Macrophage polarization by potential nutraceutical compounds: A strategic approach to counteract inflammation in atherosclerosis

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Abstract:	Chronic inflammation represents a main event in the onset and progression of atherosclerosis and is closely associated with oxidative stress in a sort of vicious circle that amplifies and sustains all stages of the disease. Key players of atherosclerosis are monocytes/macrophages. According to their pro- or anti-inflammatory phenotype and biological function, lesional macrophages can release various mediators and enzymes, which in turn contribute to plaque progression and destabilization or, alternatively, lead to its resolution. Among the factors connected to atherosclerotic disease, lipid species carried by low density lipoproteins and pro-oxidant stimuli strongly promote inflammatory events in the vasculature, also by modulating the macrophage phenotyping. Therapies specifically aimed to balance macrophage inflammatory state are increasingly considered as powerful tools to counteract plaque formation and destabilization. In this connection, several molecules of natural origin have been recognized to be active mediators of diverse metabolic and signaling pathways regulating lipid homeostasis, redox state, and inflammation; they are, thus, considered as promising candidates to modulate macrophage responsiveness to pro-atherogenic stimuli. The current knowledge of the capability of nutraceuticals to target macrophage polarization and to counteract atherosclerotic lesion progression, based mainly on in vitro investigation, is summarized in the present review.
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Prof Giovanni Mann
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FRBM-D-21-01901: "Macrophage polarization by potential nutraceutical compounds: a strategic approach to counteract inflammation in atherosclerosis" (Sottero et al.)

Turin, January 27, 2022

Dear Prof Giovanni Mann,
we finally provide you with the revised version of the quoted manuscript, that includes the implements suggested by the referees.
Hereafter please find our point to point answers to the reviewer queries.

We thank the reviewers for the thoughtful review and helpful comments, which have guided the revision of the manuscript.

Reviewer #1:

1. The first part summarizing the mechanisms involved in macrophage polarization, is clearly presented and well-documented.
We thank the reviewer for his/her appreciation.

2. The second part focused on nutraceuticals is very interesting, but a bit messy in view of the large number of works related to the subject. Note however that the authors nicely summarize the effects of the compounds in Figure 2, which is of great help. It is preferable if the authors restructure the text by separating data observed in vitro (in cultured cells) and in vivo, in animal models for atherosclerosis.
We agree with the reviewer that usually, to improve the readability of a manuscript, it would be preferable to separate in different specific sections evidences arising from "in vitro" and from "in vivo" studies. Nevertheless, in our manuscript, data from animal model are very few compared to data from cultured cells (as highlighted at the end of "Introduction"), for this reason we have preferred to keep them together in the same section in order to harmonize as a whole the text.

3. Observations of nutraceutical effect on macrophage polarization in humans though discussed in the conclusion, could be highlighted in more detail with insights for future research.
We are aware that, as regards research that evaluates nutraceutical interventions on humans, the manuscript is not exhaustive. On the other hand, and considering the abundance of the relative literature, an in-depth overview of data about it goes beyond the purpose of our manuscript, which mainly focuses on biomolecular evidence arising from pre-clinical studies (as we have specified in the abstract and at the end of the Introduction.
Nevertheless, we agree with the reviewer that an improvement in this part can be informative, therefore we have added a new section (4. Nutraceutical approaches to the treatment of atherosclerosis: outcomes from human studies), in which we have considered those studies in humans that we think more interesting and pertinent to the topic of our review, and have furtherly commented them in the "Conclusions".

Reviewer #2:

Specific points:
1. Ref. n. 1 (1993) is outdated, please substitute with a more recent ones
We have substituted this reference with a more recent one (O. Soehnlein, P. Libby, Targeting inflammation in atherosclerosis-from experimental insights to the clinic, Nat. Rev. Drug Discov. 20(8) (2021) 589-610).

2. Chapter 1 / Sections 1.1, 1.2: to improve readability, the general aspects of macrophage differentiation reported here could be usefully condensed and included (as introductory remarks) in the corresponding Chapter 2 / Sections 2.1, 2.2, thus helping to maintain the focus on the atherosclerotic process
Although this is a share opinion, the other reviewers have appreciated chapter 1 as it was in the original manuscript and for this reason we have preferred not to change it.

3. Chapter 3: a clearer title would be: "Modulation of … by nutraceuticals"
As suggested by the reviewer, we have changed the title.

4. Conclusions: as this section is quite lengthy in its present form, may I suggest to change its title to "Concluding remarks and future perspectives
As suggested by the reviewer, we have changed the title.

Reviewer #3:

Specific comments:
1. Overall the scope of the review is appropriate and the thorough evaluation of the various and sometimes conflicting findings regarding the ability of micronutrients to alter macrophage inflammation and metabolism is commendable.
We thank the reviewer for his/her appreciation.

2. Figures and tables are clearly organized, readable, and appropriate to content of the review.
We thank the reviewer for his/her appreciation.

3. At times, the organization of the sections of the review was hard to follow, in particular the introduction of some (but not all) of the micronutrients/nutraceuticals in section 3, and the further mention of additional/different compounds in the following sections. Could the authors revise section 3 to ensure that all the compounds to be discussed in later sections are introduced?
In the present version all the compounds mentioned in section 3 have been included in its introductory part.

