Chapter

MEDITERRANEAN DIET: A PRECIOUS TOOL FOR FIGHTING INFLAMMATORY DISEASES

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ABSTRACT

Epidemiological studies indicate that populations who consume foods rich in specific polyphenols have lower incidence of inflammatory diseases. In turn, Mediterranean diet, claimed for its several health benefits, provides a wide range of foods which are particularly enriched sources of polyphenols, some of which known for their anti-inflammatory properties. In this context, various herbs, vegetables and fruits, as well as fruit derivative products, such as wine and virgin olive oil, are believed to have an important role preventing and/or ameliorating inflammatory conditions through diet. Additionally, they are strong candidates for anti-inflammatory drugs.

In general, the anti-inflammatory properties of polyphenols involve the modulation of pro-inflammatory gene expression including cyclooxygenase, lipoxygenase, nitric oxide synthases and several pivotal

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cytokines such as TNF-α, interleukin-1 (IL-1) and interleukin-6 (IL-6), mainly by acting through nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) signaling.

Since inflammation is a phenomenon present in many chronic diseases including cancer, diabetes, obesity, and cardiovascular disease, the modulation of the aforementioned markers by polyphenols may positively contribute for the prevention and/or amelioration of these diseases.

The present chapter focus various edible Mediterranean typical foods known for their anti-inflammatory properties, as well as the main phenolic constituents associated to the protection process and their underlying mechanisms of action.

Keywords: Mediterranean Diet; Anti-inflammatory; Polyphenols; Virgin olive oil; Wine; Spices; Herbs; Vegetables; Fruits

INTRODUCTION

The Mediterranean Diet (MDiet), a modern nutritional recommendation inspired by the traditional dietary patterns of Mediterranean basin located countries, including Croatia, Cyprus, Greece, Italy, Morocco, Portugal and Spain, was recognized in 2013 by UNESCO as an Intangible Cultural Heritage [1].

MDiet is known to contribute for an adequate consumption of nutrients and has been closely associated to the low occurrence of chronic diseases such as cancer, diabetes, obesity, and cardiovascular disease. One of the key elements for the claimed benefits of this diet is its wide range of fruits and vegetables, as well as fruit derivative products, such as wine and virgin olive oil (VOO).

Indeed, MDiet contains an ample source of components of proved health benefit effects, among which omega-3 fatty acids, oleic acid and phenolic compounds hold a prominent place [2, 3].

In particular, phenolic compounds have been shown to interact with a wide spectrum of molecular targets involved in the cell signaling machinery, including those of the inflammatory processes. In this scenario, phenolic compounds are not only able to rescue oxidative reactive species, as they also modulate the activity of pro-inflammatory enzymes and that of signaling proteins and transcription factors [4, 5].

The present review focus on typical MDiet phenolic compounds and their target mechanisms of the inflammatory process.

1. THE INFLAMMATORY PROCESS

The inflammatory process is a complex and coordinated immunological response of the organism to a viral or bacterial infection, or to an internal injury [2]. This compromises two distinct, yet highly related and dependent processes: the innate or unspecific immunity and an acquired, or specific immunity. The first is fast and is activated by a large number, though limited, stimuli. It is present in all individuals and it is composed of physical, chemical and biological barriers, specialized cells and soluble molecules. In turn, the activation of adaptive immune system causes the increment of microbial-specific leukocytes, a process that is highly effective and specific, but that takes days to fully develop [6].

Table 1 resumes the cells and molecules of the innate system. Both circulating cells i.e., those that are found in blood circulation and then migrate to the inflammation site via the action of several mediators (e.g. monocytes, which later differentiate in macrophages) and residing cells, i.e., cells that are found in the extracellular matrix of the organism and are activated the presence of an injury (e.g. macrophages, mast cells and dendritic cells), express in their surface Pattern Recognition Receptors (PRR). The latter detect both exogenous and endogenous antigens. In particular, the exogenous antigens (e.g. nucleic acids, carbohydrates) from pathogenic agents are detected by Pathogen-Associated Molecular Patterns (PAMPs) and the endogenous ones from injured or damaged cells are detected by the Damage-Associated Molecular Patterns (DAMPs) [7].

When activated, the PRRs oligomerize and form large complexes composed of various subunits. Those complexes then initiate signaling cascades that trigger the production of several factors, causing the recruitment of specific leukocytes (adaptive immune response) [6].

Once the signaling cascade is activated, there are several changes in the vasculature of the injured/damaged tissue which end up in increased blood flow and serum proteins in the extracellular area. These events cause the visible hallmarks of inflammation, i.e., calor (warmth), rubor (redness), tumor (swelling) and dolor (pain) [2].

The intensity of those hallmarks can be increased by the acquired immune system cells, though primary signals that start and resolve them are associated with the innate immune system [6].

The signaling cascade comprises different steps: the presence of inflammation inducers; the recognition of said inducers; a signal transduction that leads to the release of pro-inflammatory cytokines; the activation of inflammatory effectors. These effectors will then cause the polarization of the inflammation, i.e, the activation of T cells, which is followed by the resolution of the inflammation.

Table 1. Innate Immune System Molecules and Cells

<table>
<tr><td colspan="3">Innate Immune System Cells and Molecules</td></tr>
<tr><td rowspan="4">Cell</td><td>Phagocytic</td><td>Dendritic Cells
Macrophages
Neutrophils</td></tr>
<tr><td>Natural Killer (NK) Cells</td><td rowspan="3"></td></tr>
<tr><td>Mast cells
Basophils
Eosinophils</td></tr>
<tr><td rowspan="3">Molecules</td><td>Complement</td></tr>
<tr><td>Acute Phase Proteins</td></tr>
<tr><td>Inflammatory Mediators</td><td>Cytokines
Eicosanoids
Chemokines</td></tr>
</table>

There are two stages of inflammatory response: the acute and the chronic inflammation. The acute phase of inflammation starts immediately upon injury and rapidly turns severe but notably, it lasts only for a short period and is usually beneficial to the host, ending up in the resolution of the inflammatory event. However, in some cases the inflammation lasts longer than it should and the chronic inflammation is settled, thus predisposing the host to various inflammatory pathologies [2].

All the events of acute and/or chronic inflammation are mediated and controlled by chemical mediators which are produced by both residing and circulating immune system cells, after a recognition of a pathogenic or injury agent.

Mediators have a very short life and are highly regulated by several mechanisms (e.g. enzymatic degradation) however, before being destroyed, mediators exercise their activity through direct binding to receptors on different cell types or, alternatively, via a direct action that does not require binding to receptors [8].

