Anti-Inflammatory Activities of Pistachio: Review

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Abstract

Polyphenols are micronutrients with an extensive range of biological characteristics including a reduction in inflammation features. Pistachio is rich in polyphenols, and therefore, contains the anti-inflammatory potential for various anti-inflammatory conditions. To date, beneficial anti-inflammatory effects of pistachio or its derivatives have been demonstrated in several inflammatory conditions such as colitis and paw edema. A number of conditions, including diabetes, obesity, and cardiovascular disorders have also been found to benefit from pistachio supplementation. Growing evidence suggests that pistachio could be more widely used in inflammatory conditions. Pistachio and its derivatives seem to exert anti-inflammatory effects through several direct and indirect mechanisms. However anti-inflammatory properties of pistachio need to be further investigated in the context of other inflammatory conditions such as inflammatory and autoimmune arthritis, systemic lupus erythematous, tendonitis etc.

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Introduction

Polyphenols are micronutrients with a broad range of anti-inflammatory, immune-modulatory, antioxidant, and anti-cancer properties [1]. The anti-inflammatory effect of polyphenols is exerted by several mechanisms, including scavenging free radicals, inhibiting nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, metal chelating, modulating the mitochondrial respiratory chain, upregulation of endogenous antioxidative enzymes, and downregulation of certain oxidative enzymes such as xanthine oxidase [1]. Polyphenol containing plants such as turmeric and ginger has been found to have anti-nociceptive and anti-inflammatory effects beneficial to a wide range of inflammatory conditions such as osteoarthritis [2- 4], rheumatoid arthritis [5- 7], and lupus erythematosus [8- 10]. Pistachio contains a high amount of different polyphenols, including anthocyanins, flavonoids, proanthocyanidins, stilbenes. Anthocyanidins exert anti-inflammatory effects by inhibiting the expression of several inflammatory genes, including cyclooxygenase-2 (*COX-2*) and also by inhibiting the production of inducible nitric oxide (iNOS) [11]. Flavonoids work in down-regulation of a variety of cell signaling routes such as nuclear factor kappa B (NF-κB), which reduces inflammation sequel as a patently obvious example [12]. Proanthocyanidins exert several anti-inflammatory actions, including scavenging free radicals and inhibiting the production of inflammatory cytokines [13]. Stilbenes are also effective anti-inflammatory compounds that act by down-regulating inflammatory cytokines such as TNFα, interleukin 1 beta (IL-1β) and IL-6. These compounds also decrease the expression of specific inflammatory enzymes such as COX-2, adenosine triphosphate (ATPase) and NF-κB [14]. Various studies have confirmed possible health benefits of pistachio for a variety of human disorders [15]. Recent evidence suggests that pistachio can help treat human inflammatory conditions such as hip pain, gout, and rheumatic disorders [16]. Anti-inflammatory effects of pistachio and its derivatives have been the subject of many recent in vivo and in vitro studies [17]. This review summarizes the anti-inflammatory potential of pistachio in inflammatory diseases and conditions (Table 1).

Table 1: Anti-inflammatory effects of Pistachio and its derivatives on different inflammatory conditions

Inflammatory condition	Authors	Laboratory Model	Year of publication	Main findings
Excremental colitis	Terzo et al.	Mice	2020	Reduced level of serum and tissue TNF-α and IL-1β
	Gentile et al.	Cell line	2015	Decreased level of PGE2, IL-6, and IL-8.
	Gioxari.et al	Rat	2011	Decreased level of tissue TNF-α, adhesion molecule-1, IL-6 and IL-8
	Naouar et al.	Rat	2016	Significant decrease in ulceration, hyperplasia, and crypt loss compared to the control group.
	Tanideh et al.	Rat	2016	Complete resolution of Acute inflammation and granular atrophy
	Gholami et al.	Rat	2016	Significant alleviation of colitis regarding pathological scores and reduction of myeloperoxidase activity
Paw edema	Khedir et al.	Rat	2016	70% decreased edema
	Esmat et al.	Rat	2012	Decreased size of edema, decreased level of PGE2, TNF-α, and NO, inhibition of myeloperoxidase activity,
	Ahmad et al.	Mice	2010	Significant antinociceptive and analgesic effects
	Giner-Larza et al.	Mouse	2002	Significantly reduced edema

