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Immunomodulation as the main characteristic of vegetable oils: a review

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SUMMARY: Known for being a functional food, vegetable oil is widely used because of its nutraceutical activity. It notable that one third of all traditional medicines are intended to treat inflammatory disorders. Vegetable oils are basically composed of linoleic and alpha-linolenic acids, which are polyunsaturated fatty acids (PUFA) classified as essential, and monounsaturated fatty acids (MUFA) such as oleic acid, are classified as non-essential. Olive, sunflower, flaxseed, and chia oil are rich in these fatty acids, and their benefits are directly linked to these fatty acid contents. The benefits in their consumption by the population worldwide is proven, mainly promoting the balance of the lipid profile, cardiovascular aspects, decrease in blood pressure, and healing effects when used topically. Most of these benefits come from the immunomodulatory effects of vegetable oils, mainly the anti-inflammatory activities triggered by the unsaturated fatty acids present in these oils.

KEYWORDS: *Chia oil; Flaxseed oil; Immunomodulation; Olive oil; Unsaturated fatty acids; Vegetable oils.*

RESUMEN: ***La inmunomodulación como principal característica de los aceites vegetales: revisión***. Conocidos por ser un alimento funcional, los aceites vegetales son ampliamente utilizados por su actividad nutracéutica. Es de destacar que un tercio de todas las medicinas tradicionales están destinadas a tratar trastornos inflamatorios. Los aceites vegetales están formados *básicamente por* los ácidos linoleico y alfa-linolénico, que son ácidos grasos poliinsaturados (PUFA) clasificados como esenciales; y los ácidos grasos monoinsaturados (MUFA), como el ácido oleico, que se clasifican como no esenciales. Los aceites de oliva, girasol, linaza y chía son ricos en estos ácidos grasos y sus beneficios están directamente relacionados con el contenido de los mismos. Están comprobados los beneficios de su consumo en la dieta de la población a nivel mundial, promoviendo principalmente el equilibrio del perfil lipídico, aspectos cardiovasculares, disminución de la presión arterial y efectos curativos cuando se usan tópicamente. La mayoría de estos beneficios provienen de los efectos inmunomoduladores de los aceites vegetales, principalmente las actividades antiinflamatorias desencadenadas por los ácidos grasos insaturados presentes en estos aceites.

PALABRAS CLAVE: *Aceite de chía; Aceite de linaza; Aceite de oliva; Aceites vegetales; Ácidos grasos insaturados; Inmunomodulación.*

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1. INTRODUCTION

According to the World Health Organization, over 80 % of the population relies on traditional medicine for primary healthcare, and approximately one third of all traditional herbal medicines are intended to treat inflammatory disorders (Flori *et al*., 2019). Vegetable oils are an example as they present nutraceutical and functional use. They are used for systemic and skin inflammatory conditions, especially when they are rich in essential and non-essential fatty acids (such as α-linolenic, linoleic, and oleic acid) because these compounds are necessary for fatty acid regulation, cellular composition, and maintenance of epidermal integrity (Vaughn *et al*., 2018).

Linoleic and α-linolenic acids are polyunsaturated fatty acids (PUFA) classified as essential. In contrast, monounsaturated fatty acids (MUFA), such as oleic acids, are classified as non-essential (Sales-Campos *et al*., 2013). The benefits of using vegetable oils are linked with these PUFA and MUFA contents.

Several oils from vegetable sources have already been used to control cholesterol, hypertension, and diabetes, demonstrating their properties through clinical trials and experimental studies (Djuricic and Calder, 2021). However, the anti-inflammatory mechanisms of these oils are poorly explained in the literature, which only highlights their nutritional properties. Therefore, this review focuses on oils with higher immunomodulatory ability, emphasizing their performance on immune cells and its consequences.

2. COMPOSITION AND MEDICINAL USES OF VEGETABLE OILS

Natural oils, mainly olive oil (OO), have been used in food for centuries. The beneficial attributes of these oils in the diet allow for the expansion of their use; many studies demonstrate antimicrobial, antioxidant, and anti-inflammatory characteristics, besides traditional benefits for arterial blood pressure, cholesterol-lowering, and diabetes, which makes them an attractive alternative for complementary treatments to the conventional medicine and to a healthy lifestyle (Vaughn *et al*., 2018). Table 1 summarizes the main health benefits derived from the intake of vegetable oils.