4. Likewise, it may strengthen the manuscript to reorganize the sections on 3.1 inflammation and 3.2 inflammasome/autophagy to bring observations/impact on similar pathways by different compounds together in one paragraph, to better compare/contrast the roles of these compounds in modulating these pathways. (Ex. in 3.2, discuss all inflammasome-related studies first, then the autophagy-related findings).
Undoubtedly, section 3 organization suggested by the reviewer is a reasonable alternative to our organization. However, since the main subject of the manuscript are micronutrients, we have preferred to organize the subsections according to the different class of compounds rather than to the different signaling pathways, for this reason we have kept the structure of the original manuscript.

5. Could the authors expand further in section 3.3 on the potential for micronutrients/nutraceuticals to exert atheroprotective effects through activation of NRF2-mediated oxidative stress pathways?
In all the section 3. we have further improved the data concerning the effects of micronutrients/nutraceuticals on NRF2 pathways and Fig. 2 was modified accordingly to it.

6. Sulforaphane from broccoli as Nrf2 activator is mentioned in the text but missing from tables, please add with relevant references.
We have added in the manuscript new references about sulforaphane and Fig. 1 and table 1 were modified accordingly to that.

7. Are there any studies that have evaluated the potential for any of the mentioned compounds to be atheroprotective in humans - i.e., are there any correlative studies that have identified specific compounds associated with atheroprotection in clinical trials?
We are aware that, as regards studies on humans, the manuscript is not exhaustive considering the abundance of literature about this topic. However, a more extensive overview goes beyond the purpose of our manuscript, that mainly focuses on pre-clinical studies (as we have specified in the abstract and at the end of the introduction).
Nevertheless, we have added a new section (4. Nutraceutical approaches to the treatment of atherosclerosis: outcomes from human studies) in which we have considered some human studies that can make more informative our manuscript. We have also improved the "Conclusion" by commenting them.

Minor comments:
In several places, RAW264.2 macrophages are referenced instead of RAW264.7 cell line.
We have checked the cell name in all manuscript and corrected it.

Readability could benefit from revision to improve syntax/flow- some sentences are overly long with multiple clauses joined together.
As suggested by the reviewer, we have modified some sentences to improve the readability of the manuscript.

Macrophage polarization by potential nutraceutical compounds: a strategic approach to counteract inflammation in atherosclerosis.

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ABSTRACT: Chronic inflammation represents a main event in the onset and progression of atherosclerosis and is closely associated with oxidative stress in a sort of vicious circle that amplifies and sustains all stages of the disease. Key players of atherosclerosis are monocytes/macrophages. According to their pro- or anti-inflammatory phenotype and biological function, lesional macrophages can release various mediators and enzymes, which in turn contribute to plaque progression and destabilization or, alternatively, lead to its resolution. Among the factors connected to atherosclerotic disease, lipid species carried by low density lipoproteins and pro-oxidant stimuli strongly promote inflammatory events in the vasculature, also by modulating the macrophage phenotyping. Therapies specifically aimed to balance macrophage inflammatory state are increasingly considered as powerful tools to counteract plaque formation and destabilization. In this connection, several molecules of natural origin have been recognized to be active mediators of diverse metabolic and signaling pathways regulating lipid homeostasis, redox state, and inflammation; they are, thus, considered as promising candidates to modulate macrophage responsiveness to pro-atherogenic stimuli. The current knowledge of the capability of nutriceuticals to target macrophage polarization and to counteract atherosclerotic lesion progression, based mainly on *in vitro* investigation, is summarized in the present review.

KEYWORDS: atherosclerosis, inflammation, oxidative stress, macrophage polarization, nutraceuticals, lipid homeostasis

