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An Overview of the Modulatory Effects of Oleic Acid in Health and Disease

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Abstract: Evidences in the last years have showed the effects of oleic acid (OA) in human health and disease. Olive oil, rich in oleic acid, is supposed to present modulatory effects in a wide physiological functions, while some studies also suggest a beneficial effect on cancer, autoimmune and inflammatory diseases, besides its ability to facilitate wound healing. Although the OA role in immune responses are still controversial, the administration of olive oil containing diets may improve the immune response associated to a more successful elimination of pathogens such as bacteria and fungi, by interfering in many components of this system such as macrophages, lymphocytes and neutrophils. Then, novel putative therapies for inflammatory and infectious diseases could be developed based on the characteristics presented by unsaturated fatty acids like OA. Finally, the purpose of this work was to review some of the modulatory effects of OA on inflammatory diseases and health, aiming at high lightening its potential role on the future establishment of novel therapeutic approaches for infections, inflammatory, immune, cardiovascular diseases or skin repair based on this fatty acid mainly found in the Mediterranean diet.

Keywords: Oleic acid, modulatory effects, cancer, autoimmune and inflammatory diseases, wound healing.

INTRODUCTION

The concept that specific fatty acids (FA) are necessary for an appropriate growth of animals including humans was first introduced by Burr and Burr in 1929, when Wistar rats were deprived of dietary fat and there was an occurrence of a "new deficiency disease" involving caudal necrosis [1]. However, until 1960s the importance of essential fatty acids for human health was poorly considered. Their relevance was primary highlighted in studies which described signs of clinical deficiency in infants fed skimmed milk-based formula [2] or in neonates receiving a fat-free parenteral nutrition [3, 4]. Therefore, based on a nutritional classification, fatty acids that are not synthesized by humans and are indispensable for development and health are known as essential while those produced by humans are classified as non-essential fatty acids. In this context linoleic and alpha-linolenic acids are polyunsaturated fatty acids (PUFA) classified as essential while monounsaturated fatty acids (MUFA) are classified as non-essential [5].

The fatty acid classification in MUFA or PUFA is based on the hydrocarbon bonds in their structural composition. When a fatty acid has no double bonds in the hydrocarbon chain it is named saturated fatty acid (SFA) and when it has one or more double bonds it is classified as MUFA or PUFA, respectively [6, 7]. Therefore, arachdonic acid [AA, C20:4 (ω-6)], linoleic acid [LA, C18:2 (ω-6)], docosahexanoic acid [DHA, C22:6 (ω-3)], eicosapentanoic acid [EPA, C20:5 (ω-3)] and linolenic acid [LA, C18:3 (ω-3)] are examples of PUFA while oleic acid [OA, C18:1 (ω-9)] is a MUFA, a non-essential fatty acid that has been recently described as a regulator of immune function and health.

MUFA contribute to dietary fat consumption in many parts of the world and in Mediterranean area it constitutes at least one third of the total fatty acid intake [8]. Olive oil is one of the most used culinary fat in Mediterranean diet [9] being mainly composed by the MUFA oleic acid (OA), which represents 70-80% of olive oil composition, besides minor phenolic compounds [10]. In the last years many studies described the contribution of olive oil to general health, partly due to its high OA content [11-17], which was demonstrated to lead to a reduction in cholesterol levels, atherogenesis risk [5, 18-21], host versus graft response [22], blood pressure and daily anti hypertensive drug intake [23]. In addition OA was demonstrated to induce beneficial anti-inflammatory effects on autoimmune diseases [24, 25], protective effect on breast cancer and improvement of immune system function [26-30]. Then, these well-documented properties reinforce the importance to a better understanding of the mechanisms of action and physiological changes caused by oleic acid intake, especially in human health.

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MODULATION OF LEUKOCYTES ACTIVITY AND INFLAMMATORY PROCESS

A full and effective immune response to a host threatening stimuli requires diverse and complementary mechanisms of inflammation, cell activation, antibody production and effector reactions, which include innate immune components like granulocytes, natural killer cells, macrophages and their soluble mediators, along with a more specialized adaptive lymphocyte response. Therefore, some evidences suggested that dietary lipids influence the activity and function of numerous immune system components. These changes comprise the modulation of innate and adaptive responses including antigen presentation, lymphocyte proliferation, cytokine production, granulocytes and natural killer cell activity that may be modified by unsaturated fatty acids [31, 32]. So far, many mechanisms have been proposed to explain the relationship between different fatty acids intake and the immune system modulation both in humans and experimental animals.