Undoubtedly, tumor necrosis factor-α (TNF-α) is one of the most important regulatory mediators of the inflammatory cascade. This cytokine (i.e., peptide with low molecular weight that isproduced by several immune system cells in response to a stimulus) is a transmembrane protein of 26 kDa. Notably, this is released in its active form (17 kDa), in a process that is strictly regulated by an enzyme called TNF-α activating converting enzyme (TACE, a disintegrin metalloproteinase that is bound to the membrane) [9].

Due to the central figure of TNF-α, several inflammatory diseases (e.g. asthma, cystic fibrosis, rheumatoid arthritis, atherosclerosis and osteoporosis) start to manifest when this is deregulated.

The pro-inflammatory effects of TNF-α are mainly due its ability to activate NF-κB [10], i.e., a transcription factor that is present in all mammalian cells. This pathway is activated upon linkage of TNF-α to the TNF-Receptor 1 (also found in all cell types of the organism), which has a cytoplasmic "death domain" that recruits several proteins (Figure 1). When the recruited protein is TRADD (TNF-receptor associated death domain), the latter further recruits TRAF2 (TNF-receptor-associated factor). The TRADD-TRAF2 complex then activates IKK (IκBα Kinase), in a process mediated by the receptor-interacting protein (RIP) and in turn, this phosphorylates IκBα. Phosphorylation of IκBα causes it to be a target for ubiquitation. This pathways destroys IκBα and releases NF-κB, allowing it to bind DNA's promoter or enhancer regions, causing an increase in the expression of some genes, like TNF-α itself and others that play key roles in inflammation, such as cyclooxygenase-2 (COX-2), 5-lipo-xygenase (5-LOX), inducible nitric oxide synthase (iNOS), cell-adhesion molecules (CAMs) and other inflammatory cytokines [9].

Notably, COX-2 and 5-LOX are pivotal players in the arachidonic acid pathway, respectively controlling the biosynthesis of pro-inflammatory eicosanoids and of leukotrienes (considered as potent mediators locally released at the inflammation site by leukocytes and other 5-LOX expressing cells) [11]. The up-regulation of iNOS deeply increases the production of NO in cells, mainly in macrophages and endothelial cells. This agent is cytotoxic (thus killing foreign agents) and is also closely associated to vasodilatation during inflammation [8]. Moreover, CAMs, namely intercellular adhesion molecule 1 (ICAM-1), vascular adhesion molecule 1 (VCAM-1) and selectins [4, 9], regulate the binding of cells to extracellular matrix, to endothelial cells and to other cells [9, 12].

In turn, the activation of TRADD-TRAF2 by TNF-α can also promote the recruitment of other proteins which contribute to inflammation through regu-

lation and/or activation of a series of cell-signalling mediators, including the JNK (c-Jun amino terminal kinase), p38MAPK (p38 mitogen activated protein kinase), AKT kinase AP-1 (Activator protein-1) and p44/p42MAPK ($ERK_{1/2}$) [9].

We must also remark that there are many other important cytokines besides TNF-α. Indeed, the inflammatory process encloses more than 100 different types of cytokines. TNF-α and other pro-inflammatory cytokines like IL-1β, IL-6, IL-18, Interferon-γ (INF-γ)) are up-regulated in the inflamed organs/tissues together with some anti-inflammatory cytokines (e.g. IL-10, Insuline-like growth factor and insulin receptor activation) which inhibit the production of inflammation [9, 13].

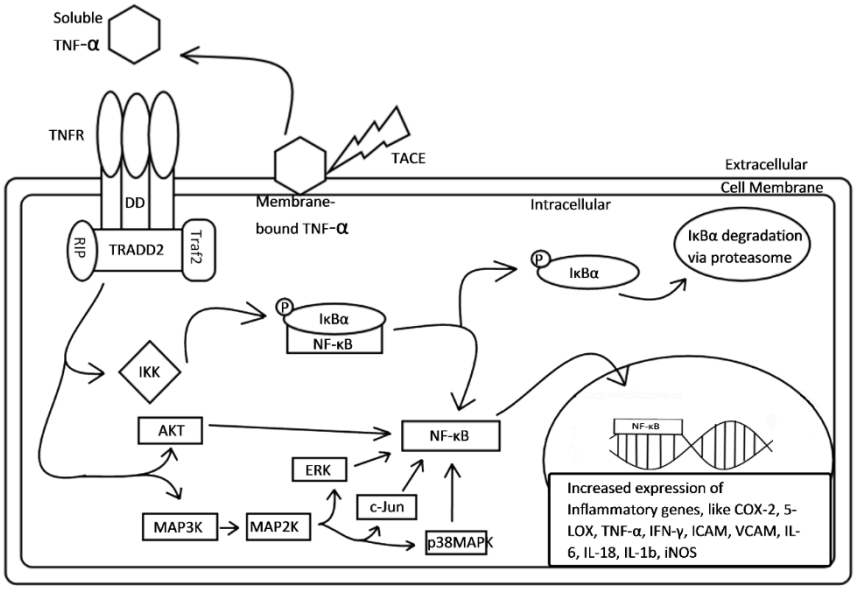


Figure 1. TNF-α and NF-κB pathways in the inflammatory process. TACE (TNF-activating converting enzyme) activity causes the release of the membrane-bound TNF-α, thus becoming soluble. TNF-α then binds to the TNFR (TNF Receptor) which causes the recruiting of TRADD (TNF-receptor-associated death domain), RIP (Receptor-interacting protein) and TRAF2 (TNF-receptor-associated factor). This complex activates IKK (IκBα Kinase) that ultimately phosphorylates IκBα and marks it to be degraded via the proteasome pathway. This degradation frees NF-κB, allowing it to migrate to the nucleus where it binds to specific inflammatory genes increasing their expression. NF-κB can also be activated by other pathways, namely AKT, $ERK_{1/2}$, c-Jun and p38MAPK.

2. WINE

Moderate red wine consumption, in particular at meals, is one of the main labels of MDiet. Indeed, high fat consumption yet low incidence of coronary heart disease is a reality found in southern France known as the "French paradox", which places wine in a high level of scientific interest [14].

At present, it is believed that polyphenols are key agents in the protective properties of this alcoholic beverage [15]. White and, in particular the red wines, are rich sources of polyphenolic compounds (see Table 2) with remarkable antioxidant and anti-inflammatory properties.