Abbreviations

ABC: ATP-binding cassette transporter

AMPK: adenosine 5'-monophosphate-activated protein kinase

AP-1: activator protein-1

ASC: apoptosis-associated speck-like protein containing a CARD

ATF: AMP-dependent transcription factor-1

Atg: autophagy-related gene

CLA: conjugated linoleic acid

CK2: casein kinase 2

COX: cyclooxygenase

CREB: cAMP-responsive element-binding

CRP: C-reactive protein

CVD: cardiovascular disease

DHA: docosahexanoic acid

EGCG: epigallocatechin gallate

EPA: eicosapentenoic acid

ER: endoplasmic reticulum

ERK: extracellular signal-regulated kinase

FA: fatty acid

FOX: Forkhead box protein

GPR: G protein-coupled receptor

GSH: glutathione

Hb: hemoglobin

HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A

HIF1α: hypoxia inducible factor 1α

HO-1: heme oxygenase-1

IFN: interferon

IL: interleukin

iNOS: inducible nitric oxide synthase

IRF: interferon regulatory factor

JAK: Janus kinase

JNK: c-Jun N-terminal kinase

KLF: Kruppel-like factor

LA: linoleic acid

0LDL: low density lipoprotein

LOX-1: lectin-like low-density lipoprotein receptor-1

LPS: lipopolysaccharides

LXR: liver X receptor

MAPK: mitogen-activated protein kinase

MCP1: monocyte chemotactic protein 1

miR: microRNA

MKP-1: MAPK phosphatase-1 NOX

MMP: metalloprotease

mTOR: mammalian target of rapamycin

MUFA: monounsaturated fatty acid

MyD88: myeloid differentiation 88

NF-κB: nuclear factor-κB

NLRP3: nucleotide-binding domain (NOD)-like receptor protein 3

NO: nitric oxide

NOX: NADPH oxidase

Nrf2: nuclear factor E2-related factor 2

oxLDL: oxidized LDL

PAMP: pathogen-associated molecular pattern

PBMC: peripheral blood monocyte

PGC: PPARγ-coactivator

PG: prostaglandin

PI3K: phosphoinositide 3-kinase

PMA: phorbol myristate acetate

PPAR: peroxisome proliferator-activated receptor

PPP: pentose phosphate pathway

PRR: pattern recognition receptor

PUFA: polyunsaturated fatty acid

ROS: reactive oxygen species

Rv: resolvin

RXR: retinoid X receptor

SIRT: sirtuin

SOCS: suppressor of the cytokine signaling

SOD: superoxide dismutase

SPM: specialized pro-resolving mediator

SREBP: sterol regulatory element binding protein

STAT: signal transducer and activator of transcription

TCA: tricarboxylic acid

TERT: telomerase reverse transcriptase

TGFβ: transforming growth factor β

Th: T-helper lymphocyte

TLR: Toll-like receptor

TNFα: tumor necrosis factor α

UFA: unsaturated fatty acid

Vit D: vitamin D

Introduction

Atherosclerosis is a chronic inflammatory disorder affecting large and medium-sized arteries and is characterized by the subendothelial accumulation of lipid species carried by low density lipoproteins (LDLs) together with fibrotic tissue and cell debris. The formation of these deposits is the consequence of endothelial cell dysfunction that triggers a cascade of inflammatory reactions characterized by the continuous and uncontrollable transmigration of circulating immune cells into the vessel wall, giving rise to the atherosclerotic plaque. Key players of atherosclerosis are monocytes/macrophages that are provided with several tasks such as lipid and cellular debris clearance, orchestration of inflammatory response, and tissue repairing. As disease progresses, plaque macrophages engulf more and more lipids, transforming themselves into foam cells able to secrete inflammatory molecules and proteolytic factors, and to release reactive oxygen species (ROS). If the insult to the vasculature persists, the inflammatory response becomes chronic and plaque macrophages start displaying perturbed capability to migrate and phagocytize. As a consequence the

number of apoptotic/necrotic cells in the lesion core increases, leading to advanced plaque vulnerability and, eventually, rupture. On the contrary, when noxious materials, including lipids and necrotic debris, are efficiently removed, the inflammatory response can be reversed under the modulation of protective factors and lesion regression occurs. Resident macrophages can, thus, strongly participate to the resolution process by acquiring anti-inflammatory features and functions [1,2].

Lipid accumulation represents a preeminent event in the atheroma development. Hypercholesterolemia associated to high levels of the cholesterol-carrier LDLs is in fact a well-recognized risk factor for atherosclerosis. In particular, oxidative modifications of these lipoproteins favor their uptake by macrophages via specific scavenger receptors (e.g., SR-A, CD-36) and confer pro-inflammatory properties on these particles, contributing significantly to the lesion lipid-rich necrotic core expansion [3].

Macrophages are the most abundant immune cell type in atherosclerotic lesions whose expansion they significantly contribute during all stages of the disease. In fact, they play prominent roles in oxidized LDL (oxLDL) uptake and cholesterol accumulation, lesion matrix remodeling, cytokine release, and clearance of dead cell debris [1,2].

Most recent advances regarding the macrophage dynamics in atherosclerosis point out the complexity of lesional macrophage phenotype: it has been recognized that rather than a few distinct populations, a broad spectrum of cell subsets could be present depending on the environmental signals, including lipid and cholesterol loading, and that the balance among all these cell populations directs plaque evolution [4]. According to this view, a growing consideration is being given to therapeutic strategies specifically aimed at targeting the atherosclerotic macrophage phenotype, thus promoting disease regression [5,6]. In this context, various molecules of natural origin may represent an important opportunity. Thanks to their multiple activities as antioxidants, lipid-lowering agents, and cell signaling modulators, they can likely be effective in counteracting lesion development and, in particular, in regulating the macrophage inflammatory response [7,8].

The purpose of the present review is to provide the major current insights on the applicability of natural compounds in the prevention and treatment of atherosclerosis, taking advantage of their capability to affect macrophage polarization. In particular, we focus on basic research evidence that elucidates the molecular mechanisms in support of beneficial effects of micronutrients as nutraceuticals, principally focusing on macrophage cell models.

1. Macrophage polarization: a general overview

Macrophages are highly versatile cells able to adopt different functional programs in response to the surrounding microenvironmental stimuli, a process known as macrophage polarization. Classically, they are classified into two main cell phenotypes according to their state of activation: in the presence of harmful stimuli they acquire the so-called M1 phenotype, which is able to promote inflammation; conversely, they assume the alternative inflammation suppressing and reparative phenotype M2 when the inflammatory response is no longer needed [9].

Although initially well accepted, more extensive *in vitro* and *ex vivo* studies have shown that this bipolar M1/M2 classification does not accurately represent the macrophage diversity. In fact, M1 and M2 are only the extremes of a broader spectrum of cell subpopulations, overlapping with each other in terms of metabolic adaptation, gene expression, and function associated with a variety of inflammatory, anti-inflammatory, and remodeling gene program. Noteworthy, these phenotypes are transient and reversible consistently with milieu changes [9]. For instance, M2 macrophages have been further classified into M2a, M2b, M2c, and M2d subgroups, according to the different stimuli that activate them and to their protein production. Among them, M2a subgroup contributes to tissue repair, M2b stands out for the production of both pro- and anti-inflammatory cytokines that regulate immune cell functions, M2c exerts the strongest anti-inflammatory activity and is responsible for phagocytosis and apoptotic cell clearance, and finally M2d has angiogenic properties [10].

1.1. Cell signaling involved in macrophage polarization

The inflammatory orientation of macrophages is under strict control by a variety of transcription factors and coregulatory molecules.