Regarding innate granulocytes function, an increase in reactive oxygen species (ROS), that is essential for neutrophil microbicidal activity, was observed in patients who received olive oil emulsion when compared to those who were given soybean oil emulsion [33, 34]. However, no effect of olive oil emulsion was observed in other inflammatory and immune parameters such as erythrocyte sedimentation rate, production of C-reactive protein, TNF-α, IL-6, IL-8 and soluble receptors for IL-2 in humans [35]. Furthermore, the olive oil intake did not change the mitogen stimulated human lymphocytes proliferation while in rats there was an inhibition of this parameter. Indeed, feeding laboratory rodents a diet rich in olive oil resulted in the suppression of natural killer cell activity (Fig. **1**) [36], mitogen stimulated proliferation [37, 38] and the expression of receptors for IL-2 and transferrin [37] in spleen lymphocytes. These differences were probably due to the higher olive oil content provided to the experimental animals that had reduced proliferation when fed diets containing a range of 35.6-71.6% of olive oil (approximately 60-130 g/Kg) in the total fatty acids while humans received only 18.4% of olive oil content [39, 40]. Thus, in middle aged men who consumed either a control diet or a diet containing foods enriched in highly refined olive oil for 8 weeks there was no change in proliferation of either whole blood cultures or peripheral blood mononuclear cells in response to concanavalin A (Con A) [39].

However, contradictory findings are reported in the literature regarding the effects of OA on immune function. Cury-Boaventura *et al.* demonstrated that an olive oil-based emulsion given to healthy volunteers led to decreased *ex-vivo* lymphocyte proliferation (Fig. **1**), besides having no effect on neutrophils [33]. Additionally, studies conducted in rats suggested that an olive oil emulsion, rich in OA, had no effect in the inhibition of interleukin-2 (IL-2) receptor expression [41], IL-2 production by lymphocytes, bacteremia [42], chemotaxis, migration or pro-inflammatory cytokines released by neutrophils [43], while these effects were observed with soybean emulsion administration [33]. Then, the modulatory role of OA on the immune response seems to be dependent on the amount and the content of fatty acid received by the subjects, animal species or the immune parameter evaluated, although most studies provide strong evidences for a relevant participation of this MUFA in the immunity control. Moreover, further comparisons among the effects of olive oil, safflower oil and a high OA sunflower oil on the immune cell functions suggested that the effects observed were due to OA rather than to the non lipid component of olive oil [44].

Adhesion molecules are also implicated in the immune responses, by interfering with the immunological synapse formation and trans endothelial migration of leukocytes to the antigen site in the inflammatory reactions. These molecules also mediate leukocyte traffic to synovial fluid and tissue in rheumatoid arthritis (RA), as well as the formation of atherosclerotic plaques dependent on the leukocyte endothelium interaction in cardiovascular diseases [8]. A study using human saphenous vein endothelial cells (HSVEC) preincubated with arachidonic acid (AA), eicosapentanoic acid (EPA), docosahexaenoic acid (DHA) or OA prior to stimulation with TNF-α showed that OA and DHA significantly decreased the expression of vascular cell adhesion molecule-1 (VCAM-1) by HSVEC (Fig. **1**) [45]. Other studies showed a decreased expression of the adhesion molecules CD2, ICAM-1 and LFA-1 on spleen lymphocytes of rats fed olive oil (Fig. **1**) and fish oil containing ω-3 PUFA [22]. In addition, middle-aged men fed a diet with 18.4% content in MUFA showed a decreased expression of the leukocyte adhesion molecule ICAM-1 in the peripheral blood mononuclear cells, after 2 months of diet consumption, when compared to values from a normal diet control group [39]. Furthermore, healthy men and women living in a religious community were subjected to different fat content in diet during four consecutive dietary periods differing in the fat content of saturated fatty acid, MUFA, linolenic (ω-3) and linoleic (ω-6) PUFA. There was a lower monocyte adhesion to endothelial cells and the resistance of low-density lipoprotein (LDL) to oxidation was greatest during the MUFA period (Fig. **1**) [46].