The main characteristic of the Mediterranean diet is the consumption of extra virgin OO as the essential dietary fat. In recent years, many scientific reports have pointed out the nutraceutical and nutritional value of the Mediterranean diet, suggesting that its consumption reduces the incidence of oxidative- and inflammatory-related diseases, such as cardiovascular diseases and cancer (Flori *et al*., 2019). Indeed, the bio-functional components of OO positively affect genes involved in the pathogenesis of most prevalent age- and lifestyle-related human conditions. OO is a food composed of a significant fat fraction (about 98–99%) represented by oleic acid (55–83%) and other saturated and unsaturated acids (linoleic, palmitic, and stearic acids, 3–21%) and of a minor non-fat fraction (about 1–2%), including a high number of vitamins (α-, β-, γ- and δ- tocopherols), polyphenols (mainly tyrosol, hydroxytyrosol, and oleuropein) and squalene (Flori *et al*., 2019).

Many reports have demonstrated the beneficial effects of olive oil ingestion, as shown by Widmer *et al*. (2013), where patients who consumed 30 mL/day for four months improved endothelial functions. The literature proved the OO cardioprotective effect aiming at different targets, improving cardiovascular diseases, such as lowering obesity, increasing antioxidant capacity, diminishing reactive oxygen species (ROS) and inflammatory cytokines, controlling lipid profile levels, decreasing waist circumference and insulin concentration, and the control of blood pressure parameters (Casas *et al*., 2017). However, OO is contraindicated in skin lesions because it can impair the skin barrier function (Vaughn *et al*., 2018).

Sunflower oil (SFO) is traditionally used in cooking due to its easy accessibility and health benefits. It is widely preferred in European countries, Mexico, and some places in South America (Petraru *et al*., 2021). The significant components are linoleic acid (59–65%) and oleic acids (30–70%), representing 48−78% of the total fatty acids profile. However, it also contains palmitic and stearic acids (15% for both fatty acids). SFO is also rich in vitamins, minerals, and phytochemicals such as carotenoids, tocopherols, phenols, and tocotrienols with antioxidant activity. The composition variation depends on the plant species and extraction method (Petraru *et al*., 2021).

Akrami *et al*. (2020) demonstrated that seven weeks of SFO ingestion (25 mL/day) significantly increased antioxidant activity. The use of SFO on the skin is widespread, and due to the presence of linoleic acid, SFO can improve the skin barrier function by activating peroxisome proliferator-activated receptor-α (PPAR-a), which regulates keratinocyte proliferation, accelerating skin barrier repair, as demonstrated by *in vitro* studies and animal models (Vaughn *et al*., 2018).

Flaxseed/linseed oil (FO) can be considered a medicinal and nutritional product due to its high PUFA content (especially ω-3 and ω-6 groups), lignans, high-quality proteins, fibers, and carbohydrates (Yang *et al*., 2021). FO is a rich source of essential PUFA, such as linoleic acid (ω-6) and α-linolenic acid (ω-3), which regulate prostaglandin synthesis and enhance wound healing. Also, these essential fatty acids improve the development of the nervous system and reduce cardiovascular disease and cancer. α-linolenic acid is known to lessen the severity and minimize chronic inflammatory and inflammatory bowel disease symptoms. Furthermore, ω-3 fatty acid consumption reduces plasma triglyceride