Table 2. Relative Phenolic Content of Red Wine

Phenolic group	Compound	Content* (mg/L)
Flavonols	Quercetin	127.8
	Kaempferol	1.0
	Myricetin	12.3
	Rutin	7.4
Anthocyanins	Malvidin-3-glucoside	46.7
	Peonidin-3-glucoside	19.0
	Petunidin-3-glucoside	21.0
	Cyanidin-3-glucoside	38.0
	Delphinidin-3-glucoside	10.9
Flavan-3-ols	Catechin	94.0
	Epicatechin	44.3
	Procyanidins	215.0
Hydrobenzoic acids	Protocatechuic acid	88.0
	Gallic acid	63.8
	Syringic acid	11.5
Hydroxycinnamic acids	Caffeic acid	8.7
	Caftaric acid	80.9
	Coutaric acid	52.2
	Ferulic acid	10.9
	p-Coumaric acid	4.7
Stilbenes	Resveratrol	1.2

Table adapted from Beer et al. [16].

*These are average values that can vary depending of the wine brand and aging time.

Anti-inflammatory properties of red wine have been proved in an *in vivo* human model of coronary high-risk volunteers. In more detail, Chiva-Blanch et al. [17] showed that the administration of red wine and dealcoholized red wine (both from Merlot grapes) to the volunteers reduced several serum inflammatory markers. Both samples significantly reduced the levels of monocyte chemotactic protein (MCP)-1, the cytokine IL-6 and IL-16, the adhesion molecules ICAM-1 and VCAM-1 and of CD40 antigen. While decrement of E-selectin and increment of IL-10 were more pronounced on patients consuming dealcoholized wine, reduction of macrophage-derived chemokine was observed in patients administrated with normal wine, suggesting that either ethanol and polyphenols contribute to the wine´s anti-inflammatory properties [17].

The antioxidant and anti-inflammatory properties have also been demonstrated for wine´s phenolic-enriched extracts. In accordance to the greater phenolic content of red wines regarding that of white wines, Xanthopoulou et al. [14] proved that the antioxidant and anti-inflammatory properties of phenolic extracts obtained from red wine conferred superior protection against lipid peroxidation and lipoxygenase activity. Moreover, it has been observed that lipopolysaccharide (LPS)-stimulated human colon-derived CCD-18Co fibroblast cells treated with red wine phenolic extracts (from Lenoir grapes) significantly reduced the gene expression of pro-inflammatory cytokines IL-6 and TNF-α. Likewise, the red wine extract treatment also reduced the activation of NF-κB, which is responsible for the transcription of those same genes [18].

Figure 2 is a simplified representation of the multiple inflammatory cellular targets of wine phenolics. A description of these effects for individual phenolics is further detailed hereinafter.

Among the phenolic compounds of the red wine, malvidin, mostly in its 3-*O*-β-glucoside form, is the most abundant and also responsible for the red wine´s color [19]. According to literature data, this anthocyanin interacts in distinct inflammatory processes, capable to directly impair several inflammatory mediators.

On CD23-stimulated human monocyte-derived macrophages, the treatment with malvidin-3-*O*-β-glucoside (50μM) dramatically down-regulated IL-6 secretion (from 62±24 to 34±9 pg/ml) as well as the gene expression of TNF-α, MIP-α (macrophage inflammatory protein), IL-1and IL-8 (35-88% inhibition) [20].Moreover, as demonstrated by Descendit et al. [20], this phenolic is able to reduce the iNOS-mediated NO production by decreasing transcription of iNOS encoding mRNA [20]. Additionally, the aglycone form

of this phenolic was shown to block the p65-subunit of NF-κB (necessary for activation of the transcription factor), as well as the binding of the activated NF-κB to the correspondent DNA binding site [21].

Besides, Bognar et al. [21] documented that malvidin (at 50 μM) impaired the MAPK signaling pathway, per order of effectiveness $ERK_{1/2}$<p38-MAPK<JNK, and enhanced MAPK phosphatase-1 mRNA and protein expression thus down-regulating every MAPK signaling steps.

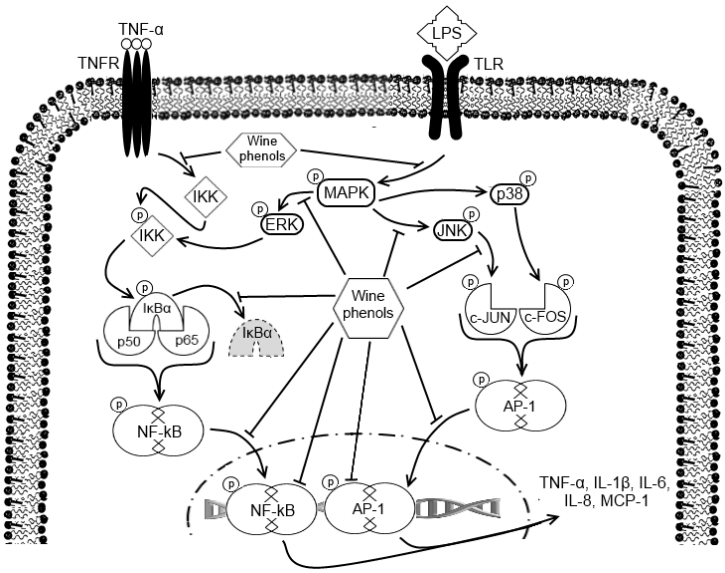
Cyanidin and quercetin are also major phenolics in red wine [19] that can contribute for the wine´s anti-inflammatory effects. The fact that the two compounds inhibit monocyte adhesion to TNF-α-induced HAEC cells suggest that these have anti-atherogenic properties. Both cyanidin and quercetin were shown to effectively attenuate VACM-1, IL-8 and CD40 expression while quercetin was also able to significantly attenuate ICAM-1 and E-selectin expressions [22].

Quercetin has also been demonstrated to exhibit potent inhibitory effects on the three groups of central inflammatory enzymes, i.e., iNOS, COX and LOX, thus causing a significant reduction on both mRNA and protein expression of either iNOS and COX-2 and consequently, on their derivative products (NO and prostaglandins PGE_2 respectively) [23, 24].

Besides, other markers of inflammation, including TNF-α, IL-1β, IL-6 and MCP-1 (also involved in atherogenic processes), have likewise been described to be effectively inhibited by quercetin on several activated macrophages such as RAW 264.7 or PBMC macrophages [4, 23].

Additionally, both quercetin and cyanidin notably reduced NF-κB expression and its binding to the DNA, as well as the $ERK_{1/2}$ and p38-MAPK expression, hence impairing both NF-κB and MAPK signaling pathways on stimulated HAEC cells [22, 25].

Other wine´s minor phenolic compounds have also been reported for their anti-inflammatory capacities. Examples of these are myricetin, kaempferol, catechins, ferulic acid, coumaric acid and many others which have been described for their ability to inhibit and interfere with many inflammation mediators, i.e. COX, LOX and iNOS enzymes, NF-κB and MAPK signaling pathways and even enhance anti-inflammatory cytokines such as IL-10 [4].