Cytokines released by T-helper 1 (Th1) lymphocytes, such as interferon γ (IFNγ), interleukin-1β (IL-1β), and tumor necrosis factor α (TNFα), but also pathogen-associated molecular patterns (PAMPs) detected by pattern recognition receptors (PRRs), lipopolysaccharides (LPS) and lipoproteins activate the M1 phenotype, or classically-activated macrophages, via involvement of the signal transducer and activator of transcription (STAT) family member STAT1/2 [9,11,12]. Among the inflammatory factors pointed to promote M1 differentiation rather than M2 is also included C-reactive protein (CRP) [13]. Conversely, alternatively-activated M2 macrophages are activated by the Th2-derived cytokines IL-4 and IL-13, or by other anti-inflammatory stimuli through STAT3 or STAT6 modulation [9,12]. Nuclear transcription factors involved in lipid homeostasis, namely peroxisome proliferator-activated receptor (PPAR)-γ and liver X receptors (LXRs), are also identified as mediators in M2 anti-inflammatory phenotyping [14]. More in detail, M2a macrophages express high levels of mannose receptors and respond to IL-4 and IL-13, M2b macrophages are activated by

immune complexes and Toll-like receptor (TLR) ligands or IL-1 receptor agonists, M2c macrophages by IL-10 and glucocorticoids [15], and M2d macrophages by TLR-signals through the adenosine receptor [16].

In response to their activation, M1 macrophages release ROS, nitric oxide (NO) via inducible nitric oxide synthase (iNOS), as well as pro-inflammatory cytokines such as TNFα, IL-1β, IL-12, and IL-23, while all types of M2 macrophages produce anti-inflammatory cytokines and growth factors, such as IL-10, IL-4 and transforming growth factor β (TGFβ), and are angiogenic and pro-fibrotic [10,12,17].

1.2. Metabolic requirements associated to macrophage polarization

Macrophages with M1 and M2 phenotypes significantly differ also for the metabolic requirements necessary to sustain their specific activity: while M1 macrophages depend almost on glucose uptake, glycolysis, and pentose phosphate pathway (PPP), bioenergetic supply in M2 macrophages is ensured mainly by oxidative phosphorylation and fatty acid (FA) oxidation [18,19]. On the other hand, metabolic shifts switched on by growth factors and nutrient availability can themselves be the up-stream signals that control macrophage polarization. Overall, polarizing and metabolic cues finely communicate with each other to coordinate the induction of different phenotype activities and the metabolic processes needed to sustain them [17].

Metabolic signaling pathways activated by polarizing signals include Akt, mammalian target of rapamycin (mTOR), and adenosine 5'-monophosphate-activated protein kinase (AMPK) [18]. In fact, activation of the TANK-binding kinase/inhibitor of nuclear factor-κB kinase/Akt pathway or of the mTOR/Akt pathway drives to different glucose utilization in LPS- and IL-4-activated macrophages [20,21]. The transcription factor hypoxia-inducible factor 1α (HIF1α) mediates the M1 reprogramming by LPS and hypoxia through up-regulation of genes involved in glycolysis [22], whose metabolites in turn stabilize HIF1α protein itself [23]. Induction of HIF1α by mTOR also can be responsible for shifts towards glycolytic reactions [24]. Conversely, the oxidative metabolism typical for the anti-inflammatory phenotype is prompted by STAT6 and PPARγ-coactivator (PGC)-1β in response to IL-4 [25], and by AMPK in response to IL-10 [26]. The tricarboxylic acid (TCA) cycle and oxidative phosphorylation are enhanced by IL-4 macrophage activation by up-regulation of genes linked to these routes too, as for example the sedoheptulose kinase carbohydrate kinase-like protein (CARKL), which restricts the glucose flux through the PPP [27]. As a consequence, also mitochondrial metabolism adjustment is associated to macrophage polarization [28]. By perturbing the electron transport chain in mitochondria, both NO and ROS affect energetic supply and metabolic

profile of macrophages, accounting for the suppression of the oxidative phosphorylation and for the switching to glycolytic commitments [18,29,30]. In particular, NO regulates the amount of the catalytic Complex I subunits in murine macrophages and, besides that, the balance of succinate and citrate, the key metabolites of TCA cycle [31]. In addition, ROS overproduction is promoted in mitochondria of inflammatory macrophages by excessive glucose utilization and leads to dimerization of the glycolytic enzyme pyruvate kinase M2 (PKM2), further sustaining glycolysis and the PPP pathway [32]. Activation of NOTCH represents another mechanism to reprogram mitochondrial metabolism in favor of glycolysis and glucose flux to the TCA cycle, thus contributing to mitochondrial ROS generation and ROS-dependent induction of nuclear and mitochondrial M1 genes [33].

2. Macrophage polarization in the atherosclerotic plaque

Macrophage heterogeneity has been recognized in the context of atherosclerosis. Different macrophage populations can originate in response to systemic factors circulating in the blood and to local plaque-specific stimuli; the prevalence of some cell subsets on others can drive plaque evolution and atherosclerosis outcome [34,10]. It has been observed that plaques from symptomatic patients suffering from acute ischemic attack have indeed a greater concentration of M1 macrophages, while M2 macrophages prevail in plaques from asymptomatic patients [35]. At least in mice models, M2 cells are more numerous in early lesions but they shift toward a M1 phenotype as lesion progresses [36]. Moreover, pro-inflammatory macrophages are preferentially located on the rupture-prone shoulders of the plaque, while there are no significant differences between cell subsets in the fibrous caps [37].

In addition to the typical M1 and M2 classes, other macrophage subsets have been specifically recognized in the atheroma (Fig. 1), whose proportion and distribution might reflect plaque vulnerability [5,17].

