

**THE ROLE OF PHENOLIC COMPOUNDS AS ANTI-INFLAMMATORY IN OBESE INDIVIDUALS****Nabila Randenia, Etika Ratna Noer*, Gemala Anjani**

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*etikaratna@fk.undip.ac.id**ABSTRACT**

Dietary polyphenols have chemopreventive and protective roles in maintaining human health and disease. Strong antioxidant effects are exhibited by dietary polyphenols and flavonoids against reactive oxygen species (ROS) and cellular oxidative stress (OS), thereby protecting against OS-related pathological conditions or diseases. This study generally aims to see the impact of phenol and bioactive compounds on inflammation in obese individuals. The method used in this study is a literature review. The stages involved in this process encompass identifying the central topic or issue to be discussed, conducting a comprehensive search for pertinent references or literature related to the topic, thoroughly reading, evaluating, and analyzing the literature in alignment with the study objectives, and finally, composing a narrative report that presents the review findings along with a concise summary. The time frame for the analysis was April 2013 to June 2023. A total of 323 publications with phenolic compounds as anti-inflammatory in obese were identified. From the initial 323 studies, 12 studies were selected for final analysis. The search for relevant articles or references will be conducted in the online databases Science Direct, Springer, Wiley Library, PubMed, and Google Scholar. The keywords used to search for references are obesity, inflammation, phenol compounds, bioactive compounds, antioxidants, and antioxidants. This literature review found that out of the 12 articles reviewed, 12 had similarities, stating that interventions with different doses of phenol compounds can reduce inflammatory cytokines in obesity with different periods. Overall, antioxidant bioactive compounds regulate pro-inflammatory and anti-inflammatory cytokines, reduce oxidative stress by decreasing the accumulation of reactive oxygen species, and enhance antioxidant capacity and gene expression to prevent DNA damage in obese individuals.

Keywords: inflammation; natural product; obesity; phenolic compounds

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INTRODUCTION

Metabolic syndromes, including insulin resistance (IR), type 2 diabetes, hypertension, cardiovascular disease, dyslipidemia, and even cancer, are caused by obesity, which is a chronic low-grade inflammatory condition (Hotamisligil, 2017). Obesity is a condition of excess fat in adipose tissue. This adipose tissue is important in maintaining a balanced energy supply (Vegiopoulos et al., 2017). Obesity is a condition of excess fat in adipose tissue. This adipose tissue is important in maintaining a balanced energy supply (Morgan-Bathke & Jensen, 2019). Obesity-induced dysfunction supports the deregulation of adipokine secretion and favors increased secretion of proinflammatory adipokines that may contribute to immune infiltration and insulin resistance (Zorena et al., 2020). Obese individuals have higher levels of proinflammatory adipokine in the circulation. A high-fat diet induces blood levels of proinflammatory adipokines, such as TNF- α , IL-6, PAI-1, leptin, and resistin, while

simultaneously lowering anti-inflammatory adipokines. So, inflammation in obesity can be prevented with lifestyle modifications, changes in eating habits, and regular physical activity that will contribute to weight loss. In addition, dietary antioxidants can maintain sufficient levels of antioxidants in the organism's body (Lobo et al., 2010).

A diet low in saturated fatty acids (especially those of animal origin), polyunsaturated fatty acids, simple sugars, salt, and rich in fiber such as raw vegetables and fruits is beneficial for improving health. In addition, plant-based products also contain many natural antioxidant compounds such as polyphenols, flavonoids, isoflavones, carotenoids, capsaicinoids, isothiocyanates, and catechins that have biological activity (Bray et al., 2018). Numerous epidemiological studies have shown that consumption of phenolic-rich foods can reduce the incidence of chronic diseases, including obesity and obesity-related complications such as insulin resistance, gastrointestinal disorders, and dyslipidemia (Aloo et al., 2023). Levels of reactive species in cellular systems can be reduced by using antioxidants by limiting the expression or activity of free radical-producing enzymes such as *xanthine oxidase* (XO) and *NAD(P)H oxidase* or by increasing the expression and activity of antioxidant-dependent antioxidants such as *glutathione peroxidase* (GPx), *catalase* (CAT), and *superoxide dismutase* (SOD) (Vona et al., 2021). Therefore, dietary changes can help increase adipose tissue metabolism in obese people by reducing oxidative stress (Pérez-Torres et al., 2021).