P - phosphorylated.

Figure 2. Wine polyphenols may impair inflammation by blocking activation of mitogen-activated protein kinases (MAPKs) and IκB kinases (IKK), preventing their signaling pathways progression and activation of nuclear factor-kappa B (NF-κB) and activator protein (AP)-1. Wine polyphenols may prevent inflammatory tumor necrosis factor alpha (TNF-α)/TNF receptor (TNFR) or lipopolysaccharide (LPS)/toll-like receptor (TLR) signaling to IKK inhibiting the IκBα phosphorylation and further degradation, thus preventing the p50 and p65 dimers from complexing and forming the NF-κB. Likewise, MAPK kinases signaling and their down-stream, extracellular signal-related kinase (ERK) and terminal kinases JNK and p38 are also blocked, preventing the phosphorylation and further complexation of c-JUN and c-FOS in AP-1. As these two pivotal inflammatory transcription factors are inactivated, the transcription of inflammatory genes [e.g., TNF-α, IL-6, IL-8, IL-1β, and monocyte chemoattractant protein (MCP)-1] no longer occurs, thus ceasing the inflammation progress.

Resveratrol

Notably, resveratrol (another minor phenolic in red wine) has been attracting huge attention in the scientific community due to its unquestionable great potential [26]. This phenol is mainly present in grapes skin (red ones) and seeds. Therefore, because of the removal of the skin and seeds before the

fermentation of the white wine, resveratrol is much abundant in red wines as compared to the white ones [27].

Many studies have been targeting and demonstrating resveratrol promising anti-inflammatory properties on immune cells.

Martinez and Moreno [28] assayed the influence of resveratrol in the producing levels of two reactive oxygen species (ROS) species on phorbol esters (PMA) or LPS-stimulated murine resident peritoneal macrophages. The authors concluded that the levels of superoxide radicals (O_2^-) and hydrogen peroxide (H_2O_2) were significantly reduced. Moreover, they also reported a marked decrease of the levels of [^{3}H]-arachidonic acid and on COX-2 activity, overall resulting in a considerable reduction of the prostaglandin synthesis. Furthermore, this stilbene was also shown to suppress the proliferation of splenocytes from BALB/c mice, as well as their differentiation into macrophages and T- or B- cells.

Moreover, CD28 and CD80 expressions were notably down-regulated while the IL-10 anti-inflammatory cytokine production was stimulated [29].

Recently, further assays on LPS-stimulated RAW 264.7 macrophages showed more of the resveratrol capacities, namely its ability to not only inhibit the NO and TNF-α secretions but also to down-regulate the expression of TNF-α, IL-1β, IL-6 and iNOS genes and, more importantly, to inhibit NF-κB activation, as also demonstrated in human embryonic kidney cells (HEK-293T). Since NF-κB is responsible for the expression of several pro-inflammatory genes, its inhibition contributes to the down-regulation of the mentioned genes themselves[30].

The intensive research focusing on resveratrol already allow us to conclude that its anti-inflammatory effects can occur in distinct inflammatory conditions/diseases, affecting the lung, bowel, articulations, brain and especially the circulatory system. For example, in an animal model of asthma (an obstructive pulmonary disorder caused by an excessive T helper 2 (Th2) inflammatory response), the treatment with resveratrol caused the attenuation of numerous inflammatory parameters including the reduction of the plasma pro-inflammatory cytokines IL-4 and IL-5, airway hyperresponsiveness, mucus hypersecretion and eosinophilia [31].

Moreover, this stilbene has been compared to the well-known drug budesonide, due to their close effects for the reduction of the neutrophil recruitment, inhibition of TNF-α, IL-1β, myeloperoxidase (MPO) and cytokine-induced neutrophil chemoattractant 1 (CINC-1), as demonstrated on LPS-treated mice. Also, despite Birrell et al. [32] showed a low impact of resveratrol in COX-1 or COX-2 gene expression on the lung tissue, a

significant reduction on PGE_2 levels was registered, suggesting that this phenolic can act on other enzymes involved in the prostanoid production and/or release. Besides, a study performed with human airway epithelial cells concluded that resveratrol interfere with NF-κB activation and COX-2 expression, as well as with the iNOS expression and the release of the cytokines IL-8 and granulo-cyte-macrophage colony-stimulating factor (GM-CSF), thus impairing the production of new granulocytes [33].

Advantages of resveratrol on inflammatory bowel diseases have also been described in a study performed in human colon cell lines of Caco-2 and in SW480. Once exposed to LPS, both cell lines, previously treated with resveratrol, presented a dose-dependent inhibition of iNOS either on mRNA and protein expression. Additionally the Toll-like receptor-4 (responsible for activation of MAPK signaling pathway) expression was observed to be significantly lowered after resveratrol treatment [9]. The authors reported that this could be due to the non-activation of the NF-κB, since they observed that the phosphorylation of the IκB was impaired [34]. These results are in agreement with those reported by Cianciulli et al. [35] whom also described the reduction of COX-2 mRNA and protein expression (and consequent decreased PGE_2 production) on LPS-challenged Caco-2 cells treated with resveratrol, as well as its inhibitory effects on IκB phosphorylation and NF-κB activation, specifically on IκBα and p65-subunit of NF-κB .

Regarding rheumatoid arthritis, a systemic autoimmune disease characterized by chronic inflammation of multiple joints resulting in the destruction of joint cartilage [36], it was suggested for the first time by Elmali et al. [37] that intra-articular injection of resveratrol could protect the cartilage against the development of induced arthritis. This hypothesis is corroborated by a recent study reporting that collagen-induced arthritis mice treated with resveratrol had their inflammatory condition rapidly and significantly reduced after the application of a second dose of this stilbene. While exploring these results, it was observed that the levels of collagen-specific IgG1 and IgG2a (but not the total levels of these IgGs) were markedly reduced compared to the controls, suggesting that the resveratrol treatment selectively acts against collagen-specific B-cells rather than general B-cells.

Additionally, a relevant reduction of the Th17 cells expression on the draining lymph node was also noted and, according to the serum cytokine level assessments, the pro-inflammatory cytokines IFN-γ, TNF-α, IL-6, IL-1 and IL-4 were substantially decreased, while IL-17 expression was practically nullified on mice after resveratrol treatment [38].

Resveratrol has also been demonstrated to have an important role in brain diseases, particularly affecting the microglia.

Overall, resveratrol-mediated neuroinflammatory protection can be essentially explained by three mechanisms: (1) inhibition of ROS production; (2) MAPK signal transduction pathways suppression and (3) suppression of the NF-κB signaling pathway activation [39].

