

Significance of olive oil in the host immune resistance to infection

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The effects exerted by polyunsaturated fatty acids (PUFA) on immune system functions have been investigated in recent years. These studies have reported the important role that *n*-3 PUFA play in the diminution of incidence and severity of inflammatory disorders. Nevertheless, less attention has been paid to the action of monounsaturated fatty acids (MUFA) upon the immune system. The administration of a diet containing a high amount of olive oil in experimental animals produces a suppression of lymphocyte proliferation, an inhibition of cytokine production and a reduction in natural killer (NK) cell activity. Despite these alterations in immune functions, it has been reported that olive oil-rich diets are not as immunosuppressive as fish oil diets. An important aspect in immunonutrition is focused on the relationship between fats, the immune system and host resistance to infection, particularly when these nutrients are supplied to patients at risk of sepsis. Different studies have determined that olive oil-rich diets do not impair the host resistance to infection. Therefore, olive oil constitutes a suitable fat that may be applied in clinical nutrition and administered to critically ill patients. In the present review, we summarize the current knowledge on olive oil and immune system functions, the biological consequences derived from the administration of diets containing olive oil and the impact of olive oil on immune defence.

Olive oil: Immune system: Host resistance

Epidemiological studies supported by experimental data from both animals and humans, have made a significant contribution to increasing knowledge of the relationship between diet and the immune system, considering nutrient intake as a critical determinant of immunocompetence¹. This association was confirmed after the recognition of long chain *n*-3 polyunsaturated fatty acids (PUFA) as nutrients that participate in the regulation of immune system functions². Olive oil, a fundamental constituent of the Mediterranean diet, is also able to modulate the immune system, since it contains numerous components that possess some biological activities. Olive oil has been associated with the suppression of different immune functions, although less attention has been paid to the effects of monounsaturated fatty acids (MUFA), compared with PUFA, upon the immune system. Classically, MUFA have been considered as neutral fatty acids and have often been applied as placebo in studies investigating the anti-inflammatory properties of other fatty acids³. Overall, the action of MUFA on the human immune system has allowed their application in the resolution or attenuation of diseases characterized by inflammatory disorders^{4,5}, in the reduction of cancer risk⁶ and in clinical nutrition⁷. This article will summarize the current state of knowledge concerning the effects and interactions of olive oil on immune system functions, as well as the action of this fat in the preservation of host immune defence.

Immunomodulation by fatty acids

Since the 1970s, a number of epidemiological studies have suggested that certain dietary fatty acids (particularly long-chain *n*-3 PUFA contained in oily fish and fish oils) affect the immune response in both animals and humans.

Early studies in Greenland Eskimos indicated the low prevalence of inflammatory disorders in this population⁸, and the reduction of death from ischemic heart disease, in spite of the consumption of diets high in fat and cholesterol⁹, or the low incidence of cancer¹⁰. Despite their beneficial effects in the reduction of inflammatory disease prevalence, other studies have demonstrated that the administration of diets containing long-chain *n*-3 PUFA may contribute, at least in part, to the reduction of host resistance against infectious agents. Indeed, epidemiological investigations described a high incidence of tuberculosis in native Eskimos¹¹, who consume a great amount of *n*-3 PUFA. These data are illustrative of the potential action of certain fatty acids, and of the consequences derived from an excessive immunosuppression. Nevertheless, this aspect requires more detailed investigation, because several studies have also shown that the administration of diets containing fish oil improves immune defence against infectious microorganisms¹². It is possible that differences in experimental design may explain the disparities between studies.

Olive oil: a fat involved in the modulation of immune system functions

Olive oil is mainly composed of oleic acid, plus additional different chemical components such as sterols, alcohols, antioxidants, and other fatty acids (apart from oleic acid) of minor relevance. An interesting study examined the biological constituents of olive oil responsible for the modulation of the immune functions and revealed that the immunosuppressive effects attributed to olive oil are likely due to oleic acid rather than to other minor components of this fat¹³. However,

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a recent study has demonstrated that the polyphenolic substances contained in olive oil possess anti-inflammatory properties¹⁴.