Oxidative stress is undoubtedely one of the main promoter of atherosclerotic macrophage polarization towards more inflammatory phenotypes: overproduction of oxidant species by macrophages is not only a hallmark of their inflammatory adaptation, but it is also responsible for LDL modification in more pro-atherogenic particles that can in turn trigger and sustain the inflammatory response by the cells. Indeed, in mouse models of atherosclerosis, oxidized phospholipids present in oxLDLs have been established to induce a subtype of macrophages with a Mox phenotype. Compared to M1 and M2, Mox macrophages display reduced phagocytic and chemotactic properties but express antioxidative and detoxifying genes, mainly regulated by the

nuclear factor E2-related factor 2 (Nrf2), which are fundamental for intracellular redox balance maintenance [38].

A non-foam cell type of macrophages, termed as hemoglobin (Hb)-stimulated macrophage, or M(Hb), was identified at hemorrhagic sites of human atherosclerotic lesions. Besides an enhanced cholesterol efflux, they are characterized by a decrease in ROS production and by the expression of anti-inflammatory factors such as IL-10 [39]. Heme also polarizes macrophages towards an atheroprotective hemorrhage-mitigating phenotype, the Mhem subtype, which, by expressing heme oxygenase-1 (HO-1), contributes to cholesterol efflux, Hb clearance via erythrocyte phagocytosis, and oxidative stress reduction [40]. Finally, a very recent publication reported the macrophage polarization towards a pro-atherogenic phenotype after cell exposure to ferrylHb, an oxidized form of Hb commonly present in hemorrhagic atheromas as a consequence of damaged erythrocyte accumulation. FerrylHb internalization by macrophages seems to lead to HO-1 up-regulation and iron overloading within lysosomes. The event induces a transcriptome profile, distinct from that of native Hb and overlapping with gene expression found in human complicated lesions; this gene profile is associated with macrophage activation, inflammation, iron metabolism, apoptosis, and lipid transport, and appears to be driven by activation of the phosphoinositide 3-kinase (PI3K)/HIF1α pathway [41].

A further macrophage state, completely distinct from all the other known phenotypes, namely M4, was described to be induced by the platelet chemokine CXCL4 and to lack phagocytosis capacity but to possess pro-atherogenic properties, including the secretion of metalloprotease (MMP)-7 and MMP-12 [42]. This subtype is predominantly present in the tunica adventitia and intima of coronary arteries of patients with severe coronary artery disease [43].

2.1. Cell signaling and metabolic requirements driving atherosclerotic macrophage polarization

Intra-plaque macrophages, in particular macrophage-derived foam cells, express several PRRs, including TLRs and scavenger receptors (e.g. CD36), and the intracellular PRR inflammasomes [44]. As M1-promoters, PRRs are implicated in the onset and progression of lesions: upon their activation by binding to a multitude of ligands, they trigger diverse signaling cascades in macrophages, resulting in the expression of pro-inflammatory proteins. Ligands of PRRs are PAMPs present in atherosclerotic plaques such as bacterial nucleic acids, peptidoglycans, and exogenous heat shock proteins (HSPs). Beside them, damage-associated molecular patterns (DAMPs), which include cholesterol crystals, oxLDLs, necrotic cell debris, and extracellular matrix components accumulating in growing lesions, also interact with PRRs [11,12]. In response to them, myeloid differentiation 88 (MyD88)-dependent and/or TIR-domain-containing adaptor protein inducing IFNβ (TRIF)-

dependent pathways are triggered leading to TLR activation and final induction of transcription factors such as interferon regulatory factors (IRFs), nuclear factor- κB (NF-κB), c-Jun, Forkhead Box (FOX) O3a, and p53 [11,12]. For example, TLR4 is stimulated by saturated FAs and by minimally modified LDLs via either MyD88-dependent or MyD88-independent/ROS-dependent mechanisms, while oxLDLs stimulate TLR4/6 after binding to the scavenger receptor CD36 [11]; macrophage activation by lysosomal damaging cholesterol crystals requires the involvement of the intracellular nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3) inflammasome [45]; other factors able to induce NLRP3 are ROS, oxLDLs, mitochondrial dysfunction, and endoplasmic reticulum (ER) stress [46-48]. Upon NLRP3 activation, both apoptosis and pyroptosis, a caspase-dependent form of cell death characterized by plasma membrane pore formation and intracellular content release [49], occur contributing to the necrotic core formation [50].

Furthermore, the on-off switch of inflammasome can depend on autophagy, a process aimed at eliminating intracellular macromolecules and aged/damaged organelles, and essential to maintain cellular energy balance and nutritional status, including lipid availability. In particular, lipophagy, namely the autophagic clearance of intracellular lipid materials, regulates cholesterol efflux from macrophages by modulating the lysosomal acid lipase, which is responsible for the hydrolysis of cholesteryl esters stored in the lipid droplets [51]. Autophagy is relevant in determining the macrophage inflammatory state; indeed, its loss promotes systemic inflammation by polarizing macrophages towards M1 cells at the expense of M2 cells [52], thus it is reasonable that it acts in the same way in the plaque. In support of this, in ApoE-null mice macrophages autophagy was seen to become dysfunctional with plaque progression, triggering inflammasome hyper-activation and IL-1β overproduction [53]. *In vitro* and *in vivo* studies pointed to the metabolic anti-inflammatory PI3K/Akt/mTOR pathway being critical for autophagy execution by atherosclerotic macrophages and, ultimately, for determining their differentiation [54,55]. Certain sirtuins (SIRTs), a class of deacetylases involved in various physiological processes, including cell metabolism and cellular response to stress, have also been reported to promote autophagy. This occurs through deacetylation of autophagy-related nuclear and cytosolic factors, such as FOXO1, FOXO3, and autophagy-related genes (Atgs), through involvement in rapamycin complex 1 (mTORC1)- and AMPK-dependent signals, counteracting foam cell formation [56].