The main neuronal ROS-production system is NADPH oxidase, which contributes to oxidative stress condition and plays a critical role in inflammation-induced neurodegeneration. This enzyme has been demonstrated to be inhibited by resveratrol resulting in a reduction of ROS levels and preventing LPS-challenged microglia from further stimulation and activation of the inflammatory MAPK and NF-κB signaling pathways [40]. Moreover evidences point that resveratrol can likewise directly interfere with central inflammatory molecules, impairing their correct signaling transmission.

This has been shown by some authors that reported the impairment of the MAPK signaling pathway by suppressing the phosphorylation of $ERK_{1/2}$, p38 MAPK and JNK, and more importantly, the phosphorylation of IκBα [40-42].As a result, the production and functioning of pro-inflammatory enzymes and mediators including iNOS, COX-2, PGE_2, NO, IL-1β, IL-6 and TNF-α are hampered by resveratrol, reducing the stimulation and activation of more microglial cells and preventing inflammation [43, 44].

Finally, resveratrol has been described to exhibit great benefits on coronary heart diseases (CHD), in particular in atherosclerosis, that is an artery inflammatory disease and also the most relevant CHD. A resume of the potential beneficial effects of resveratrol (and other phenolics) in the typical cellular events of atherosclerosis is represented in Figure 3. Studies revealed that resveratrol antioxidant properties are crucial in preventing the low density lipoprotein (LDL) oxidation. This event thus blocks the triggering of the endothelial dysfunction and its consequent deregulation of NO production and vasoconstriction, as well as the expression of the adhesion molecules and further adhesion of the leukocytes to the endothelium [16-18]. Resveratrol has been found to up-regulate, in a dose-dependent manner, the endothelial nitric oxide synthase (eNOS) mRNA expression on human umbilical vein endothelial cells (HUVEC) and their consequent NO production [45] and to reduce the adherence of human monocytic cells (THP-1) to the same LPS-challenged endothelium cell line for more than 50% [46]. To better understand these results, resveratrol effect on the expression of E-selectin (primarily responsible for the initial monocyte adhesion to endothelium) was evaluated

leading to the observation of a significant dose-dependent reduction of the adhesion molecule resultant from the suppression of its gene expression [46].

Other inflammatory markers are influenced by resveratrol during this phase. Csiszar et al. [47] found that resveratrol could also diminish the adhesiveness of THP-1 cells to TNF-α- or H_2O_2-challenged HAEC cells. More importantly, the authors reported that in TNF-α-stimulated THP-1 cells, the treatment with resveratrol caused a reduction of >50% on the activation of NF-κB and on the NF-κB-dependent inflammatory markers including iNOS synthase, IL-6, ICAM-1 and VCAM.

On the fatty streak stage of atherosclerosis, the recruited macrophages engulf the oxidized LDL (oxLDL) and migrate to the intimal vessel layer [48]. At this stage, resveratrol has been shown to be a very effective regulator of cholesterol homeostasis having the ability to reduce the cholesterol influx and enhance cholesterol efflux of J774 macrophages.

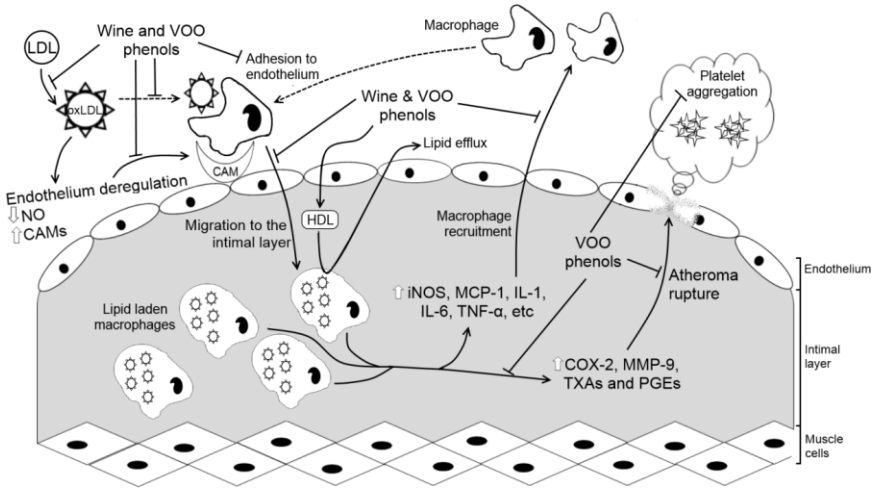


Figure 3. Wine and virgin olive oil (VOO)'s phenolic compounds may interfere in several steps of atherosclerotic progression. During the first stages of the process, these compounds prevent the oxidation of low density lipoprotein cholesterol (LDL) into its oxidized form (oxLDL) that in turn will no longer interfere and deregulate endothelium function. In an endothelium deregulation scenario, wine and VOO´s compounds prevent the over-expression of adhesion molecules (CAMs) as well as the macrophages oxLDL uptake, their adhesion to the endothelium and migration to the vessel intimal layer. Moreover, wine and VOO´s phenolic compounds may up-regulate high density lipoprotein cholesterol (HDL) levels that in turn will interact with the lipid laden macrophages in the intimal layer, promoting their cholesterol efflux. Besides, by interfering with the pro-inflammatory enzymes and cytokines [inducible

nitric oxide synthase (iNOS), monocyte chemoattractant protein (MCP)-1, interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, etc.], the compounds may prevent the recruitment of other leukocytes, thus blocking the inflammatory progress. On the later stages of the inflammation VOO´s phenols play an extremely important protective role by inhibiting the expression of several markers [metalloproteinase (MMP)-9, cyclooxygenase (COX)-2 and their derivative products such as thromboxanes (TXAs) and prostaglandins (PGEs)], and their influence on the atheroma rupture and further platelet aggregation upon extravasation.

Moreover, the oxidative stress induced by Fe/ascorbate ion caused on these same macrophages a blockage of apoA-1 (apolipoprotein A-1) and HDL_3-mediated efflux which was reverted, in a dose-dependent manner, on resveratrol-pretreated macrophages [49].

3. VIRGIN OLIVE OIL

Alongside with the red wine, virgin olive oil (VOO) is one of the prime ingredients of the MDiet and one of the great contributors for its beneficial properties [50]. In fact, VOO is the main source of fat in MDiet, and it has been claimed to have several health benefits, particularly those related to CHD and atherosclerosis inflammatory processes [51].

As VOO results from the first pressings of the olives without using any kind of solvents, many of the phenolic compounds present in the fruit (e.g. hydroxytyrol, tyrosol, vanillic acid and oleuropein) and their degradation compounds are partially drawn within the oil [50].