Obesity	Sari et al.	Human		Decreased level of fasting blood glucose, low-density lipoprotein, and triacylglycerol, serum IL-6, total oxidant status, lipid hydroperoxide, and malondialdehyde, increased serum levels of antioxidants (superoxide dismutase)
	Edwards et al.	Human	1999	Decreased total cholesterol, increased HDL
	Kocyigitet .al	Human	2006	Decreased plasma total cholesterol, malondialdehyde, total cholesterol/HDL and LDL/HDL ratios
	Sheridan et al.	Human	2007	Significant reductions in TC/HDL-C, LDL-C/HDL-C and a significant increase in HDL-C
Cardiovascular disorders	Gebauer, et al.	Human	2008	Decreased total cholesterol, LDL cholesterol, non-HDL cholesterol, apo B, apo B/apo A-I, and plasma SCD activity
	O'Neil	Human	2011	Lower percentage and prevalence of hypertension and HDL-C
Type 2 Diabetes	Parham et al.	Human	2014	Reduced HbA1c, fasting blood glucose, systolic blood pressure, body mass index, and CRP.
	Sauder Et al.	Human	2015	Significantly lower total cholesterol and the ratio of total to HDL cholesterol, triglycerides, and fructosamine. Inflammatory markers and endothelial function were unchanged.
	Lalegani et al.	Cell line	2018	Strong antioxidant activity, significantly lower starch digestibility and glycemic index

***TNFα:** Tumor necrosis factor α; IL: Interleukine; PGE2: Prostaglandin E2, HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TC: Total cholesterol; C: Cholesterol; NO: Nitric oxide; SCD: Stearoyl-coa desaturase.

Anti-inflammatory effect of pistachio on excremental colitis

Pistachio and its derivatives have been frequently reported to have an anti-inflammatory effects in experimental colitis. Terzo et al. studied the effect of regular pistachio intake (16 weeks) on preventing high-fat diet (HFD) induced inflammation in mice. Markers of inflammation in serum, hepatic, and adipose tissue were compared between a group of mice fed a high-fat diet (HFD) and another group fed a high-fat diet supplemented with pistachios named HFD-P. Results from this study demonstrated that HFD-P significantly reduced serum levels of tumor necrosis factor alpha and interleukin 1 beta compared to HFD. Moreover, the examination of subcutaneous and visceral adipose tissues of the HFD-P group demonstrated significantly smaller areas of crown-like structure density, adipocytes, TNF-α, IL-1β, F4-80, and chemokine (C-C motif) ligand (CCL-2) mRNA expression levels compared to the HFD group. The number of inflammatory foci also considerably decreased in the HFD-P group's liver [18]. Gentile et al studied the effect of hydrophilic extract from Sicilian pistachio nut (HPE) on the IBD cell model which demonstrated that the level of prostaglandin E2, IL-6, and IL-8 decreased after a course of HPE treatment. The treatment was also effective in down-regulating the expression of cyclooxygenase 2 and inhibition of NF-kappa B activation as a necessary factor for transcription and development of an inflammatory response [19]. Gioxari et al. investigated the role of coriander in limiting intestinal damage and inhibiting inflammation and oxidative stress in intestinal epithelium in inflammatory bowel disease. In this experimental study, TSA-induced colitis mice were injected orally with four different doses of powdered P. lentiscus. Colon damage was assessed through microscopic examination of colon samples and measurements of TNFα, intercellular adhesion molecule-1, interleukin 6, interleukin 8, interleukin 10 as well as malondialdehyde in the samples. Significant improvement was observed in colitis tissues (P:0.00) and the indices of colon after three days of treatment (P:0.0٠1). The study also demonstrated that powdered pistacia (100 mg/kg/day) decreases whole related parameters inflammation that considered in this study (P- value ≤0.050) as well as malondialdehyde levels (P≤.01), while IL-10 levels remain unaffected. Overall, the results of this study suggest that P. lentiscus powder may have therapeutic benefits for inflammatory bowel disease, mainly by regulation of antioxidant and oxidant system stability as well as adjustment of inflammation [20]. Another in vivo study by Khedir et al. evaluated the

anti-inflammatory effect of Pistacia lentiscus fruit oil (PLFO) and its effects on oxidative stress. The study concluded that PLFO can be used in production of natural health products that may prove useful in treating local inflammation [21]. The anti-inflammatory properties of pistachio have been reported in several other in-vivo and in-vitro studies [22-26].