Phenolic and polyphenolic products, either alone or combined with vitamins, such as carotenoids, vitamin E, and vitamin C, act as antioxidants that protect tissues in the body from the damaging effects of oxidative stress (Rahman et al., 2021). Phenolics are beneficial because they have strong antioxidant activity (Matsumura et al., 2023). Numerous epidemiological studies have shown that consumption of phenolic-rich foods can reduce the incidence of chronic diseases, including obesity and obesity-related complications such as insulin resistance, gastrointestinal disorders, and dyslipidemia (Alara et al., 2021). Based on this background, the author conducted this literature review to inform readers about the *Role of Phenolic Compounds as an anti-inflammatory* in obese individuals. This study generally aims to see the impact of phenol and bioactive compounds on inflammation in obese individuals

METHOD

This research uses the literature review method. The stages in conducting this research used the Cronin, Ryan, and Coughlan (2008) method, which consists of four steps. The first step is to find a topic or problem we desire to focus on. Second, search and collect research articles that will be used as references for the literature review. Third, read, summarise, and analyze the literature according to the research objectives. The fourth stage describes the review results in tabular form and narrates them in the discussion section (Prasetia, 2020). The criteria for the articles reviewed are as follows: 1) Inclusion criteria for published articles/magazines: study population: Obesity, intervention or exposure: Phenol compounds, bioactive compounds, antioxidants; results: Inflammation levels; English or Indonesian language; published 2013-2023) Exclusion criteria: or primary research (natural literature/narrative); journal articles in the form of opinions or editorials.

Searching for articles or reference materials involved utilizing Springer, Wiley Library, PubMed, Science Direct, Proquest, Ebsco Host, and Google Scholar databases. The search terms were obesity, inflammation, oxidative stress, antioxidants, phenolic compounds, and bioactive chemicals. The literature search method was undertaken by combining keywords using boolean operators "OR," "AND," and "NOT." After acquiring articles that satisfied the

predetermined criteria for inclusion, an evaluation and examination were carried out. The literature underwent analysis utilizing the narrative review approach, considered the most basic review form. Narrative review is a research method that involves analyzing narratives, text narratives, photographs, and events. These elements are categorized into data based on the research objectives. The published papers that satisfied the requirements were further categorized and condensed. Following the compilation of the published articles.