Studies conducted thus far have demonstrated that the VOO´s health benefits are mainly associated with its richness in mono and polyunsaturated fatty acids (MUFAs and PUFAs, respectively), plus to the oil´s phenolic constituents [52]. In fact, phenolics are the VOO´s greatest contributors for its anti-inflammatory properties, capable of reducing the expression of pro-inflammatory cytokines, inhibiting the activity of LOX and COX-2, decreasing the production of adhesion molecules and eicosanoids derived from arachidonic acid and, more importantly, blocking the NF-κB activation [53].

From all the VOO´s phenolic compounds, hydroxytyrosol is undoubtedly one of the key elements in the regulation of the inflammatory processes [54]. In this context, Zhang et al. [54] showed that the exposure of THP-1 cells to hydroxytyrosol remarkably suppressed LPS-induced NO production and TNF-α release. Activities of iNOS and COX-2 plus their corresponding mRNA transcription were also inhibited by this phenolic.

The latter results are supported by those of Richard et al. [55] whom additionally referred that the treatment of LPS-induced RAW 264.7 cells with hydroxytyrosol diminished the secretion of cytokines IL-1α, IL-1β, IL-6, IL-12, TNF-α, the chemokines IFN-γ-induced protein 10 (IP-10), MCP-1 and even the gene expression of IL-1α, IP-10, macrophage inflammatory protein MIP-1β, matrix metallo-proteinase-9 (MMP-9), and prostaglandin E_2 synthase. The authors further concluded that these results were, in part, a consequence of NF-κB pathway impairment by hydroxytyrosol.In fact, this theory corroborates previous studies that linked the hydroxytyrosol anti-inflammatory properties to its ability of preventing the NF-κB activation [56].

However, hydroxytyrosol is not the only responsible for VOO's health benefits. Visioli et al. [57] reported that both hydroxytyrosol and oleuropein were better ROS scavengers and inhibitors of platelet aggregation than butylated hydroxytoluene (BHT), which is a well-known commercial antioxidant. Furthermore, hydroxytyrosol, oleuropein, caffeic acid, and tyrosol were shown to lower leukotriene B_4 levels as a result of 5-LOX inhibition on rat peritoneal leukocytes [58], while on human blood cultures, the IL-1β or PEG_2 production were significantly reduced by oleuropein glycoside and caffeic acid or by kaempferol, respectively [59].

Moreover, similarly to hydroxytyrosol, oleuropein is also able to hamper the NF-κB signaling pathway causing the blockage of other inflammatory processes dependent on this transcription factor [60].

Oleocanthal is one of the VOO's phenolics that is being target of interest in the recent years due to its strong anti-inflammatory capacity. This has a mechanism of action closely similar to that of the well-known ibuprofen (a strong commercial anti-inflammatory drug), i.e., it negatively interacts on prostaglandin and thromboxane biosynthesis throughout inhibition of both COX-1 and COX-2. Furthermore, for equimolar concentrations, oleocanthal was proven to be even more effective than ibuprofen [50, 61].

Because of its particular composition, VOO is a strong edible tool against certain diseases as it is the case of inflammatory bowel diseases (IBD) and especially atherosclerosis. The latter protection has been closely associated to the oil´s phenolic composition. *In vivo* studies reported that individuals submitted to a diet based in phenolic-enriched VOO had their levels of LDL decreased while that of HDL were increased, thus improving the lipid efflux [49, 62].

Once more, hydroxytyrosol and oleuropein play an important role in atherosclerosis preventive effects (see general resume in Figure 3), acting on the vascular endothelium cells. Indeed, due to their potent antioxidant activity,

the two phenolics were shown to prevent endothelial dysfunction of HUVEC and pulmonary artery endothelial cells, restraining further ROS production and NF-κB activation [63, 64]. Atherosclerosis progress is associated to the overexpression of adhesion molecules (ICAM-1, VCAM-1 and E-selectin) in order to recruit more leukocytes [65]. However, according to Dell'Agli et al. [66], HUVEC cells treated with oleuropein, hydroxytyrosol and homovanillyl alcohol demonstrated that the two first polyphenols decreased the expression of ICAM-1 and VCAM-1 (surface and mRNA), while homovanillyl alcohol reduced the cell surface expression of the three adhesion molecules, despite not affecting their mRNA levels.

Finally, the aforementioned shared ability of hydroxytyrosol and oleuropein to restrain MMP-9, COX-2 activity (and consequent eicosanoid synthesis) and platelet aggregation is extremely important during the latter stages of atherosclerosis, particularly on the arterial thrombosis events which are closely related to these markers [54, 67, 68].

From the IBD, ulcerative colitis is one of the most common inflammatory conditions of the bowel, characterized by a diffuse mucosal inflammation limited to the colon [69]. Strong impairment of the bowel inflammation has also been correlated to VOO´s phenolic compounds. In mice models of colitis submitted to a diet of VOO´s phenolic enriched extracts, it was observed a significant decrease of the expression of TNF-α and COX-2, iNOS and MCP-1, as well as the reduction of IκBα degradation and inactivation of the JNK and p38-MAPK, overall resulting in a decreased NF-κB and MAPK signaling [70]. In agreement with the later results, Sánchez-Fidalgo et al. [71] reported that colitis-induced mice fed with hydroxytyrosol-enriched VOO not only reduced iNOS and COX-2 expression and p38-MAPK activation, but also enhanced the release of the anti-inflammatory cytokine IL-10, thus suggesting that hydroxytyrosol is a key factor in the modulation of this disease.

Oleuropein anti-inflammatory properties are also associated to bowel disease as this was demonstrated to reduce the production of IL-6 and IL-1β, and the expression of COX-2 and iNOS, while increasing the IL-10 levels [72].

Moreover, treatment of colitis mice with oleuropein caused the simultaneous reduction of p38-MAPK phosphorylation and NF-κB activation, together with a remark stimulation of Annexin A1 production, which is a strong endogenous anti-inflammatory agent acting by inhibiting COX-2 and iNOS in injured colon tissue [72].

Despite these two inflammatory conditions where VOO is clearly involved, it is also claimed that the oil exerts beneficial effects in other

inflammation-related diseases. It is the case of some cancers where inflammatory conditions have been estimated to contribute in 15-20% for the development of phenomena related with all types of cancer [73, 74].

The antitumor activity of VOO was demonstrated in ulcerative colitis related-carcinogenesis C57BL/6 mice models, that presented a minor number of dysplastic macroscopic lesions, accompanied by a reduction of the cytokines TNF-α, IL-6 and IFN-γ, as well as a decreased expression of COX-2 and iNOS in the colonic tissue [75].

