil) group. The sociodemographic data of the study subjects are presented in Table 1. The median age in the EVOO group was 45.5 (28-58), and in the placebo group, 55 (26-59). The most types of cancer obtained from the sample were colorectal cancer, with as many as 29 samples. As many as 19 of the total sample (33%) were terminal cancers that had metastasized. In the EVOO group, 9 patients (60%) underwent chemotherapy cycle 1 and 6 (40%) cycle 2. In contrast, in the placebo group, 13 patients (87%) underwent chemotherapy cycles 1 and 2 (13%) cycle 2. The median BMI of research subjects was 19.7 (14.8-31.2), and the mean performance status score was 77.6 ± 5.6.

Table. 1 Characteristic of Research Subjects

Variable	Group		Total (n=30)	P value
	EVOO (n=15)	*Plasebo* (n=15)		
Gender				
Man	7 (46.7%)	8 (53.3%)	15 (50%)	0.715[a]
Woman	8 (53.3%)	7 (46.7%)	15 (50%)	
Age*	45,5 (28-58)	55 (26-59)	48,6 (26-59)	0.540[b]
Cancer Stage				
Metastasis	9 (60%)	10 (67%)	19 (63%)	0.705[a]
Non-metastatic	6 (40%)	5 (33%)	11 (37%)	
History of chemotherapy				
Cycle 1	9 (60%)	13 (87%)	22 (73%)	0.09[a]
Cycle 2	6 (40%)	2 (13%)	8 (27%)	
BMI*	18.4(14.8-25.8)	20.8(16.8-31.2)	19.7(14.8-31.2)	0.12[b]
Performance Status*	75.3 ± 7.4	76.2 ± 5.8	77.6 ± 5.6	0.16[b]

*Shapiro Wilk normality test, data is usually distributed if p> 0.05, a) chi-square test, b) Mann-Whitney test

As seen in table 2, CRP levels after treatment had no significant difference (p=0.218) in the EVOO and placebo groups. In the EVOO group, there was a decrease in serum CRP levels from 19.8 ± 19.4 to 14.8 ± 15 (p=0.01), while in the placebo group, there was a decrease from 25.8 ± 26 to 22 ± 20.5 (p=0.06).

Table 2. Characteristics of serum CRP levels, as well as changes between groups

	Group								
	EVOO				***Corn Oil***				**P'**
	Before	**After**	**Change**	**P**	**Before**	**After**	**Change**	**P**	
CRP	19.8 ± 19.4	14.8 ± 15	-4.9 ± 6.5	0.01[a]	25.8 ± 26	22 ± 20.5	3.8 ± 7.2	0.06[a]	0.218[b]

p: p value before and after the intervention. p': p value after intervention between groups. a) Wilcoxon test b) Mann-Whitney test

3.2 Discussion

The mean age of colorectal cancer patients in this study was 45.5 years, with the same proportion of men and women. The incidence of colorectal cancer is often associated with an average age of over 50 years, with the US Preventive Services task force recommending colorectal cancer screening in asymptomatic adults aged 50 to 75 years [13, 14]. However, in recent years, the average age of colorectal cancer has decreased, and the incidence of colorectal cancer has increased in those under 50. In 2018, the *American Cancer Society* updated its guidelines in which screening for colorectal cancer is recommended starting at age 45 (Siegel et al., 2017)

This decrease in the incidence of colorectal cancer is often associated with access to better health services, such as more colonoscopies and the widespread use of antibiotics. Inappropriate long-term use of antibiotics is often correlated with changes in the gut microbiota, which is a risk factor for colorectal cancer. (Wolf, 2018; Cao 2018). 67% of patients had metastases at the time of diagnosis. This is due to colorectal cancer, which is usually asymptomatic. By the time symptoms of colorectal cancer appear, most patients are in an advanced stage of cancer. The advanced stage of this cancer itself gives a worse prognosis (Shang, 2018).

This study found a significant decrease in serum CRP levels in the EVOO group. This indicates the anti-inflammatory effect of EVOO. Extra virgin olive oil in its content, especially the polyphenol consisting of oleuropein, hydroxytyrosol, and tyrosol, acts as an anti-inflammatory agent with its capacity to modulate the over-activation of NF-kB signaling, thereby reducing its destructive effect in all tissues. In addition, polyphenols can also prevent the formation of ROS. Beyond direct oxidant effects, ROS play essential roles in the modulation of intracellular signaling pathways and the activity of various transcription factors, including NF-B and activator protein-1 (AP-1) and hypoxia-inducible factor-1α (HIF-1α). (Arnold, 2017; Esposito, 2004).

Statistical analysis of the administration of EVOO compared to placebo did not have a significant effect on reducing CRP rates. This can be attributed to the effect of chemotherapy, which reduces inflammation in the body, as well as from the choice of a placebo, where *corn oil* itself is still questionable whether it has anti-inflammatory or pro-inflammatory properties.

This study has several limitations. First, the number of samples in this study is limited, so further research with a more significant number of samples is needed. Second, the placebo choice should be more neutral, which is not proven pro-inflammatory or anti-inflammatory.

4. Conclusion

Colorectal cancer has a high incidence, morbidity, and mortality, where the incidence is often associated with inflammation. Extra Virgin Olive Oil (EVOO) has an anti-inflammatory effect that has been widely studied, especially the phenol components in the form of hydroxytyrosol and oleocanthal, which have anti-inflammatory properties. C - reactive protein is an acute inflammatory protein that is expressed in the presence of tissue damage. CRP levels themselves run parallel to the progression of malignancy, and elevated CRP is a predictor of poor prognosis. This study was conducted to determine the effect of EVOO on changes in CRP levels in colorectal cancer patients undergoing capecitabine chemotherapy. This study showed that EVOO could significantly reduce CRP levels. However, compared with the placebo, it did not show a statistically significant difference.

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