Besides basic studies, several pre-clinical and clinical trials have also reported the beneficial effects of OA consumption in the immune response, especially in autoimmune diseases. By evaluating the effects of fish oil on the severity and progression of active human RA, Kremer *et al.* observed that olive oil, used as a placebo in these experiments, had unexpected beneficial effects on the improvement of clinical aspects of the disease, once this treatment was associated to decreased macrophage IL-1 production after stimulation with Con A, although not to the same extent as to the fish oil group supplemented with EPA or DHA [25]. Linos *et al.* [24] also demonstrated some beneficial anti-inflammatory effects of OA consumption on RA, comparing the relative risk of disease development in relation to lifelong consumption of olive oil (almost every day) in a Greek population. This population was four times less likely to develop RA when compared to those who consumed olive oil less than six times per month [24]. In recent years olive oil/OA has been experimentally used to treat inflammatory bowel disease (IBD) induced experimentally by dextran sodium sulphate (DSS). Borniquel *et al*. [47] by giving OA and a nitrated oleic acid (OA-NO_2) subcutaneously to DSS treated mice observed both *in vitro* and *in vivo* the

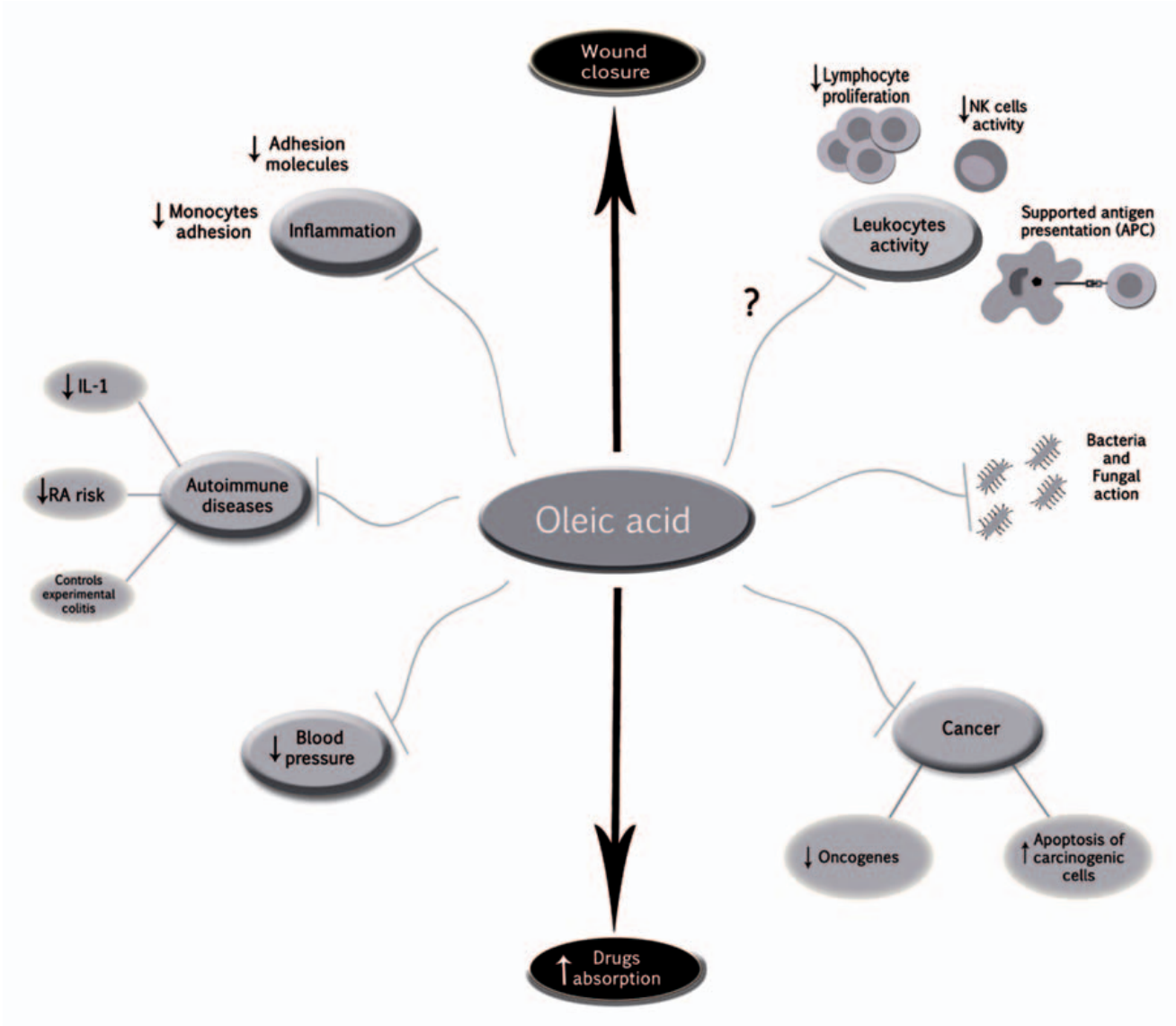

Fig. (1). Summary of oleic acid (OA) effects and actions. Highlighted in black are conditions in which OA acts as enhancer such as in wound closure or drugs absorption. In light grey, the effects of oleic acid in the reduction of inflammation, modulation of leukocytes activity, enhancement of bactericidal and fungicidal action, inhibition of cancer proliferation and oncogenes expression, reduction of blood pressure and attenuation of the effects of autoimmune diseases. Note that the real role of OA in leukocytes activity is still a matter of debate.