Again, hydroxytyrosol and oleuropein have been recognized for their cell survival modulatory action by mechanisms that include the decreased of 5-LOX expression, reduced synthesis of prostaglandin E_2 and alteration of tumor eicosanoid biosynthesis. Also, apoptosis promotion and prevention of oxidative DNA damage have been attributed to these two phenolic compounds as concluded from studies in human tumor-cell lines [76, 77].

Furthermore, inflammatory angiogenesis, a key element for the tumor growth, has been suppressed as a consequence of the MMP-9 down-regulation, together with the reduction of ROS and inhibition COX-2 expression in cultured endothelial cells treated with both hydroxytyrosol and oleuropein [78].

Although scarcely studied, some experiments have already been published reporting VOO´s neurodegenerative protective effects. According to Pérez-López et al. [79], consumption of VOO significantly improved learning and memory of Alzheimer disease mice models SAMP8. Moreover, oleocanthal aforementioned for its COX-1 and COX-2 inhibitory properties, is also able to counteract the synapses loss of function and neurofibrillary tangles caused by β-amyloid oligomers and of fibrillization of tau-protein, respectively [80-83]. Besides, by forming a non-covalent complex with β-amyloid peptide, oleuropein can prevent Aβ-aggregation resulting in a decreased deposition of these neurotoxic molecules [84].

4. HERBS, VEGETABLES AND FRUITS

The Mediterranean area has a vascular flora of about 25 000 species, both in wild or cultivated forms, belonging to distinct families [85]. In this way, several plant species are included in MDiet and consumed as vegetables, fruits, culinary spices (in flavoring salads, soups, stews and sauces), and herbs (e.g. as ingredient of dishes or herbal infusions) [86].Notably, some of them have been proposed to act as beneficial agents in inflammatory-related

diseases (e.g. atherosclerosis, rheumatoid arthritis, asthma, obesity, diabetes, neurodegenerative diseases and even cancer).

As previously mentioned, chemical *in vitro* tests for 5-LOX and COX-2 are routinely used for assessment of anti-inflammatory activities. Based on that, Trouillas et al. [87] concluded that from sixteen French hydro-alcoholic plants extracts, those obtained from meadowsweet (*Filipendula ulmaria*), lady's mantle (*Alchemilla vulgaris*) and rosemary (*Rosmarinius officinalis*) were the most effective in inhibiting LOX, with an IC_{50} about 0.5 mg/mL.

In other study, Khasawneh et al. [88] reported a particular low IC_{50} value (1.41 μg/mL) for the inhibition of LOX by a phenolic extract from the aerial parts of *Leptadenia pyrotechnica*, that is a plant traditionally used in Mediterranean region in the treatment of a variety of inflammation-related disease.

The general anti-inflammatory activity of some typical Mediterranean plants and fruits have also been accessed in biological models such as the *in vitro* culture cell line leukocytes. Total inhibition of LOX activity was registered in rat polymorphonuclear by Prieto and colleagues [89, 90] upon the treatment with methanolic extracts of the plant species *Cytisus aeolicus* (at 200 μg/ml) and *Thymus richardii* (at 50 μg/ml). In these experimental conditions, the two extracts also significantly inhibited leukotriene B4 production. Moreover, other study reported remarkable negative effects of phenolic-enriched extracts of cinnamon (*Cinnamomum zeylanicum*), nutmeg (*Myristica fragrans*) and clove (*Eugenia aromatica*) on COX-2 activity and synthesis of prostaglandins [90].

Also, the plant species *Nigella sativa* (i.e. cumin, used in several Mediterranean countries for culinary and medicinal purposes) has been shown to inhibit nitric oxide release with an IC_{50} of 6.20 μg/mL, in LPS-stimulated macrophage model [91]. For the same biological model, Muller and colleagues [92] also concluded that the extracts of *Ocimum basilicum* (basil) *Laurus nobilis* (bay leaves), *Glycyrrhiza glabra* (licorice), *Origanum onites* (oregano), *Salvia officinalis* (sage) and *Thymus vulgaris* (thyme) could inhibit the production of IL-6 or TNF-α and the expression of COX-2 or iNOS, while enhancing the production of IL-10. Moreover, the decrement of IL-8 levels was documented for H_2O_2-stimulated human peripheral blood lymphocytes (PBLs) co-incubated with uncooked, cooked or digested extracts of important ingredients in MedDiet culinary, namely *Rosmarinus officinalis*, *Salvia officinalis*, and *Thymus vulgaris*. Part of the anti-inflammatory effects of *Rosmarinus officinalis* and *Salvia officinalis* were attributed to their content in rosmarinic acid, carnosic acid and carnosol [93-95].

Interference of typical Mediterranean fruits on general inflammatory mechanistic events has also been reported in distinct biological models and further associated to their phenolic composition. In this context, phenolic extracts of *Capsicum annuum* (chili pepper) and *Pimenta officinalis* (allspice) could reduce the production of IL-6, increase the production of IL-10 and decrease the expression of COX-2 in a lipopolysaccharide-stimulated macrophage model. In turn, *Piper nigrum* (black pepper) and *Myristica fragrans* (nutmeg) phenolic extracts reduced the expression of COX-2 and the production of IL-6 or TNF-α in the same experimental model.

With exception of the latter species, the remaining could inhibit the expression of iNOS [92]. Also, phenolic extracts of apple (*Malus domestica* Borkh) were described to reduce the production of IL-6 and the expression of COX-2 in the previous cellular model [96].

Paw edema induced by carrageenan, histamine, dextran and ear edema induced by toxics as croton oil, arachidonic-acid and xylene [97-100] are major *in vivo* models for assessing inflammatory actions of plant and/or fruit extracts.

In this way, distinct extracts of *Lamium* plants, namely *L. garganicum* subsp. *laevigatum*, *L. garganicum* subsp. *pulchrum* and *L. purpureum* var. *purpureum* have demonstrated good anti-inflammatory activities in carrageenan-induced paw edema model, causing a reduction of the edema of approximately 12 to 30% [101]. Furthermore, in the same *in vivo* model, Lee and colleagues [102] showed that an hydroethanolic extract of *Leonurus sibiricus* (siberian motherwort) could suppress the activation of inflammatory mediators.

In turn, inhibition of the croton oil-induced ear edema in mice model was used to evaluate topical anti-inflammatory activity of several dietary Mediterranean plants such as *Malva sylvestris* (Mallow), *Borago officinalis* (Borage), *Capparis sicula* (Caper), *Raphanus raphanistrum* (Radish) and *Mentha aquatica* (water mint). These plants are traditionally used in local medicine for the treatment of external inflammation and inflammation-related diseases. Overall, the hydroethanolic extracts of the cited plant species provided an inhibition of 21 to 27%, with the best result being obtained for water mint, in accordance to its best antioxidant activity on DPPH scavenging and lipid peroxidation tests [103]. Also, hydroalcoholic extracts of the edible plants *Cichorium intybus* L. (chicory), *Papaver rhoeas* L. (poppy), *Lepidium sativum* L. (cress) and *Echium vulgare* L. (viper's Bugloss) provided 18% to 43% of edema reduction in the same model [104].