Table 1. Studies describing the health benefits of vegetable oils

Reference	Vegetable oil	Application	Health benefit
Widmer *et al*., 2013	Olive oil	Consumption of 30 mL/day for four months	Improved endothelial function
Casas *et al*., 2017	Olive oil	Consumption of 1 L/week (family) for three weeks	Significant reduction of IL-6, IL-8, MCP-1, and MIP-1β
Vaughn *et al*., 2018	Sunflower oil	Topic use in skin	Enhanced barrier function
Akrami *et al*., 2020	Sunflower oil	Comsumption of 25 mL/day for seven weeks	Increased antioxidant activity
Tanideh *et al*., 2021	Flaxseed oil	Consumption of 2.5 mg/kg daily for eight weeks	Improved plasmatic levels of calcium, estrogen, and progesterone in ovariectomized rats
Parker *et al*., 2018	Chia oil	Controlled diet with 10.4 % w/w of chia	Reverted the antioxidant system depletion and decreased ROS, IL-6, and TNF-α plasmatic levels in dyslipidemic rats
Jeong *et al*., 2010	Chia oil	Topic use in skin	Improved skin hydration and solved lichen simplex chronicus, and prurigo nodularis cases

IL – Interleukin; MCP – Monocyte chemoattractant protein; MIP – Macrophage inflammatory protein; ROS – Reactive oxygen species; TNF – Tumor necrosis factor

levels and increases HDL-C, improving the lipid profiles (Tanideh *et al*., 2021).

Chia oil is a preferred and attractive choice for healthy food and cosmetic applications as it has the lowest saturated fatty acid content (palmitic and stearic acid) and an adequate concentration of linoleic acid (18–20%), with a high fatty acid content of α-linolenic acid (55–60%) (Imran *et al*., 2016). Seeds and biochemical components from *Salvia hispanica L*. help maintain serum lipid levels, increase the satiety index, and prevent cardiovascular diseases, inflammation, nervous system disorders, and diabetes. A larger supply of α-linolenic acid improves the antioxidant status, fat oxidation capacity, ω-3 long-chain PUFA content, and reduces the activity of fat synthesis biological tissue (Imran *et al*., 2016).

Other benefits include the capacity to lower blood glucose, waist circumference, and weight in overweight adults and improve pruritic skin and endurance in distance runners (Parker *et al*., 2018). A topical approach demonstrated the benefits of products containing a chia oil formulation. Five patients with pruritus caused by end-stage renal disease and five healthy volunteers with xerotic pruritus received a topical formulation containing 4% chia oil for eight weeks. The measurement of itching indications, trans epidermal water loss, and skin capacitance demonstrated that chia oil significantly improved skin hydration, lichen simplex chronicus, and prurigo nodularis in all the patients (Jeong *et al*., 2010).

3. IMMUNOMODULATION BY UNSATURATED FATTY ACIDS

Immunomodulators have received interest in many areas, mainly because it is possible to target innate and adaptative immunity. Some compounds from plants or food, like polyphenols, can also act as immunomodulators (Yahfoufi *et al*., 2018), since they have been shown to present anti-inflammatory properties which modulate the immune system. They can abrogate the nuclear factor kappa B (NF-κB), together with the inhibition of the TLR signaling pathway, including phosphatidylinositide 3-kinases/protein kinase B (PI3K/Akt) proteins and mitogen-activated protein kinases (MAPk) complex, which are essentials proteins involved in the process of inflammation (Yahfoufi *et al*., 2018).

The presence of fatty acids and polyphenols is primarily responsible for the immunomodulation capacity of vegetable oil. The main composition of the oil with immunosuppression properties is composed of oleic (ω-9), linoleic (ω-6), and α-linolenic (ω-3) acids, which are characterized as immunomodulator fatty acids. However, other substances present in lower concentrations, such as phenolic compounds, have been described as substances with properties able to modulate the immune system. So, this section will focus on the immunomodulatory activities of detached fatty acids.

PUFA plays an active role in inflammatory processes (Kwon, 2020), and ω-3 and ω-6 are the two main classes of PUFA which are obtained mainly from plants (canola, soybean, sunflower, and flaxseed) and fish oil. The primary ω-3 fatty acids are α-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid, while linoleic acid is the main ω-6 PUFA. These fatty acids are not synthesized in animals, so both fatty acids must be obtained from the diet. Once in the body, α-linolenic acid and linoleic acids can be converted into ω-3 PUFA and ω-6 PUFA, respectively. Still, only α-linolenic acid can be converted into eicosapentaenoic acid and docosahexaenoic acid (Cavalli *et al*., 2021). ω-3 PUFAs are preferred substrates for desaturase and elongase enzymes involved in eicosanoid biosynthesis (Ruiz-Lopez *et al*., 2015), favoring the production of anti-inflammatory eicosanoids from the higher intake of α-linolenic acid. Eicosapentaenoic acid and docosahexaenoic acid act as precursors of potent specialized pro-resolving mediators (SPM), such as protectins, resolvins, and maresins (Duvall and Levy, 2016), and their beneficial effects on health are related to the production of less potent pro-inflammatory mediators by preventing the conversion of arachidonic acid to pro-inflammatory eicosanoids or serving as alternative substrates.