In addition, dysregulation of lipophagy accounts for inefficient removal of apoptotic cells by efferocytosis, contributing to accumulation of toxic cell debris in the lesion core [57]. One of the main regulators of the efferocytic machinery, which appears to be compromised in the lipid engulfed macrophages, is Mer tyrosine kinase (MerTK). Activation of this kinase depends on NADPH oxidase (NOX)-derived ROS and TLR4, and is promoted by oxidized polyunsaturated fatty acids (PUFAs)

[58,59]. Of note, efferocytosis presumably addresses macrophages to an anti-inflammatory phenotype since its inhibition promotes IL-1β, IL-6, and TNFα expression, but decreases IL-10 and TGFβ levels [60]. In addition, LXR signaling has been shown to be critical for a functional efferocytic process [61]. A close relationship exists also between efferocytosis and the lipid mediators lipoxins, resolvins (Rvs), protectins, and maresins; all these molecules favor a correct efferocytosis execution contributing to pro-resolving macrophage skewing and quelling of inflammation [62]. In this connection, biosynthesis of these lipid mediators appears higher in M2 compared to M1 macrophages, where biosynthesis of pro-inflammatory autocoids prevails, demonstrating that different macrophage subtypes are also characterized by a specific profile of endogenous lipid mediators [63].

Besides PRRs, other signal cascades have been suggested to drive macrophage polarization. For example, NOTCH pathway promotes the activation of M1 macrophages in atherosclerotic plaques [64], whereas its inhibition raises the secretion of IL-10 by M2-like population [65]. Members of the transcription factor Kruppel-like factor (KLF) family can also underlie macrophage differentiation: KLF4 promotes M2 polarization by inhibiting NF-κB signaling, and likely cooperates with STAT6 and PPARγ, constituting an alternative axis for the anti-inflammatory transition [66]. Conversely, exposure to oxLDLs switches M2 macrophages to a pro-inflammatory M1 profile by preventing the expression of KLF2 [67].

As regards the macrophage classes specifically present in the atherosclerotic plaque, Mox differentiation by oxidized phospholipids depends on Nrf2 activation [38], M(Hb) differentiation depends on haptoglobin-Hb complex formation [39], while Mhem differentiation occurs through induction of activating cyclic AMP-dependent transcription factor-1 (ATF-1), which subsequently induces both HO-1 and LXRβ [40].

Moreover, polarization of atherosclerotic macrophages can be affected by dysfunctional metabolism. Limited oxygen supply in the lesion leads to HIF1α-dependent suppression of FA oxidation and favors, instead, glucose metabolism and lipid accumulation, likely contributing to the inflammatory activation of macrophages [68-70]. Furthermore, ROS overproduction through the mitochondrial oxidative metabolism of foam cells causes mitochondrial damage and blockage of oxidative phosphorylation, and consequently directs to M1 polarization [71].

3. Modulation of atherosclerotic macrophage polarization by nutraceuticals

Classical pharmacological approaches for the prevention and treatment of atherosclerosis aim to correct disorders in the lipid profile, mainly in cholesterol metabolism; however, new strategies, able

to counteract the inflammatory boost that drives plaque progression, are gaining increasing consideration by the clinical community.

Given the importance of dietary habits for health, constituents of foods can offer a reliable support. It is well recognized that the consumption of fruits, vegetables, spices, nuts, fish, and olive oil is able to decrease atherosclerosis incidence, not only by regulating lipid levels but likely also by regulating other processes that contribute to atheroma development [8]. Indeed, the majority of these foods have a high content of bioactive compounds with proven antioxidant, cell signaling, and metabolic activity, which are thus strong candidates for the inhibition of the pro-inflammatory activation of immune cells and consequently for plaque stabilization and even regression [8]. Noteworthy, some advantages derive for the long-term use of natural origin molecules compared to synthetic drugs due to their more relative safety, fewer side effects, and greater efficacy. The list of potentially anti-atherogenic micronutrients includes polyphenols, carotenoids, terpenoids, unsaturated fatty acids (UFAs), and vitamins (Table 1).

Polyphenols are undoubtedly the most important and abundant phytochemicals in the human diet. They are classified in different subclasses, among which are flavonoids, phenolic acids, phenolic alcohols, stilbenes, and lignans; they are chemically characterized by the presence of one or more benzene rings joined to hydroxyl groups, which confers them with antioxidant capacity [72]. Among them are curcumin, isolated from the rhizomes of turmeric and present in the spice curcuma, resveratrol, the main polyphenol in wine, and the olive oil derivatives oleuropein, tyrosol and hydroxytyrosol, all of which have been extensively investigated in the contest of vascular pathology [8].

Other antioxidants of plant origin are carotenoids, a class of lipophilic pigments that comprises carotenes and xanthophylls, according to the presence or absence of oxygen groups, respectively. Lycopene, abundant in tomato, and β-carotene, present in green leafy vegetables, and in orange and yellow fruits and vegetables, are the most widespread carotenes in nature, whereas lutein, from crucifers and egg yolk, is the most common xanthophyll; all of them have been considered for their positive health outcomes. Noteworthy, carotenoids cannot be synthesized by most animals where they are substrates of the enzymatic cleavage that gives rise to vitamin A. The latter, in its active form (i.e. retinoic acid), is the ligand of the transcriptional factors retinoid X receptors (RXRs), fundamental for immune system differentiation and function, as well as for energy metabolism [73].