Different studies investigating the effects of fatty acids on the immune system have demonstrated that a diet containing olive oil administered to animals is able to promote a significant reduction of lymphocyte proliferation in response to the mitogen concanavalin A (Con A)¹⁵. In contrast, human studies have produced conflicting results, where for example, the administration of a diet containing an increased amount of olive oil did not affect proliferation of mitogen-stimulated lymphocytes¹⁶. It is possible that the observed differences between animal and human studies may be attributed in part to the amount of MUFA administered. Thus, MUFA contributed approximately 25 to 30% of total energy in the animal studies, whereas diets constituted by MUFA supplied approximately 18% of total energy in human studies¹⁷. Although some animal investigations have reported a reduction of lymphocyte proliferation in response to Con A, we did not find a significant effect of olive oil on the proliferation of murine lymphocytes stimulated with either Con A or lipopolysaccharide (LPS)¹⁸. The specific factors that contribute to the contradictory results observed in both mice and humans should be elucidated in further research, which will help to explain the discrepancies in the findings published to date. However, it is important to note that other factors different from the amount of olive oil in the diet, such as ingestion of other types of nutrients, could undoubtedly be involved in the different experimental results observed between humans and animals.

Cytokine production is reduced after the administration of certain dietary lipids. These proteins regulate the growth and differentiation of different lymphocyte subsets and they activate and regulate cells that participate in the inflammatory response. Interleukin-2 (IL-2) is an important cytokine responsible for the proliferation of T-lymphocytes. Administration of diets containing olive oil for 8 or 12 weeks produced an increase in IL-2 production in mice^{19,20}. IL-4 production, a cytokine with anti-inflammatory functions was increased in mice after the administration of a diet containing olive oil for 4 weeks²¹. In contrast, the production of IL-10, a cytokine with similar functions to IL-4, was decreased after the administration of a diet containing olive oil, although the production of IL-10 was not different from that seen after feeding mice a low fat diet¹⁵. Finally, the concentration of IL-12, a cytokine that participates as a pro-inflammatory protein, was reduced in mice fed with diets containing olive oil²¹. Other cytokines are

produced mainly by monocytes/macrophages. The synthesis of these proteins is also modulated by the administration of a diet containing olive oil. Thus, IL-1 production was diminished, whereas TNF- α or IL-6 production were increased or not modified in mice^{22,23}. Overall, diets containing olive oil are also related to the suppression of cytokine production, but this effect is not as severe as that produced by the administration of a fish oil-rich diet.

Natural killer (NK) cell activity is modulated by the action of certain dietary lipids. NK cells constitute a central lymphocyte subset found in blood and spleen that destroy virus-invaded cells or transformed cells. In animal studies, the administration of an olive oil diet reduced NK cell activity²⁴. Comparison of data among animals fed different amounts of oleic acid showed a linear negative relationship, indicating that oleic acid is responsible for a reduction of NK cell activity in rats²⁵. In fact, this activity is significantly reduced in mice fed with an olive oil diet after receiving LSTRA tumor transplantation (an ascitic Moloney virus-induced lymphoma), although the greatest suppression was observed in mice fed with a fish oil diet²⁶. Once again, human studies have not confirmed the animal results; the measurement of NK cell activity after the administration for one or two months of a diet containing olive oil did not show significant differences from the control group, although the activity of these cells declined after two months of consuming of this diet¹⁶.

Consequences derived from the administration of a diet containing olive oil in the modulation of the immune system

Resistance to infectious agents

Several lines of evidence have demonstrated that the suppression of immune system functions exerted by certain dietary lipids may cause a reduction of host resistance to infection^{27–30}. Obviously, available data only refer to experimental animals, and the effect of dietary lipids that may specifically modulate host defence to infectious pathogens in healthy humans has not been clearly established (see Tables 1 and 2). As previously described, early epidemiological studies reveal that the consumption of diets containing very high amounts of long chain *n*-3 PUFA increases the risk of infection and the incidence of tuberculosis in native Eskimos¹¹, despite the beneficial effects in the reduction of inflammatory disorders^{4,8}. Subsequently, experimental studies have demonstrated a significant reduction

Table 1. Summary of human studies examining the effects of olive oil on immune system function

Study characteristics	Findings of the study	References
Administration of a diet containing olive oil (18.4% of energy) to healthy middle-aged men for 2 months	Unmodified PBMC proliferative response. Suppressed NK cell activity. Reduced ICAM-1 expression.	16
Risk factors for rheumatoid arthritis in elderly subjects	Risk decreased by high consumption of olive oil	5
Administration of olive oil (6.8g oleic acid/d) to patients suffering from rheumatoid arthritis	Altered in immune function associated with beneficial effects on the progression of rheumatoid arthritis	4
Administration of extra virgin olive oil to healthy subjects	Decreased markers of oxidative stress	39
<i>In vitro</i> exposure of PBMC to an olive oil-based lipid emulsion	Decreased production of pro-inflammatory cytokines	34
<i>In vitro</i> exposure of PBMC to an olive oil-based lipid emulsion	Maintenance of immunity and reduced inflammatory response	38

Abbreviation: PBMC, peripheral blood mononuclear cells; ICAM-1, intercellular adhesion molecule-1.