ability of OA-NO_2, better than OA, to improve inflammation and clinical score in this experimental intestinal inflammation (Fig. **1**). It is important to note that OA-NO_2 is a product of unsaturated fatty acids, known as nitroalkene, that is endogenously produced [48, 49] and has anti-inflammatory properties due to its interactions with numerous pathways such as nuclear factor-κB (NF-κB) or signal transducer and activator of transcription (STAT) [50]. Nitroalkene was already described as a strong activator of peroxisome proliferator-activated receptor γ (PPAR γ) in IBD [51]. In another study in which mice were fed different oils it was observed a lower mortality, lower clinical/ macroscopic intestinal inflammation score and a reduction in the activity of COX-2 and iNOS in olive oil fed group, when compared to sunflower oil fed mice [52]. Altogether, these findings indicate that olive oil or OA present well-defined anti-inflammatory effects on autoimmune and chronic inflammatory diseases.

HEALING OF CUTANEOUS WOUNDS

Tissue wounds also trigger various cellular events based on inflammation like cell migration, angiogenesis, extracellular matrix deposition and re-epithelialization [53]. Thereby, many biological mediators are necessary to control these different processes, like nitric oxide (NO), which is important to skin wound healing since it influences the functions of fibroblasts, macrophages and keratinocytes during the healing process [54]. Inhibition of NO synthesis induces the release of some mediators by fibroblasts and inflammatory cells which then causes the reduction on collagen deposition at the site of the wound [55].

MUFA and PUFA can be therapeutically used as an option to treat cutaneous wounds. Regarding NO, OA treatment inhibited its early production in contrast to ω-6 and ω-3, which induced higher levels of NO in experimental skin wounds, respectively, at 48h and 3h post surgery [56]. These authors also demonstrated that after 5 and 10 days of treatment of surgically induced skin wounds in mice, the group treated with OA showed smaller wounds area mainly when compared to ω-3 treated group (Fig. **1**). Moreover the OA and the ω-6 groups had less edema at 48 hours when compared to control. On the other hand, after 5 days of treatment, the ω-3 group showed greater edema and thicker clot cover than ω-6 or OA treated groups. The treatment with ω-3 induced increased amount of connective tissue fibers deposition in the wounds site, although OA favored tissue repair [56].