RESULTS

Table 1.
A summary of the articles reviewed can be seen in the matrix below

Authors	Intervention	RCT Design	IMT	Result
(Narotzki et al., 2013)	GTVE; 3 cup and 400 IU	An interventional <i>randomized controlled prospective trial</i> .	BMI:: 28.3	Daily doses of GTVE in healthy elderly men and women may increase the benefits of exercise in body composition and glucose tolerance and may also decrease oxidative load.
(Ganjali et al., 2014)	curcumin at a daily dose 1 g	<i>crossover</i>	BMI) $\geq$ 30)	curcumin can exert immunomodulatory effects through changes in circulating IL-1 β , IL-4, and VEGF concentrations.
(Baldrick et al., 2018)	capsul 400 mg which contains 100 mg of seaweed	<i>Crossover</i>	(in kg/m ²) $\geq$ 25.	SPE consumption decreased DNA damage—albeit only on a small scale—in obese individuals.
(Saraf-Bank et al., 2019)	500mg curcumin	<i>Paralel</i>		Curcumin supplementation had significant effects on IL-6 levels and markers of oxidative stress including TAC and MDA in crude models
(Rabbani et al., 2021)	combination of trans-resveratrol and hesperetin (tRES-HESP),	<i>crossover</i>	-BMI 25–40 kg/m ² ,	The HATFF study showed that an optimized Glo1 inducer response, tRES-HESP, was associated with increased dysglycemia, blood pressure, dyslipidemia, and low-grade inflammation.
(Roach et al., 2022)	2/g/d or 4g/d SXRG84	<i>crossover</i>	(BMI)29 kg/m ²	In the first study, CRP markers were significantly reduced (27%) in the four g/day dose group. In Study 2, a wider range of proinflammatory cytokines was reduced, including decreased TNF-alpha and IL1B.
(Vodouhè et al., 2022)	500g ebrown seaweed extract	<i>paralel</i>	BMI >27kg/m2	An initial decrease in the inflammatory response is observed concerning small changes.
(Longhi et al., 2021)	EV))52 mL+ diet Bra	<i>Paralel</i>	BMI >25kg/m2	nutritional intervention with DietBra + EVOO promotes a significant reduction in inflammatory biomarkers, namely leukocytes and LMR. CRP was reduced in the EVOO group, and DieTBra and NLR were reduced in the DieTBra group.
(Ruiz-García et al., 2023)	EVOO 32 g	<i>crossover</i>	obesity (BMI 30–40 kg/m ²)	Status antioksidan total meningkat dan peroksida lipid dan organik menurun setelah perlakuan EVOO
(Panahi et al., 2016)	500 mg curcumin capsule	<i>parallel</i>	BMI >27kg/m ²	significant reductions in serum concentrations of TNF- α , IL-6, TGF- β , and MCP-1
(Lee et al., 2016)	Black soybean Extract 2,5g/d)	<i>parallel</i>	>23kgm2	Decrease in TNF-Alpha and MCP-1
(Ribeiro et al., 2017)	500ml orange juice	<i>Paralel</i>	30-40kg/m2	Decrease in CRP and TNF Alpha