Table 2. Summary of animal studies examining the effects of olive oil on immune system function

Study characteristics	Findings of the study	References
Rats fed a diet containing 200 g/kg of olive oil for 10 weeks	Decreased spleen and lymph node proliferation	15
Rats fed a diet containing 200 g/kg of olive oil for 10 weeks	Decreased spleen NK cell activity	24
Mice fed a diet containing 150 g/kg of olive oil for 12 weeks	Increased IL-2 and TNF- α production compared with a low fat diet	23
Mice fed a diet containing 200 g/kg of olive oil for four weeks and challenged with <i>Listeria monocytogenes</i>	Higher survival rates and decreased recovery of viable bacteria from spleen compared with a fish oil diet	31
Rats fed diets containing 200 g/kg olive oil, sunflower oil or high oleic sunflower oil for 6 weeks	The immunosuppressive effects attributed to an olive oil diet are mainly due to oleic acid	13
Balb/c mice fed diets containing 200 g/kg olive oil, fish oil or hydrogenated coconut oil for 4 weeks and infected with <i>L. monocytogenes</i>	Increased invasion and adherence of <i>L. monocytogenes</i> to splenic cells	18
Balb/c mice fed diets containing 200 g/kg olive oil, fish oil or hydrogenated coconut oil for 4 weeks and subsequently infected with <i>L. monocytogenes</i>	Production of IL-12 is not modified, but increased IL-4 production after <i>L. monocytogenes</i> infection	21
C57B1/6J mice fed a diet containing 7% (w/w) olive oil diet for 6 weeks and injected with LPS	Decreased inflammatory response and improved survival	40
Rats received an olive oil-based lipid emulsion in a model of <i>Escherichia coli</i> bacteraemia	Preserved mononuclear phagocyte system, although mortality is unaffected	35
Rats received an olive oil-based lipid emulsion for 4 weeks	Increased expression of the IL-2 receptor (CD25)	37

Abbreviations: NK, natural killer; LPS, lipopolysaccharide; IL, interleukin; TNF, tumor necrosis factor.

of survival percentage as well as an increase of viable bacteria in the spleen³¹ or liver³² after the administration of diets containing long chain *n*-3 PUFA to mice experimentally infected with a virulent pathogen. These data indicate that the suppression of the immune system caused by these fatty acids leads to a reduction of host resistance against infectious microorganisms^{27–30}. Although the mechanism by which some dietary lipids affect host resistance to infection are not clearly defined, changes in pro-inflammatory eicosanoid and cytokine production may be particularly involved in these processes.

Numerous investigations have reported the involvement of long-chain *n*-3 PUFA in the modulation of natural resistance against *Salmonella typhimurium* serovar Typhimurium, *Mycobacterium tuberculosis*, *Listeria monocytogenes*, influenza virus or parasites^{29,30}. Currently, the information on the effects of olive oil on host resistance is very poor, but the results obtained have indicated that the administration of diets containing MUFA are able to reduce infection severity and to prolong survival in murine models after the challenge with *L. monocytogenes*. In addition, the recovery of viable bacteria from spleen³¹ of mice is reduced at an early stage of infection. Finally, bactericidal activity of peritoneal cells from mice fed a diet containing olive oil is more efficient than that from mice fed a diet containing fish oil³³. In contrast, the number of adhering bacteria as well as the number of invading bacteria is substantially larger in the group fed a diet containing olive oil¹⁸.

An important cytokine involved in the activation of Th1 response is IL-12, which plays a relevant role in the elimination of intracellular bacteria. Thus, IL-12 production is not initially reduced in mice fed a diet containing olive oil, although the production of other pro-inflammatory cytokines such as IL-1, IL-6 and TNF- α was modified after *L. monocytogenes* infection, especially at 24 h of challenge (Fig. 1).

The administration of a diet containing olive oil in mice infected with *L. monocytogenes* and intraperitoneally treated with cyclophosphamide, an immunosuppressive agent, does not have an effect as great as a fish oil diet on the survival of mice after infection, or on the recovery of viable bacteria

from mice spleen and liver. It is possible that the immunosuppression exerted by diets containing fish oil is aggravated in this model, whereas in our experience an olive oil diet moderately reduces host resistance to infection (unpublished results).