Anti-inflammatory effect of pistachio on paw edema

Several studies have reported the anti-inflammatory effect of pistachio on paw edema. Khedir et al. compared the anti-inflammatory effect of PLFO with inflocine in the carrageenan-induced paw edema rat model by measuring edema diameter at a 1-hour interval for five hours. Based on their report, edema inhibition was 70% in the PLFO group and % 51.5 in the control group [27]. Esmat et al. Evaluated the reduced inflammatory response of Pistacia khinjuk L. by measuring paw volume on three experimental models. Markers of inflammation, including Prostaglandin E2 (PGE2), tissue myeloperoxidase (MPO) activity, nitric oxide (NO) level, and TNF-α level, were also assessed. The decreased size of edema, accompanied by reduced level of PGE2, significant inhibition of MPO activity, and significant reduction of histopathological inflammation provided evidence for anti-inflammatory effects of Pistacia khinjuk L. Inhibition of NO production and TNF-α release was also observed in one of the models [28]. A prospective study by Sari et al. assessed the effect of a diet rich in pistachio on parameters of fat, endothelial function, inflammation and oxidative status. 32 healthy young men (mean age 22 years) with no history of lipid disorders were put on a Mediterranean diet for a period of 4 weeks. At the end of week four, pistachio was added to their diet for another period of four weeks. The amount of pistachio in this diet covered the need for monounsaturated fat content, which should comprise 20% of the daily caloric intake before and after each diet, fasting blood samples were collected and measures of biracial endothelial function were recorded. Several parameters of interest including blood glucose homeostasis, endothelial function, as well as indicators of inflammation and oxidative status were improved in healthy young men on pistachio diet. The observed benefits were in line with the hypothesis that a diet that relies on nuts, specially pistachio nuts, due to its fat content, is beneficial in controlling lipid parameters of blood and preventing lipid disorders [29]. Sheridan et al. designed a randomized crossover study to determine the effect of pistachio consumption on serum lipid levels. 15 subjects with moderate hypercholesterolemia were put on a modified four-week diet with 15% of total caloric intake from pistachio nuts. All subjects underwent a comprehensive

profiling for blood lipd parameters, including cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, apolipoprotein B100, apolipoprotein A1 as well as other relevant measurements including body mass index (BMI), blood pressure and nutrient intake, both before and after the intervetion. In this study, pistachio nuts significantly reduced TG / HDL-C, LDL-C / HDL-C, B-100 / A-1 levels while increasing HDL-C levels in blood. Pistachio diet also lowered the energy quota unsaturated fats in the diet. Overall the results indicate that a four-week meal including 15 percent energy of pistachio fruits may help improve some of the blood lipid parameters in patients with moderate hypercholesterolemia, while also lowering the risk of coronary heart disease [30]. The beneficial anti-inflammatory effects of pistachio on paw edema has also been demonstrated in a number of other studies [31, 32].

Anti-inflammatory effect of pistachio on obesity

Obesity causes a chronic low-grade inflammation. Adipose tissue produces and releases a variety of inflammatory cytokines such as TNF-α and IL-6 [33]. 32 normal, lively, and healthy youths were investigated by Sari et al. in terms of their plasma glucose, lipid panel, and inflammatory indicators as well as oxidative stress before and after adding Antep pistachio to their Mediterranean diet. According to their results, adding pistachio to the diet significantly decreased the level of fasting blood glucose, low-density lipoprotein, and triacylglycerids. Pistachio supplementation also significantly reduced serum IL-6, total oxidant status, lipid hydroperoxide, and malondialdehyde, while it increased serum levels of antioxidants (superoxide dismutase) [29]. Kocyigit et al. tried to confirm the effects of pistachio consumption on blood lipid levels and indicators of oxidative stress in healthy normocholestromic volunteers. 24 healthy men and 20 healthy women were enrolled in the study. The participants resumed their regular diet only by adding pistachio fruits up to 20 percent of total every day energy intake over a 21-day period. Total plasma cholesterol, LDL, HDL, triglycerides, malondialdehyde (MDA), and antioxidant potential were recorded for all participants before and after intervention. After a period of three weeks the pistachio diet significantly lowered mean plasma total cholesterol, MDA and total cholesterol / HDL and LDL / HDL levels. This study demonstrated that pistachio consumption is associated with reduced oxidative stress and improved cholesterol and HDL levels in healthy individuals [31]. Also in another study, Edwards et al. demonstrated that substituting pistachio nuts for other fat sources in the diet can improve lipid

profile, and reduce overall coronary risk [34]. Several other studies have also reported the beneficial effects of pistachio consumption in obese people [35, 36] suggesting that the anti-inflammatory properties of pistachio combined with its lipid lowering and antioxidant qualities may be of therapeutic interest.