The anti-inflammatory effects of α-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid are demonstrated in the literature with several studies. Rodríguez-Cruz *et al*. (2018) showed that supplementation with ω-3 long-chain PUFA in Duchenne muscular dystrophy patients increased eicosapentaenoic acid and docosahexaenoic acid concentrations in erythrocytes from the test group compared to the placebo group after six months. Further, the supplementation promoted a downregulation of the nuclear factor kappa B (NF-kB), interleukin-1 beta (IL-1β), and IL-6 expression compared to the placebo group. In addition, ω-3-PUFA intake decreased the serum levels of IL-1β and IL-6 and increased IL-10. *In vitro* models demonstrated that eicosapentaenoic acid and docosahexaenoic acid obtained from fish oil could modulate the presence of M2 (cells with anti-inflammatory hallmarks) in obese rat models, reducing the expression of pro-inflammatory genes (IL-6, TNF-α, MCP-1, IL-1β, and iNOS) while increasing the expression of anti-inflammatory genes (arginase-1, IL-10, Mgl-1) (Akinkuolie *et al*., 2011). Cell experiments showed that α-linoleic acid (10–60μM) inhibited the pro-inflammatory phenotype of M1-like macrophages and reduced the expression of IL-6, TNF-α, MCP-1, and IL-1β in LPS-stimulated human THP-1 cells (Pauls *et al*., 2018). Also, α-linoleic acid (10–200 mg/kg) improved LPS-induced cystitis in mice through the reduction in the expression of IL-6, TNF-α, COX-2, PLA2, and iNOS, inhibiting the activation of the NF-κB signaling pathway (Ok *et al*., 2020).

Hogenkamp *et al*. (2011) demonstrated the immunomodulation promoted by PUFA in two murine models: influenza vaccine in C7BL/6 mice and experimental allergy in BALB/c mice. The animals were fed vegetable oils (SFO and linseed), fish oil (salmon), and beef fat. The animals that ingested oil from the marine source had the best results in influenza immunization and showed fewer allergy symptoms. Although the linseed had similar concentrations of ω-3 PUFA to fish oil, the last had higher eicosapentaenoic acid and docosahexaenoic acid amounts. Using Th1 (C57BL/6) and Th2 (BALB/c), models demonstrated that ω-3 PUFA presents immunomodulating characteristics.

Oleic acid is an ω-9 monounsaturated fatty acid (MUFA) present in OO and is responsible for the beneficial effects observed in this oil (Casas *et al*., 2017). Oleic acid has been demonstrated to possess immunomodulatory ability, acting on T lymphocytes, neutrophils, and macrophages. The action on neutrophils has a dual role, depending on the model (stimulated or not stimulated*).* The oleic acid reduced cell migration in an *in vitro* LPS-induced model (Reyes-Quiroz *et al*., 2014). However, when applied isolated, oleic acid showed stimulatory characteristics on neutrophils, increasing ROS production in human and rat cells under *in vitro* assays (Carrillo *et al*., 2011). It also increased the release of vascular endothelial growth factor-α (VEGF) and IL-1β in rat neutrophils (Carrillo *et al*., 2011). The oleic acid action on macrophages seems to have an anti-inflammatory attribute once a diet rich in this MUFA elevates the levels of M2 macrophages (cells with anti-inflammatory hallmarks) in the adipose tissue of mice and increases the levels of M2 markers (CD206, MGL1, and ARG1) in RAW 264.7 macrophages *in vitro* (Camell and Smith 2013).