More recently, Cardoso *et al.* [57] demonstrated in BALB/c mice with surgically induced skin wounds, that at 120 h after surgery there was faster wound closure, elevated levels of collagen III mRNA, tissue inhibitor of metalloproteinase (TIMP1) and metalloproteinases-9 (MMP9) in OA treated group in comparison to ω-3 and control groups. Moreover in OA group there were lower levels of cyclooxygenase-2 (COX-2) expression, which is important for the production of pro-inflammatory mediators, when compared to ω-3 treated wounds. The OA treated group also presented an increased gene transcription for TNF-α, IL-10 and IL-17 when compared to ω-3 and control groups, especially at 120 h post surgery. The wound inflammatory infiltrate was also investigated and there was a less prominent detection of $CD11b^+$, $CD4^+$ and $CD8^+$ cells in OA treated group [57], thus demonstrating that this MUFA may actually influence the skin inflammatory process and thus wound repair. Additionally, another study showed that OA exerts pro-inflammatory effects on wound healing as observed by increased neutrophil migration to the lesions, protein and DNA contents, besides the stimulation of mediators release by neutrophils such as VEGF- α and IL-1, thus accelerating the wound healing process [58]. This same group showed recently that oral administration of OA to rats with skin wounds led to an initial NF-kB activation and increased TNF-α production 1h after tissue injury with a reduction in pro-inflammatory cytokines 24h later, suggesting an acceleration of the inflammatory phase of wound healing after OA oral administration [59]. Therefore, these studies suggest that OA modulate or have a beneficial effect on wound closure that is an inflammation-dependent phenomenon.

OLEIC ACID IN THE IMMUNE RESPONSE TO INFECTIOUS AGENTS

The effects of OA in the immunomodulation of infectious diseases are far less investigated than those from other fatty acids like PUFA. Even though, several studies have tried to elucidate the possible benefits of olive oil intake on infectious events [60-64]. It is known that the cytokines released during an infectious or inflammatory response, apart from modulation of the immune system, bring about enhanced lipolysis, gluconeogenesis, muscle proteolisis and redistribution of tissue zinc in order to provide substrate for cells of the immune system and amino acids for the synthesis of acute-phase proteins [21]. However, although excess inflammatory reactions may help in the pathogen elimination, it can also lead to extensive tissue damage.

Regarding the putative immunomodulatory actions of fatty acids, some studies have investigated the inflammatory response to TNF-α administration or to *Escherichia coli* endotoxin in rats previously treated with corn, fish, coconut, olive oils or butter (rich in OA). The results demonstrated that especially in groups treated with OA, a suppression in tissue zinc content, liver protein synthesis and serum ceruloplasmins levels was achieved when compared to a corn oil diet or standard laboratory chow [19, 21].

Listeria monocytogenes is a gram-positive facultative intracellular bacterium that can cause severe infections, especially in immunocompromised hosts, pregnant women, newborns and elderly, reaching mortality rate of 20% or higher. The murine infection with *L. monocytogenes* is a well-characterized model for understanding cellular immunity against intracellular bacteria [65, 66]. Puertollano *et al.* [67] demonstrated in mice experimentally infected with *Listeria monocytogenes* and fed a diet rich in olive oil a better immune response to this bacteria as well as a faster elimination of the infectious agent along with a lower mortality rate when compared to a group that had received fish oil. They also demonstrated an improved macrophage capability to destroy these pathogens in the olive oil group (Fig. **1**). Moreover, when these animals were reinfected with *Listeria monocytogenes* the secondary immune response in olive oil group was more effective than in fish oil treated-mice [67]. Additionally, mice infected with *L. monocytogenes,* which uses spleen as a supportive environment to survival [68] and fed fish oil presented a significant increase in spleen weight at 72 hours after secondary infection, whereas there was a significant decrease in the olive oil fed group at the same period evaluated [66]. It was also observed elevated levels of serum ICAM-1 and VCAM-1 in mice experimentally reinfected with *Lysteria monocytogenes* and fed olive oil or high oleic sunflower oil when compared to fish oil fed group. These results could suggest a relevant effect of olive oil in the spleen leukocyte accumulation or bacteria clearance, in comparison to other dietary fats. In addition, another study demonstrated that olive oil presents bactericidal activity against *Helicobacter pylori*, the main causative agent of gastric ulcers which may also be related to gastric cancers development [69].