Olive oil in clinical nutrition

Lipid emulsions constitute an essential component of total parenteral nutrition, which represents an indispensable strategy to improve nutritional status of critically ill patients. The interaction between fatty acids and the immune system has increased the interest in the manipulation of fatty acid composition in lipid emulsions, which have widely been used in clinical practice for over 30 years. The administration of an olive oil-containing emulsion (ClinOleic or SMOFLipid) appears to be more beneficial to immune system functions than soybean oil-based emulsions, because it does not alter inflammatory cytokine production. This property constitutes an important factor that allows the administration of this lipid emulsion in patients for whom a reduction of immune resistance constitutes a drastic event, because they are at a high risk of infection³⁴. In fact, with the purpose of finding a lipid emulsion capable of protecting mononuclear phagocyte system functions, a study revealed that the administration of a lipid emulsion enriched with olive oil to rats infected with *Escherichia coli* is efficient and may be used in the preservation of mononuclear phagocyte system functions³⁵.

The lipid emulsions most commonly applied as nutritional therapy support contain *n*-6 PUFA such as safflower oil or soybean oil, but they may be involved in adverse effects on the immune system, especially when are administered in high doses over a short time period. In fact, an excess of *n*-6 PUFA and the low amount of *n*-3 PUFA are related to adverse effects on immunological functions⁷. ClinOleic offers clinical advantages in severely burned patients, with improved liver functions after administration³⁶. Therefore, emulsions containing olive oil are an important alternative to soybean oil in parenteral nutrition, because an olive oil-based lipid emulsion offers better maintenance of immunity and reduces the inflammatory response^{37,38}.

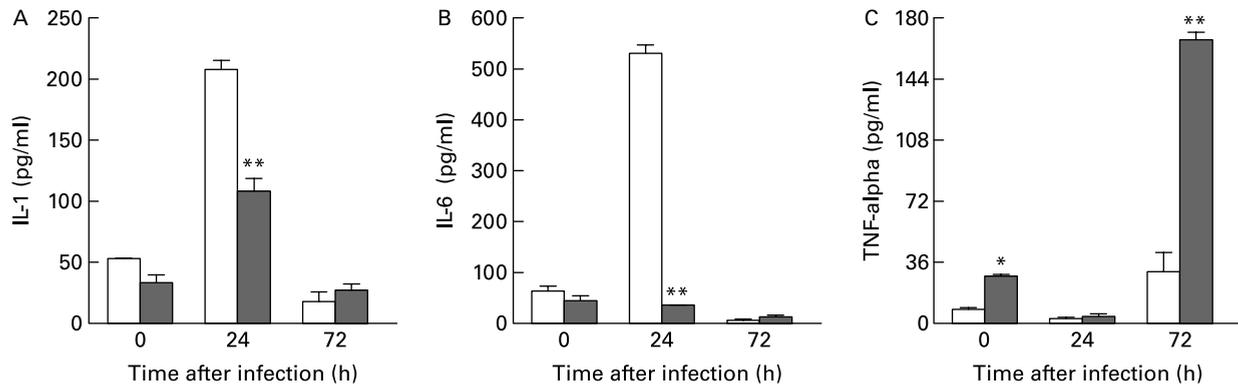


Fig. 1. Pro-inflammatory cytokine concentrations in sera from mice fed an olive oil diet or a low fat diet (control diet) and experimentally infected with *Listeria monocytogenes*. The concentration of interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor- α (TNF- α) was measured in the serum of Balb/c mice fed with a low fat diet (open bars) or with an olive oil diet (close bars) for four weeks. After the feeding period, animals were experimentally infected with *L. monocytogenes* and the serum was collected at 0, 24 and 72 h of challenge. Significant differences (two-way ANOVA) between experimental groups in each time are indicated as follow: * $P < 0.05$; ** $P < 0.001$.

Concluding remarks

Diets containing olive oil may exert beneficial effects when they have been applied in the resolution of inflammatory disorders. Experimental studies have indicated that the immunomodulatory action of olive oil is due to oleic acid, but recent investigations have suggested that anti-inflammatory properties are also attributed to phenolic compounds. The immunosuppressive effects related to olive oil diet administration in animals are not as great as those produced by long chain *n*-3 PUFA, which are considered as the most immunosuppressive fatty acids. The biological properties exhibited by MUFA may result in a moderate reduction of host defence to pathogens. Therefore, it is important to determine the effects produced by olive oil in patients at risk of sepsis, to ensure that olive oil does not impair host immune resistance against infectious microorganisms.

Conflict of interest statement

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