The Role of Phenolic Compounds in Dietary Sources As Inflammatory in Obesity

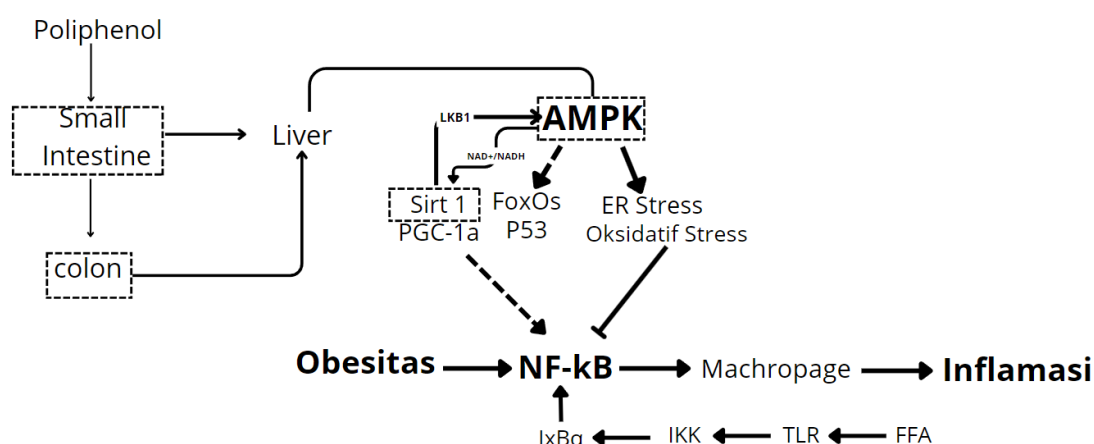


Figure 1. Mechanism of the role of polyphenols in obese individuals

DISCUSSION

The Role of Phenolic Compounds in Dietary Sources as Inflammatory in Obesity

Oxidative stress is "an imbalance between oxidants and antioxidants that support oxidants, leading to disruption of redox signaling and control and molecular damage" (Sies, 2015). ROS and RNS are both messengers of intracellular signal transduction, participate in gene expression, positively affect the immune system, regulate angiogenesis, and support vascular smooth muscle cell relaxation and cell proliferation (de Almeida et al., 2022). Therefore, a diet rich in vitamins and minerals is essential for intracellular redox regulation (Birben et al., 2012). In addition, there is an increased interest in supplementation with natural compounds that exhibit high antioxidant potential. The toxic effects of ROS/RNS are countered by enzymatic (e.g., superoxide dismutase catalase, glutathione reductase) and non-enzymatic (e.g., vitamin C (ascorbic acid), vitamin E, phenolic, and PC antioxidants) (Mishra et al., 2023). Obesity can also induce systemic oxidative stress through mechanisms such as Superoxide Formation of NADPH Oxidase (NOX) Fosoforylation Oxidive, Glyceraldehyde Autooxidation, Protein Kinase C(PK-C) activation, and Polyol and Hexosamine pathways (Serra et al., 2013). Various Polyphenols in foods, including gallic acid, ellagic, quercetin, myricetin, rutin, kaempferol, resveratrol, catekom, ECGCG, etc., exhibit dual roles (antioxidant and pro-oxidative). However, the anticancer, antiobesity, and antimicrobial effects of green tea polyphenols (EGCG, ECG) are primarily due to harmful activity caused by pro-oxidative effects(Ouyang et al., 2020)

Green Tea

Contain large amounts of polyphenols, specifically phenolic acids and hydrolyzed tannins, flavan-3-ol and its oligomers, flavonols and their glycosides, theaflavins, and thearubigins (L. Zhang et al., 2019). Recent research has shown that polyphenols have antioxidant and anti-inflammatory characteristics, which result in health gains and aid in managing disorders associated with inflammation(Rathod et al., 2023). Dietary tea polyphenols have been shown to reduce inflammation by functioning as antioxidants, stimulating cytoprotective mechanisms, and blocking pro-inflammatory signaling pathways (Yan et al., 2020). Tea polyphenols also provide anti-inflammatory properties by regulating cellular signal transduction (e.g., Nrf2, NF-κB, AP-1, and STATs)(Truong & Jeong, 2022). For 12 weeks, 22 men were randomly assigned to consume green tea plus vitamin E (GTVE; 3 cups and 400 IU, respectively, increased antioxidant enzymes expected to reduce oxidative stress. In the investigation of the study, examination of plasma protein carbonyl concentrations revealed a

significant decrease only in the GTVE group. The GTVE group, which received antioxidant supplementation, showed increased antioxidant enzyme activity. Green tea, a possible inhibitor of NF- κ B, does not impede physical performance due to exercise; therefore, it makes sense that the function of ROS in muscle adaptation to exercise is not entirely dependent on NF- κ B activation. (Narotzki et al., 2013)