Considering fungal infections, mice submitted to isolation stress showed a temporarily delayed clearance of *Paracoccidioides brasiliensis,* especially when their diets were enriched in olive oil in comparison to soybean oil [70]. Thereby, olive oil seems to be less effective in the attenuation of the stress-induced effects on host defense against this fungus than soybean oil. It is important to note that psychological stress, just as the isolation stress, is related to alterations in many aspects of immune response, such as decreased activity of natural killer (NK) cells, increased metastasis of tumors transplanted into mice [71], reduced mitogen-stimulated lymphocytes proliferation and abnormal production of cytokines by these cells [72].

Besides modulating cell fatty acid content and *paracoccidioidomycosis*, dietary lipids can alter innate

immune functions that are also essential to pathogens control. Monocytes and macrophages are able to phagocyte microorganisms and kill them as an important first line cell defense [73]. In this context, Martins de Lima-Salgado *et al.* [74] observed that high OA content *in vitro* can increase the fungicidal capability of macrophages infected with *Candida albicans* when compared to other fatty acids such as palmitic acid and linoleic acid. The authors also demonstrated that OA induces a sustained effect on reactive oxygen species (ROS) production and this may be related to the increased fungicidal activity observed in cells treated with OA.

Overall, the findings above suggested that OA may be beneficial to patients suffering from diseases that require a more efficient pathogen control, such as in bacteria or fungal infections (Fig. **1**).

EFFECTS OF OLEIC ACID ON CANCER

Different epidemiological surveys pointed to the lower incidence of cancer occurrence in Mediterranean when compared to Scandinavian countries, the United Kingdom and the United States, especially those that involve the intestine, breast, endometrium, skin and prostate [75-79]. One of the most important findings related to such observations was associated to Mediterranean dietary habits, especially the low consumption of meat and high consumption of fruits, vegetables and mainly olive oil, rich in OA [80]. Furthermore, high OA and olive oil consumption was already associated to a reduction in the cancer risk development (mainly breast, colorectal and prostate cancer) (Fig. **1**), while diets rich in total fat and linoleic acid or saturated fatty acid were related to an increased cancer risk [81].

Llor and Plons [82] developed some *in vitro* studies to evaluate the effect of olive oil and/or OA on colorectal cancer cells and found that olive oil induced apoptosis, cell differentiation and down regulated the expression of COX-2 and Bcl-2 (Fig. **1**), which are associated to inflammation and apoptosis. It was not demonstrated that OA has direct effects on COX-2 or Bcl-2 in this study, but the authors showed a specific induction of apoptosis in HT-29 cells [82]. Olive oil consumption also influences the initiation, promotion and progression of carcinogenesis and in these cases tumors achieved a lower degree of clinical and histopathological malignancy [83, 84]. In accordance, OA was demonstrated to play an important chemoprotection role on breast cancer cell lines. The *in vitro* treatment of breast cancer cells with OA suppressed the oncogene Her-2/neu expression that is overexpressed in approximately 20% of breast carcinomas and encode the oncoprotein p185 Her-2/neu which controls, in normal cellular conditions, many cell functions such as cell differentiation, proliferation and apoptosis. A deregulation on this protein expression enhances the risk of cancer development. Moreover, the OA capability to act synergistically with the monoclonal antibody trastuzumab, used as a therapeutical drug on cancer by targeting $p185^{Her\text{-}2/neu}$, was already described by Menendez *et al.* [85].

INFLUENCE OF OLEIC ACID ON NUTRITION AND METABOLISM

Some patients, mainly those who are hospitalized and require intravenous nutrition therapy need adequate energy sources which may be provided by essential fatty acids, thus preventing metabolic disturbances associated to intravenous feeding of amino acids and glucose [86-88]. The first well-tolerated lipid emulsion was based on soybean oil, which is composed mainly by ω-6 PUFA (linoleic acid) [33]. This emulsion showed significant immunomodulatory effects in patients treated with parenteral nutrition then increasing their susceptibility to infection [61, 89-93]. One possible mechanism by which lipid emulsion can cause these side effects may be the induction of leukocyte death [94-97]. Therefore, other lipid emulsions did not induce this immunosuppressive effect and constituted an alternative to intravenous emulsion content. Thus, although many reports point to the modulatory role of OA on the immune system as discussed before, emulsions containing olive oil have been suggested to offer an immunologically neutral alternative to soybean emulsion for use in parenteral nutrition [35, 41-43, 98, 99].