The action of poly and monounsaturated fatty acids could occur in human microbiota, indirectly reaching the immune system. A review showed that in addition to the biological activities, ω-3 PUFAs seem to impact the gut microbiome, mainly by three effects: altering the diversity and quantity of gut microorganisms, modulating the concentration of pro-inflammatory cytokines such as intereleukin-17, and altering the levels of short-chain fatty acids (SCFA) (Djuricic and Calder, 2022). This effect was demonstrated previously by Watson *et al.* (2018), who found that that ω-3 PUFA may be capable of interacting with the gut microbiota and changing the SCFA levels to modulate immune functions. In a randomized controlled trial, healthy participants with ω-3 PUFA supplementation resulted in increased quantities of *Bifidobacterium*, *Roseburia*, and *Lactobacillus*, known for their immunoregulatory properties. The decrease in intestinal bacteria diversity also affects gut dysbiosis, which are associated with neuroinflammation. So, a diet enriched with ω-3 PUFA can provoke an anti-inflammatory shift, leading to the prevention or amelioration of neuroinflammation (Kerman *et al.*, 2024).

4. EFFECTS OF VEGETABLE OILS ON THE IMMUNE SYSTEM

As explained above, vegetable oils are an essential source of ω-3 (α-linoleic acid) and ω-6 (linoleic acid) PUFAs, and ω-9 MUFA (oleic acid), all of which have prodigious immunomodulation activities. The various effects of vegetable oils on the immune system are explained in this section and summarized in Figure 1.

Different studies support and describe the beneficial role of OO in the prevention of cardiovascular disease and degenerative diseases, together with breast, skin, and colon cancers, as well as the benefits in the prevention and reduction of hypercholesterolemia, lipoprotein concentrations, atherosclerosis, hypertension, thrombotic risk, oxidation, oxidative stress, obesity, and type 2 diabetes (Cicerale *et al.*, 2012). These functions and immunosuppressive activity are attributed to oleic acid, the most predominant fatty acid in the OO formulation.

Studies have shown that ingesting extra-virgin OO could decrease inflammation markers such as IL-6 and C-reactive protein, demonstrating that consuming 50 mL daily for two or three weeks diminished these parameters (Camargo *et al.*, 2010). Widmer *et al.* (2013) described an improvement in endothelial function in a group ingesting 30 mL of pure extra-virgin OO and another group receiving a 30-mL extra-virgin OO supplement (epigallocatechin 3-gallate), with a significant reduction in inflammatory parameters and oxidative stress only in the group consuming the pure extra-virgin OO.

Puertollano *et al.* (2004) demonstrated that an OO-enriched diet could increase the levels IL-4 in mice sera after a challenge with *Listeria monocytogenes*, an intracellular bacterium. An augment in IL-4 activates the Th2 pathway response, showing an immunosuppressive effect of the OO ingestion, promoting better control of inflammation.

The beneficial immunosuppressive effects of OO were also observed in an autoimmune Systemic Lupus Erythematosus (SLE) animal model (Aparicio-Soto *et al.*, 2016). SLE mouse models were fed with SFO or OO. Animals treated with the OO diet significantly reduced the characteristic renal damage and decreased MMP-3 in the serum while decreasing PGE2 in the kidney. The production of the pro-inflammatory cytokines TNF-α, IL-17, and IL-6 in LPS-stimulated splenocytes was diminished compared to the SFO group. Further, the Nrf-2 and HO-1 protein expressions were up-regulated in those mice fed with extra-virgin OO, drastically facilitating the activation of JAK/STAT, MAPK, and NF-κB pathways. OO seems to possess anti-inflammatory effects, beneficiating the control of the exacerbated inflammation.

Chia seeds are rich in antioxidant properties, and the originated oil is a natural source of ω-3-fatty-acids and α-linoleic acid, containing α-linoleic, linoleic, and oleic acid (Kulczynski *et al.*, 2019). Using a rheumatoid arthritis rat model under obesity induced by a high-fat diet, Mohamed *et al.* (2020) showed that the oral intake of 300 mg of chia oil promoted a decrease in swelling, decreasing the volume of inflammation, as well as TNF-α levels in the plasma.