Olive oil and other vegetable oils provide monounsaturated fatty acids (MUFAs), also recognized to be beneficial for cardiovascular health [74].

Certain organosulfur compounds, such as allicin from garlic and sulforaphane from cruciferous vegetables and mustard, appear beneficial against cardiovascular diseases (CVD) by improving lipid metabolism and modulating crucial redox sensitive pathways [8,75].

Phytosterols are steroid compounds found in vegetable sources such as oils, nuts, fruits, and cereals. The family includes β-sitosterol, stigmasterol, campesterol, and brassicasterol. Thanks to their structure similarity to cholesterol, they have been considered to correct aberrations in cholesterol homeostasis [76].

Ginseng is another world-wide used herbal medicine potentially effective in the treatment of cardiovascular and, more generally, of metabolic diseases. Its anti-inflammatory activity relies principally on members of the saponin family, ginsenosides [77]. Another saponin of interest is diosgenin from fenugreek seeds and soy beans [78].

Berberine, an alkaloid extracted from the root, rhizome, and stem bark of many medicinally important plants, such as *Hydrastis canadensis* (goldenseal), *Coptis chinensis Franch* (Coptis orgoldenthread), *Berberis aquifolium* (Oregon grape), *Berberis vulgaris* (barberry), and *Berberis aristata* (tree turmeric), has been found to regulate lipid metabolism and homeostasis **[**79].

More recently, research attention focused on iridoids, which are secondary metabolites of alkaloid biosynthesis occurring in several plants and some animals. These monoterpenes are provided with anti-inflammatory and antioxidant properties [80].

Another promising natural compound is the diterpene tanshinone IIA, the main fat-soluble monomer component of the root of Danshen (*Salvia miltiorrhiza*), extensively used in traditional folk medicine for the treatment of cerebrovascular disease and CVD [81]

Although fruits and vegetables are preferentially recommended for healthy diets, foodstuffs of animal origin can be sources of bioactive molecules as well. Indeed, not only nuts and vegetable oils but also fish, fish oil, and animal fats are supplies of UFAs, which might be taken into account as potential valuable micronutrients. It is worth to be underlined, however, that ω-6 PUFAs also possess pro-inflammatory features, thus their consumption should be carefully considered [8,82]. Dietary intake of ω-3 and ω-6 PUFAs, many of which cannot be synthesized *in vivo* and therefore are called essential FAs, is determinant for the endogenous production of eicosanoid molecules involved in the inflammatory response. The major examples are the ω-3 eicosapentenoic acid (EPA) and its metabolite docosahexanoic acid (DHA). Besides the intake from fish such as salmon, herring, cod, and bluefish, minimal amount of EPA can also be provided by conversion in the body of the other essential ω-3 PUFA α-linolenic acid [82].

The carotenoid astaxanthin too is commonly found in seafood such as salmon, trout, fish eggs, and crustaceans, to which it confers the typical pink or red color [83].

In addition, eggs, fish, meat, and milk fat are sources of the lipophilic cholesterol-based vitamin D (vit D). Of note, although vit D is commonly considered an essential micronutrient, its content in foods is very low; thus, additional provision by means of supplements might be necessary to reach the effective dose. Vit D, initially identified as a crucial hormone in the metabolism of bone calcium, is now gaining growing consideration for its role in other physiopathological processes, including lipid metabolism, oxidative stress, immune and inflammatory responses. For this reason, it has been suggested as a coadjuvant in atherosclerosis treatment, but its real benefit is still questionable, since pro-atherogenic consequences have also been reported for oral vit D intake over time, at least in animal models [84,85].

The nervous system and skeletal muscles of mammals and poultry also store carnosine, a natural histidine-containing dipeptide known as a metal chelator as well as scavenger of ROS and reactive aldehydes [86]. Thanks to these properties, carnosine is recognized to be beneficial against atherogenesis, in particular against foam cell formation [87,88].

3.1. Nutraceuticals as modulators of inflammation: direct effects on inflammatory pathways

Almost all the transcription factors and up/down-stream effectors of the signaling pathways, accounted for macrophage pro- or anti-inflammatory polarization, appeared sensitive to the intervention of micronutrients.

In human peripheral blood mononuclear cells, quercetin lessened the oxLDL-induced TLR2 and TLR4 mRNA levels and modulated the TLR/NF-κB signaling pathway, thereby inhibiting cell inflammatory response [89]. In both murine and human macrophages, the flavonoid apigenin counterbalanced the LPS-induced increase of crucial pro-inflammatory cytokines, partly through mRNA destabilization, thus favoring IL-10 expression. Apigenin was also found to block NF-κB and extracellular signal-regulated kinase (ERK)1/2 activation, as well as to interfere with inflammasome assembly [90]. Hydroxytyrosol, a main polyphenol of olive oil, attenuated the expression of pro-inflammatory molecules, including various cytokines and MMPs, in different macrophage models, principally interfering with NF-κB and protein kinase C (PKC) α and PKCβ1 signaling [91,92], but also with STAT1α and IRF-2, through ROS generation [93]. Epigallocatechin gallate (EGCG), the most abundant flavonoid in green tea, markedly attenuated the cyclooxygenase-2 (COX-2)/membrane-bound prostaglandin (PG) E synthases-1 (PGES-1)/PGE_2 pathway in U937 cells activated by oxidized lipids; also in this case, the flavonoid reduced secretion of inflammatory cytokines and MMP-9, which are responsible for plaque instability [94]. Alternative M2 polarization was promoted by a bacterial metabolite of antocyanins, namely protocathecuic acid, which is present