On the other hand, one of the most important cytokines usually found in metabolic inflammatory process is TNF-α, which is produced by a wide range of leukocytes in inflammatory conditions, as well as by the adipose tissue cells. This cytokine is thought to play a central role in the metabolic syndrome development, which is characterized by the presence of three or more metabolic disorders, such as high blood glucose, low high-density lipoprotein cholesterol (HDL-c), high blood pressure, high serum triglycerides (TG) levels and abdominal obesity [100-103]. In this case, TNF-α leads to increased insulin peripheral resistance, inhibition of its secretion and promotion of inflammation [104-110]. A positive correlation between increased TNF-α in type II diabetes patients and the development of inflammatory process in muscle fibers was already demonstrated in skeletal muscle biopsies [111]. In this context, the potential of OA to exert pleiotropic effects such as the induction of insulin production and inhibition of TNF-α action was demonstrated by *in vitro* studies using a rat pancreatic cell lineage which displays glucose dependent insulin secretion (INS-1 cells), in response to a culture medium containing high glucose levels [112]. The molecular mechanism by which OA exerted its role in the reversion of TNF-α action is quite varied and PPAR-γ receptor may be involved, since it is known that fatty acids and its metabolites are activators of PPAR-γ, besides being able to ameliorate the inflammatory effects of TNF-α [1]. Furthermore the translocation of PPAR-γ to the nucleus is though to mediate the anti-inflammatory properties of fatty acids [112]. Thus, OA may present potential applications and benefits in human health regarding the prevention of metabolic and nutrition disturbances in a selective group of patients.

BLOOD PRESSURE AND CARDIOVASCULAR DISEASES

The protective action of OA regular intake on health risk parameters, especially in cardiovascular disease, is mainly reported in the Mediterranean area, where people's diet is associated to elevated MUFA intake due to higher consumption of olive oil [113, 114]. So far, the potential of OA to ameliorate cardiovascular risks may be associated to an improvement of serum lipoprotein profile (HDL-to-LDL) in patients with hypercholesterolemia [115, 116], besides an

enhanced endothelial function due to an increase in flow-associated vasodilatation in hypercholesterolemic patients [117] and reduction in inflammation and oxidative stress [118]. Subsequently, there is a diminishment in the anti-hypertensive drugs consumption and in the occurrence of degenerative diseases [119-123] together with a better blood pressure control both in humans [124] and rats fed a diet rich in OA (Fig. **1**) [125, 126].

The α and β adrenergic receptors are essential in controlling central and peripheral blood pressure and these pathways can be regulated by OA [127] because of its effects on cell membrane structures [127, 128]. For some time, the action of olive oil on blood pressure control was considered to be due to the properties of less representative compounds of this oil such as α-tocopherol, polyphenols and other phenolic substances [23, 129-132]. However, Terés *et al.* [14] demonstrated *in vivo*, that the high OA content in olive oil and not its minor compounds, are responsible for the normotensive effects attributed to olive oil consumption, both in chronic and acute experimental treatments using olive oil (Fig. **1**) [14]. Furthermore, this MUFA may act through modulation of membrane lipid structures and cell signaling platforms, with additional regulation of the α2-adrenergic receptor pathways that involve G protein-dependent signaling and results in blood pressure control [127]. Then, the specific molecular mechanism by which OA controls blood pressure involves its ability to modulate the structure of plasma membrane lipids due to a regulatory pathway associated to the inhibition of G proteins both *in vivo* (in humans) and *in vitro* (cell culture) [127, 133]. Indeed, higher levels of MUFA on cell membrane can regulate the localization, activity and the expression of other important signaling molecules raising the production of vasodilator stimuli (cAMP and PKA) and reducing the action of vasoconstrictor pathways (inositol-triphosphate, Ca^{+2}, diacylglycerol and Rho kinases) [133]. To date, membrane lipids and G proteins levels are altered in experimental models [134, 135] and in hypertensive subjects [136, 137], especially after a long-term exposure to olive oil diet [138].