Curcumin

Curcumin is mostly obtained from the root tubers of *Curcuma aromatica* Salisb and the rhizomes of *C. longa* L. (Turmeric) from Zingiberaceae (J. Zhang et al., 2019). Curcumin exhibits anti-inflammatory, antioxidant, antineoplastic, and other biological properties. (Lestari & Indrayanto, 2014). The well-documented anti-inflammatory properties of curcumin can be attributed, at least in part, to its impact on the function of the enzymes cyclooxygenase-2 (COX-2), lipoxygenase, and inducible nitric oxide synthase (iNOS), as well as its ability to inhibit the production of inflammatory cytokines (such as TNF- α , monocyte chemoattractant protein 1 (MCP-1), and interleukins 1, 2, 6, 8 and 12 ((Goel et al., 2008). Trials conducted by Ganjali showed that, in obese patients, supplementation with curcumin (1 g/day) resulted in a significant reduction in serum levels of IL-1 β , VEGF, and IL-4 while having no impact on concentrations of IL-1 α , IL-2, IL-6, IL-8, IL-10, IFN γ , EGF, MCP-1, and TNF α . Another cross-over study of obese subjects was conducted for 12 weeks. In the first study, CRP markers were significantly reduced (27%) in the four g/day dose group. In Study 2 a wider range of proinflammatory cytokines was reduced, including decreased TNF-alpha and IL1B. Inhibition of NF- κ B has been suggested as the primary mechanism behind curcumin's therapeutic effects. NF- κ B is important in controlling the transcription of important inflammatory mediators such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), TNF α , IL-6, and IL-8. (Shehzad et al., 2011) Suppression of NF- κ B activation has been documented to cause curcumin's ability to reduce the production and release of inflammatory cytokines in both preadipocytes and 3T3-L1 adipocytes (Islam et al., 2023). The anti-inflammatory effects of curcumin can also be achieved through suppression of 5-lipoxygenase and p38 mitogen-activated protein kinase (MAPK), as well as reduction of the Janus kinase-STAT inflammatory signaling pathway (Sadeghi et al., 2023).

Brown Seaweed

Polyphenols in phlorotannin-rich brown seaweed extract are effective in controlling inflammation through various pathways in vitro, including inhibition of proinflammatory cytokines such as TNF- α , IL-1 β , and IL-6 (M. M. Kim & Kim, 2010). In a current study in an overweight/obese population (aged 30-65 years, BMI > 25) supplementation with phenolic (poly)seaweed significantly reduced the basal rate of lymphocyte DNA damage (by 23%) but only in the obese subpopulation (n = 36). (Vodouhè et al., 2022) phenol (poly) (Vodouhè et al., 2022) (Piao et al., 2012) and can activate Nrf2-mediated heme induction oxygenase 1 (HO-1) (Piao et al., 2012) (McDougall et al., 2017) (K. C. Kim et al., 2010) (McDougall et al., 2017), activation of erythroid nuclear factor 2-associated cytoprotective pathway factor 2/antioxidant response element (Nrf2/ARE) may be related. After consuming seaweed extract, the researcher saw a 28% reduction in CRP concentrations, which are markers of inflammation. (Baldrick et al., 2018) A double-blind trial was conducted with the administration of seaweed at a dose of 2 g / day or 4 g / day SXRG84 daily for six weeks in 64 participants who were overweight or obese (mean age 55 years, median body mass index (BMI) 29 kg/m²). for six weeks and then SXRG84 treatment 2 g/day for six weeks, or vice versa. . In Study 1, a dose of 2 g/day showed a significantly reduced CRP (C-reactive protein) reduction (-27% or -0.78 mg/L, p = 0.03) at a dose of 4 g/day in overweight participants.

Significant shifts in intestinal flora include improvement (Roach et al., 2022). Another clinical trial giving 500mg of mah seaweed extract for four weeks showed small changes in reducing inflammation for diabetes prevention.

Olive Oil

Polyphenols in Extra Virgin Oil. EVOO consumption attenuates inflammatory responses in subjects with high cardiovascular risk or metabolic syndrome (Longhi et al., 2021). The beneficial effects of EVOO have been associated with decreased regulation of proinflammatory gene expression and decreased CRP levels, such as total plasma/serum concentrations (Rees et al., 2019). regular consumption of EVOO offers an important biological protection mechanism, modulating nuclear factor pathways (2-like erythroid-derived 2, Nrf2) that stimulate the expression of antioxidant enzymes, superoxide dismutase, catalase, etc. In a randomized control trial with EVOO administration for four weeks, a decrease in interferon γ was observed after EVOO treatment, achieving inter-treatment differences ($P = 0.041$). Total antioxidant status increased, and lipid and organic peroxides decreased after EVOO treatment (Ruiz-García et al., 2023). Later, in RCT assays, significant reductions in several inflammatory parameters (leukocytes and LMR) were observed when both interventions were combined– (DieTBra + EVOO)(Longhi et al., 2021).