Anti-inflammatory effect of pistachio on cardiovascular disorders and type 2 diabetes

Inflammation plays a crucial role in the development of cardiovascular disorders and types 2 diabetes [37]. Inflammatory markers such as serum CRP, IL-6, and TNF-α have been recognized as independent predictors of cardiovascular disorders and type 2 diabetes [38]. On the other hand, pistachio consumption significantly decreases these inflammatory markers [15, 18, 39, 40]. Therefore, it can be concluded that pistachio consumption might reduce the risk of cardiovascular disorders and type 2 diabetes. The study of Gebauer, et al. revealed that adding pistachio to a healthy nutrition could be an important element to reduce the risk factors of cardiovascular disorders by dose proportional behavior [32]. Neil et al. attempted to compare several risk factors for cardiovascular disease, diabetes mellitus type 2, and metabolic syndrome between groups of nut consumers and non-consumers. In this study nuts/tree nuts' consumption was associated with reduced BMI, waist circumference and systolic blood pressure [41]. Silva et al. also studied the possible relationship between nut consumption and cardiovascular disease. This study demonstrated that the high unsaturated fatty acids, antioxidant minerals and phenol contents of nuts are effective in reducing inflammation, oxidative stress and improving lipid profile. The study concluded that regular nut consumption could lower the risk of several chronic diseases [42]. Other studies have also reported the preventive role of pistachio nuts for cardiovascular diseases [43, 44]. Parham et al. showed in their study that adding pistachio snacks to the diet of diabetic patients significantly lowered levels of hemoglobin A1c, Fasting plasma glucose (FPG), blood pressure, body mass index as well as C-Reactive Protein (CRP), concluding that pistachio is beneficial for glycemic control, obesity, and inflammation markers in diabetic patients [45]. Ribeiro et al. examined the markers of glucose metabolism in patients with diabetes mellitus type 2 before and after pistachio consumption. Results showed significant reduction in fasting blood glucose, insulinemia, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), and fructosamine following long term pistachio consumption but no noteworthy changes in HbA1c. Prevention and treatment response in T2DM can be modified by long-term pistachio consumption [46]. Pistachio consumption

has been found to be beneficial for diabetic patients in several studies [47, 48].

Anti-inflammatory effect of pistachio on other inflammatory conditions

Pistachio anti-inflammatory effect has been shown in several other inflammatory conditions, although it has been investigated less frequently. Grace et al. evaluated the antioxidant and anti-inflammatory pistachio extract activities (skin and kernel phytochemicals) in lipopolysaccharides stimulated RAW 264.7 macrophages. According to their analysis, more phenolic compounds, particularly flavan-3-ols, were included in the skin compared to the kernel. Bioassays techniques revealed that all extracts had an inhibitory effect on lipid accumulation. All pistachio extracts significantly inhibited reactive oxygen species in radical scavenging assays. Besides, gene expression of cyclooxygenase type 2 was inhibited after pretreatment with pistachio abstract [49]. Nieman and collaborators concluded that 14 days of pistachio consumption increased post-exercise plasma levels of raffinose [50], an effective prebiotic with beneficial effects on bowel function, IBD and cancer risk [51, 52].

Conclusion

A review of the literature reveals that pistachio and its derivatives provide several direct and indirect anti-inflammatory benefits. Several inflammatory conditions such as colitis, paw edema, and obesity have been demonstrated to benefit from the anti-inflammatory properties of pistachio compounds. However, pistachio's anti-inflammatory role in many other inflammatory conditions such as arthritic disorders, psoriasis, lupus erythematosus, tendonitis, etc., remains unknown. Large prospective, controlled trials would be beneficial in providing patients with appropriate dietary recommendations regarding pistachio consumption.

Conflict of Interest

The authors of present research declare that there is no conflict of interest.

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