Fibrinogen higher levels have already been described as an independent cardiovascular risk factor [139] due to its association to the inflammatory process, initiation of atherogenesis and growth of atheromatous lesions [140]. Likewise, elevated fibrinogen was reported in coronary, cerebral disease and peripheral arteries [141]. Then, in a double-blind crossover study, Oosthuizen *et al.* (1994) reported a lowering of plasma fibrinogen levels in women who received fish or olive oils with high baseline fibrinogen concentrations [142]. Conversely, another study reported no significant difference between fish oil supplements and an olive oil placebo in preventing restenosis after coronary angioplasty [143].

CELL MEMBRANE FLUIDITY AND CUTANEOUS EFFECT ON DRUGS ABSORPTION

Fatty acids in general can change the cell membrane fluidity as well as its surface receptors. Several cell surface proteins form complex with cell membrane receptors and as a consequence, many cell functions like those mediated by MHC expression or cell adhesion molecules are regulated. Then, the initial events of cellular activation and signal transduction in specialized cells, including leukocytes, occur in cell membrane defined areas called lipid rafts [67]. Lipid rafts are cellular membrane areas composed by sphingolipids and cholesterol phospholipids [144]. This area acts as an exclusive site that helps receptors to function and trigger or sustain cell activation (intracellular signaling pathways) [67], influence on the entry of pathogen in the cell and cytoskeletal organization [145]. Shaikh *et al.* [146] suggested that unsaturated fatty acids may affect lipid raft structure and function by modifying lipid separations [146]. In addition, Ehehalt *et al.* [147] demonstrated that FA uptake is closely related and depends on lipid rafts integrity. These authors also showed a close relationship between lipid raft cholesterol content and FA levels observing an inhibition of FA uptake greater than 50% by decreasing cellular cholesterol levels [147].

Alternative routes to oral or systemic treatment of a wide range of diseases, especially those that require the use of anti-inflammatory drugs are of great interest due to the occurrence of hepatic or systemic side effects [148]. In this context, Moreira *et al.*, showed that OA enhances (Fig. **1**) the skin distribution and penetration of Lumiracoxib, by increasing its local retention both in dermis and epidermis, thus leading to a gradual and dose dependent drug absorption. To note, Lumiracoxib is a selective non-steroidal anti-inflammatory (NSAI) drug developed for the management of chronic and acute pain through the inhibition of COX-2 activities [149]. Furthermore, El Maghraby *et al.* demonstrated that OA has the ability to penetrate on stratum corneum by disrupting the intercellular lipid structures [150], a fact that could explain its action on skin physiology and drugs absorption.

By investigating the role of OA on NSAI drugs absorption, others observed that these FA, when administrated as patches in a membrane controlled transdermal drug delivery system, may provide the maximum permeability capacity to ketoprofen when compared to other permeation enhancers such as polyethylene glycol 400 and propylene glycol [151]. On the other hand, Santoyo & Yqartua using piroxicam, which is also classified as a NSAI, showed that a skin pretreated with OA has adequate drug absorption but not better than linolenic acid pretreated skin. In addition, despite the retention of drugs into the skin they demonstrated that FA pretreatment, with no differences between them, retains 3 times more drug than no pretreated skin [152]. Similarly, Larrucea *et al.* (2001) showed an enhanced capability of OA to improve percutaneous permeability to tenoxicam after skin pretreatment [153]. These data are in agreement with those from mice studies, in which Gwak & Chun (2002) observed and enhanced capability of OA to improve permeability to tenoxicam [154]. Moreover, OA when associated to diclofenac induced a higher permeation-enhancing effect than that induced by saturated fatty acids such as palmitic acid in rats skin [155].

CONCLUSION

In summary, this review demonstrated that OA, which is naturally found in olive oil and is a major component of the Mediterranean diet, presents different properties that can be

useful both in the immunomodulation, treatment and prevention of different types of disorders such as cardiovascular or autoimmune diseases, metabolic disturbances, skin injury and cancer, besides exerting proeminent role in drug absorption. However, further studies are still necessary and should be conducted in order to better clarify the properties of this fatty acid in human health and disease, as well as to provide scientific basis for the future establishment of novel therapeutic approaches for such disorders based on this MUFA.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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Declared none.

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