Chia oil is also associated with anti-inflammatory properties, as Cavalli *et al.* (2021), demonstrated. Compared to the non-treated animals, chia oil delayed the beginning of animal symptoms under an experimental model of multiple sclerosis known as EAE (experimental autoimmune enceph-

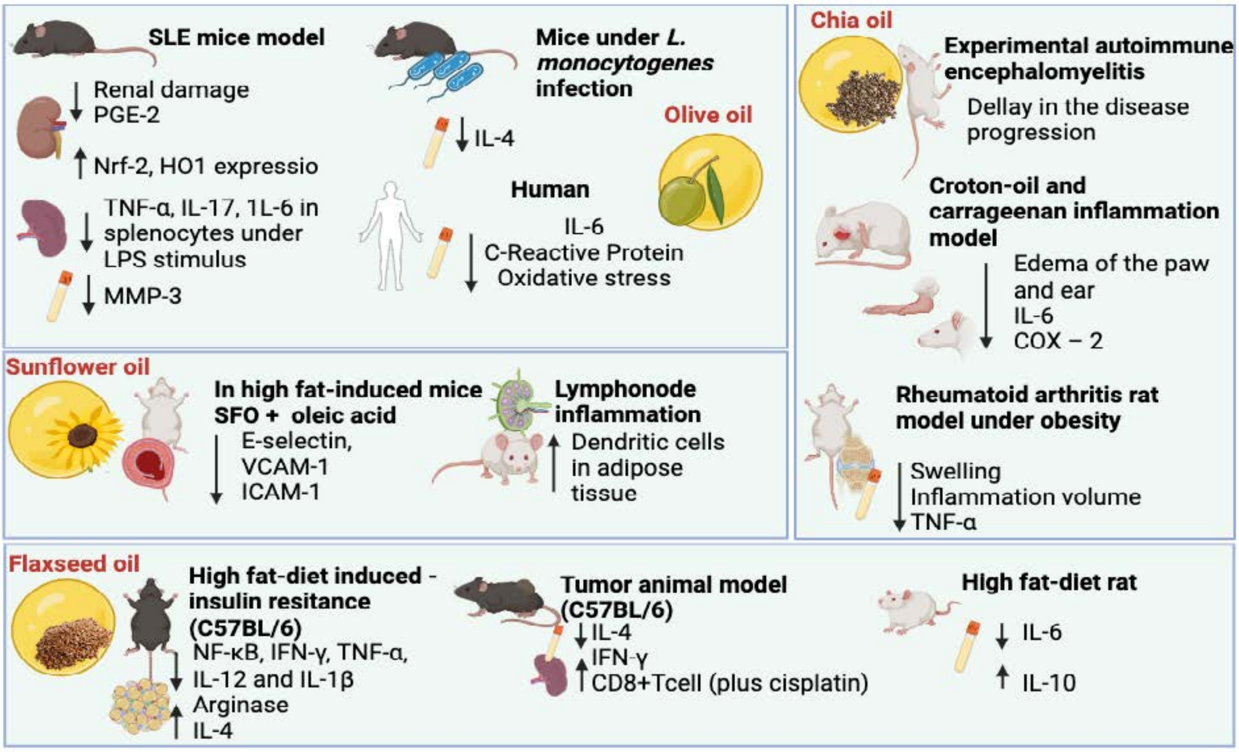

Figure 1. Immunomodulatory properties of vegetable oils. The information in this picture summarizes some of the characteristics presented in the text.
PGE-2 – prostaglandin 2; Nrf-2 - nuclear factor erythroid 2–related factor 2; TNF- tumor necrosis factor; IL – interleukin; LPS – lipopolysaccharide; MMP - matrix metalloproteinase; COX – cyclooxygenase; VCAM - vascular cell adhesion molecule; ICAM - intercellular adhesion molecule; NF-kB – nuclear factor kappa B; IFN – interferón.

alomyelitis). In croton-oil and carrageenan-induced inflammatory models, such as paw and ear edemas, the intake of chia oil, followed by the administration of a pro-inflammatory stimulus, promoted a reduction in several markers, demonstrating anti-edematogenic and anti-hyperalgesic effects. However, under nervous inflammation induced by carrageenan, the treatment with chia oil decreased the production of IL-6 and COX-2, promoting a reduction in inflammation.