Similarly, an extract obtained from the species Bear's Breech (*Acanthus montanus*) i.e., a shrub widespread in Balkans, Romania, Greece, Eastern Mediterranean and Africa, has been reported to effectively inhibit (57%) topical acute edema in the mouse ear-edema model and to suppress the development of acute edema of the rat paw-edema model, in a non-dose-related manner. The same study also showed that the extract could inhibit vascular permeability and the haemolysis of red blood cells [105].

The documented anti-inflammatory effects of typical Mediterranean fruits in *in vivo* models are scarce. Still, important data has been described for *Punica granatum* L. (pomegranate), which is commonly consumed in Mediterranean diet and used as therapeutic and cosmetic agent.In fact, besides its capacity of reducing NO levels in macrophages, this fruit was shown to decrease carrageenan-induced mice paw edema [106]. The authors have attributed the anti-inflammatory effects of the extract to the hydrolysable tannins punicalagin, punicalin, strictinin and specially granatin B [106]. Moreover, tests performed by Shukla and colleagues [107] showed that the plasma sample obtained after oral administration of a polyphenol rich extract of pomegranate in rabbits inhibited the activity of COX-2. Similar conditions also reduced IL-1β-induced PGE_2 and NO production in a rabbit chondrocytes cellular model.

Although still rare, studies performed in more specific models suggest that some of the Mediterranean diet components can counteract inflammatory-related diseases. This is the case of a *Rosmarinus officinalis* phenolic extract, which has been shown to exert potent anti-inflammatory effects (preventing swelling and decreasing the infiltration of neutrophils) in rat ethanol-induced gastric ulcer model [108]. Additionally, in a pleurisy-mouse model induced by carrageenan, phenolic extracts of *Rosmarinus officinalis* inhibited leukocytes and exudation, as well as the pro-inflammatory enzyme myeloperoxidase (MPO) and the levels of nitrite/nitrate, IL-1β and TNF-α [109]. Even more, an antiatherosclerotic effect has also been associated to *Rosmarinus officinalis*-phenolic extracts due to its ability in counteracting the migration of vascular smooth muscle cells and to decrease MMP-9 and MCP-1 expressions. In this case, the benefits were associated by the authors to the presence of carnosic acid [110]. Plus, the intestinal anti-inflammatoy effect of hydroalcoholic extracts of *Phlomis lychnitis* and *Phlomis purpurea* was observed by Algieri and colleagues in a trinitrobenze-nesulphonic acid (TNBS) model of rat colitis, i.e. an experimental model of the human inflammatory bowel disease [111].

Protective effects of phenolic extracts on inflammatory-associated cancer conditions were suggested for six native Mediterranean herbs. Specifically, the

treatment of TNF-α-stimulated epithelial colon cancer (HT29) and prostate cancer (PC3) cells with herbal infusions of Cretan marjoram (*Origanum microphyllum*), oregano (*O. vulgare*), pink savory (*Satureja thymbra*), mountain tea (*Sideritis syriaca*), pennyroyal (*Mentha pulegium*) or chamomile (*Matricaria chamomilla*) significantly reduced the cellular IL-8 levels. Also, infusions of the latter plant species could reduce the levels of NF-κB p65-subunit in HT29 cells [112].

Protective effects of fruit phenolic extracts on specific inflammatory-disease models were also reported. Accordingly, a methanolic extract of date fruit (*Phoenix dactylifera* L.) was evaluated in an adjuvant arthritis in rats, a model of chronic inflammation. The results indicated that the extract could ameliorate the plasma antioxidant state (i.e. decreased the levels of lipid peroxides while increase the levels of vitamin C, E, A and β-carotene) and reduce foot swelling by approximately 68%. Additionally in this model, the extract exposure caused a reduction on the activity of COX-1 and COX-2 by about 30 and 50%, respectively [113, 114].

Moreover, the positive effects of a methanolic extract of pomegranate on gastric inflammation has been shown to reduce the ulcer index (UI) and the intraluminal bleeding in ethanol-induced gastritis in rats. Furthermore, the extract treatment induced the decrement of TNF-α levels, while the reduction of several inflammatory protein levels (e.g. IL-4, IL-6, IL-1β, IL-10) were observed in an acetic acid-induced ulcer model [115]. Similar protective effects have been demonstrated in intestinal models [116].

Several studies indicate that strawberry, i.e. *Fragaria x ananassa* Duch possess anti-inflammatory effects that are commonly associated to the fruit´s ellagitannin content [117, 118]. Concretely, strawberry fruit juice has been shown to interfere in cytokine secretion ratios as demonstrated in murine primary splenocytes and peritoneal macrophages models [119].

Besides to the antioxidant activities demonstrated, strawberry extracts could reduce, in a dose-dependent manner, the induced activator protein-1 (AP-1) and the NF-κB activity induced by UVB or tetradecanoylphorbol-13-acetate (TPA) in JB6 P+ mouse epidermal cells, thus suggesting a chemopreventive effect [120].

Cardile and colleagues have concluded that the dose-dependent anti-inflammatory effect of red orange (*Citrus sinensis*) on a human keratinocyte line NCTC 2544 exposed to IFN-γ and histamine was due to the decrement on the expression of ICAM-1, monocyte chemoattractant protein-1 (MCP-1) and IL-8 [121].

Additionally, a phenolic extract of orange was reported to induce positive effects on endothelial function, mediated by the decrement of high-sensitivity C-reactive protein, TNF-α and IL-6 [122].

CONCLUSION

Mediterranean diet, characteristic of Mediterranean basin located countries like Portugal, Spain, Croatia, Cyprus, Greece, Italy and Morocco is claimed to be associated with several health benefits, including the anti-inflammatory.

In part, this is because MDiet includes a wide range of fruits and vegetables, as well as fruit derivative products, such as wine and virgin olive oil, which are particularly enriched in polyphenols of proven anti-inflammatory properties.

The anti-inflammatory activities of phenolic compounds include the inhibition of NF-κB activation, together with the expression decrement of cytokines and chemokines, LOX and COX-2 enzymes, with concomitant lowering levels of prostaglandins, leukotrienes and thromboxanes. Other mechanism includes the decrease of intracellular oxidative stress.

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