Black Soybean

The isoflavones in beans, namely genistein, daidzein, and glycerin, have a chemical structure comparable to endogenous estrogen and are believed to interact with intracellular estrogen receptors, likely resulting in decreased lipid accumulation and adipose distribution. Animal and human studies have shown the effects of a soy diet on weight control and obesity prevention (Velasquez & Chatterjee et al., 2018). Studies have revealed that isoflavones inhibit adipogenesis and lipogenesis with several transcription factors and upstream signaling molecules (Akhlaghi et al., 2017). Isoflavones exhibit pleiotropic properties in the human body to control metabolism and balance, potentially inhibiting and treating obesity (Akhlaghi et al., 2017). This randomized clinical study showed decreased levels of belly fat, cholesterol, triacylglycerol, and LDL, with decreased levels of TNF- α and MCP-1 (Lee et al., 2016). Studies on obesity models have shown that a soy isoflavone diet significantly reduces body weight and fat weight. It has been shown that soy isoflavones reduce the expression of sterol one-element binding protein transcription factor SREBP1 and other target genes (acetyl-coenzyme A carboxylase, ATP-citrate lyase, and FASN).

Orange

Orange juice The juice, mainly hesperidin, and narirutin, is a popular beverage drunk worldwide. Oxen juice consumption can also lower oxidative stress and inflammation levels due to the antioxidant activity of citrus flavonoids. Red orange juice effectively reduced metabolic and inflammatory markers in human subjects but did not inhibit weight loss. It improves insulin sensitivity, lipid profile(Azzini et al., 2017), and inflammatory status and contributes nutrients to food quality (Ribeiro et al., 2017). The authors suggest the consumption of fresh orange juice, without added sugar, as part of a controlled diet in obese women; combination with increased physical activity to maintain a healthy weight through healthier food choices may improve comorbidities associated with obesity (Azzini et al., 2017). In a randomized controlled trial, 78 obese patients with a body mass index [BMI] of 33 ± 3 kg/m² and an age of 36 ± 1 year were divided into two groups: The Orange Juice group followed a low-calorie diet containing 500 mL of orange juice per day. In contrast, the Control group followed a low-calorie diet that did not include orange juice. The Orange Juice group followed a reduced-calorie diet containing 500 mL of orange juice daily, while the

Control group followed a reduced-calorie diet that did not include orange juice. Analyses were conducted on food consumption, biochemical indicators, and body composition over 12 weeks. A decrease in hs-CRP (33%), indicative of the low-calorie diet and anti-inflammatory properties of orange juice, was seen. Analyses conducted during the 12-week course of the experiment showed that the hs-CRP levels of the Orange Juice group decreased from 0.5 to 0.3 mg./dL, indicating a 40% change in inflammation status at the end of the experiment, compared with a 20% decrease in inflammation status at the end of the experiment. Control group. of the 12-week course of the experiment showed that the hs-CRP levels of the Orange Juice group decreased from 0.5 to 0.3 mg /dL, indicating a 40% change in inflammation status at the end of the experiment, compared with a 20% decrease in the control group(Ribeiro et al., 2017).

CONCLUSION

This literature review found that of the 12 articles reviewed, 12 have similarities that mention that interventions with polyphenol administration with different doses can reduce inflammatory cytokines in obesity with different time frames. Polyphenols interact synergistically, not only with other polyphenols but also with other food components. The mechanisms involved in weight loss by which polyphenols may play a role are activation of β -oxidation processes, induction of satiety, stimulation of energy expenditure, inhibits adipocyte differentiation, promotion of adipocyte apoptosis, increased lipolysis, and improvement of lipid metabolism disorders.

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