The effects of SFO on inflammation have demonstrated dubious results. Despite the presence of linoleic acid (an ω-6 PUFA) in its composition, Masi *et al*. (2012) have shown that the supplementation with SFO in high-fat diet-induced obese mice did not decrease the inflammatory status, as it did not decrease IL-6 and TNF-α from peritoneal macrophages and the adipose tissue; however, supplementation with SFO improved the serum lipid profile in treated animals. In another study, rats were submitted to a higher cholesterol diet and supplemented with SFO or phenolic-enriched SFO. The concentration of E-selectin, VCAM-1, and ICAM-1 in the animals' aortas were evaluated and indicated that SFO or enriched SFO did not change the status of these molecules. However, when oleic acid was added to SFO, it improved its anti-inflammatory capacity, reverting the presence of E-selectin, VCAM-1, and ICAM-1 (Katsarou *et al*., 2015).

Also, mice under lymph node inflammation induced by LPS injection received chow supplemented with 20% SFO. The supplementation promoted an increase in dendritic cells in the adipose tissue of the animals compared to the animals that received plain chow (Mattacks *et al*., 2004). SFO has a more pronounced anti-inflammatory activity on topical use, with studies demonstrating benefits to wound healing (Lania *et al*., 2019; Vaughn *et al*., 2018).

Linseed (flaxseed) oil contains similar α-linoleic acid concentrations to fish oil and could be a vegetable source of ω-3 PUFA. The anti-inflammatory ability of linseed oil is evident, demonstrated experimentally and in clinical trials, as shown in high fat-diet (HFD) rats, with a reduction in the expression of IL-6 and an increase in IL-10 (Jordão Candido *et al*., 2019). In another animal model of HFD-induced Δ-6 desaturase knockout mice (preventing the metabolism of α-linoleic acid), Monteiro *et al*. (2013) confirmed that flaxseed oil containing α-linoleic acid could directly inhibit fat accumulation and inflammation response, demonstrating no need to be converted to EPA or DHA to be effective.

Using a tumor animal model with a C57BL/6 mouse, a research group showed that the treatment with flaxseed oil orally alone or together with cisplatin for 15 days did promote the regulation and balance of Th1/Th2 response, as the levels of IL-4 were reduced, but the IFN-γ was increased, compared to the mice treated only with cisplatin. Still, treating flaxseed oil and cisplatin promoted increased CD8+ T cells in the spleen (Deshpande *et al*., 2019).

Bashir *et al*. (2019) verified that the treatment of flaxseed oil in insulin resistance induced by high-fat resulted in a decrease in the expression of NF-κB, IFN-γ, TNF-α, IL-12 and IL-1β in the adipose tissue macrophages (ATM). While it presented an increase in the arginase-1 expression and IL-4 concentration, flaxseed oil still promoted a suppression in immune cell migration to the adipose tissue.

5. CONCLUSIONS

The importance of vegetable oils in the population's diet worldwide is proven. In addition, these oils have been shown to benefit consumers, such as the balance of the lipid profile, cardiovascular improvements and decrease in blood pressure, along with healing effects when used topically. Most of these benefits come from the immunomodulatory effects of vegetable oils, mainly the anti-inflammatory activities triggered by the unsaturated fatty acids present in these oils. However, despite the large number of clinical studies available on the prevention of cardiovascular events, these studies did not conclude categorically the full therapeutic efficacy of PUFAs and MUFA. Thus, it is essential to characterize and understand the effects of vegetable oils on the immune system, especially those with high concentrations of PUFA and MUFA.

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The authors declare that they have no financial, professional or personal conflicts of interest that could have inappropriately influenced this work.

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AUTHORSHIP CONTRIBUTION STATEMENT

D. P. Tres: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft. S. T. Nicolau: Formal analysis, Investigation, Methodology, Writing – original draft. T. S. Ayala: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. R. A. Menolli: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing.

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