in black olives, mushrooms, and chicory; in J774 macrophages the protocathecuic acid was able to abolish the PI3K/Akt/NF-κB cascade in favor of the STAT6/PPARγ pathway [95]. Deep consideration has been paid to curcumin as an agent employable to polarize macrophage inflammatory state. Originally recognized as an NF-κB suppressor in myeloid cells [96], this polyphenol has been further demonstrated to abolish NF-κB/mitogen-activated protein kinase (MAPK) activation and to contrast M1 polarization of LPS/IFNγ-primed THP1 differentiated cells by inhibiting TLR4 expression [97]. It appears to switch M0 non-activated and RAW264.7 M1 activated macrophages to M2 phenotype too, via activation of the inhibitor of NF-κBα (IκBα) and PPARγ, respectively [98]. Nevertheless, whether curcumin can act as a natural agonist of PPARγ [99] or not [100], regulating it indirectly by other mechanisms, is still debated. In addition, in RAW264.7 macrophages curcumin appeared to inhibit LPS-induced IL-6, TNFα, and COX-2 expression, as well as p38 MAPK activity, and to restore, instead, the expression and synthesis of two members of the suppressor of the cytokine signaling (SOCS) family, namely SOCS-1 and SOCS-3 [101]. Of note, curcumin ability to affect arachidonic acid metabolism in the same cell model has already been reported: it inhibited the formation of PGE_2 by blocking cytosolic phospholipase A2 (cPLA2) phosphorylation, decreasing COX-2 expression, and inhibiting the catalytic activities of 5-lipoxygenase [102]. Resveratrol was able to prevent the NF-κB-dependent macrophage switching to M1 phenotype limiting the production of inflammatory cytokines and MMPs [103]. In murine macrophages, resveratrol was able down-regulated LPS-induced TNFα and IL-6 production by limiting p38 MAPK phosphorylation and, through inhibition of the small noncoding microRNA (miR) immune response regulator miR-155, by promoting the expression of SOCS-1, a STAT inhibitor [104]. Previously, in the same cells resveratrol has demonstrated to reverse LPS effects in terms of inflammatory species' generation, by negatively regulating the cAMP-responsive element-binding protein (CREB) and MAPK pathways, and by activating the PI3K/Akt signaling [105].

Incubation with the ω-3 PUFA DHA was proven to elicit, in the murine macrophage-like lineage RAW264.7, the activation of PPARγ and, consequently, M2 macrophage polarization and efferocytosis of apoptotic cells [106]. Moreover, DHA diminished the responsiveness of human monocytic THP1 cells to TNFα in terms of ROS production and foam cell formation, in a PI3K-dependent manner [107]. To further support the pleiotropic activity of PUFAs as signaling modulators, LPS-stimulated RAW264.7 macrophages exhibited a lower expression of inflammatory cytokines after supplementation with high doses of DHA alone or DHA plus EPA. In this case, suppression of LPS-induced TLR4 expression in the lipid rafts of cell membrane has been suggested to underlie, at least in part, ω-3 PUFAs action, which resulted in the decrease and stabilization of aorta plaques of Western-diet fed ApoE-deficient mice [108]. Anti-inflammatory activity of DHA

might also rely on its interaction with the free fatty acid receptor 4 (FFA4). Acting as an FFA4 agonist, DHA limited COX-2 expression and thereby prostanoid synthesis by LPS-stimulated RAW264.7 cells, independently of COX-1 regulation. Presumably, activation by DHA would promote FFA4 coupling to β-arrestin 2; as a consequence, it would suppress TLR4-dependent Akt/c-Jun N-terminal kinase (JNK) phosphorylation and, finally, p65 nuclear translocation and binding to NF-κB response elements in the COX-2 promoter [109]. An *in vitro* model consisting of human THP-1-derived macrophages treated with chylomicron remnants was used to elucidate the properties of diverse dietary fats. The chylomicron remnants were enriched in saturated FA, MUFAs, ω-6 PUFAs, or ω-3 PUFAs, respectively derived from palm, olive, corn or fish oil. All FAs suppressed NF-κB transcriptional activity, with fish oil FAs causing the strongest inhibition followed by corn oil, palm oil, and then olive oil FAs. With a similar trend, they also enhanced cholesterol removal by the cells, suggesting that NF-κB inhibition might play a role in this modulation [110].

Interestingly, DHA and the flavonoid quercetin used in combination potentiated the anti-inflammatory effects of the single compounds, as observed in LPS-stimulated RAW264.7 cells. Indeed, they synergistically inhibited the expression and activity of NF-κB/MAPK signaling mediators [111]. In human macrophages, DHA, the flavonoid procyanidins B1, B2 and C1, and the combination of DHA with any of the procyanidins, at concentrations typical of the Mediterranean diet, all attenuated NF-κB signaling. These compounds inhibited IκBα phosphorylation, induced the cytoplasmic retention of NF-κB complex through p105 (NF-κB1) overexpression, and inhibited p65 nuclear translocation and DNA binding [112].

Naturally occurring isomers of ω-6 linoleic acid (LA), identified in milk, dairy products, and meat of ruminants, and named conjugated LA (CLA), were originally recognized as ligands for PPARγ and thus able to exert anti-inflammatory effects on murine macrophages [113]; but more recent data indicated a PPARγ suppressive regulation by these compounds, at least in human macrophages, due to diminished ERK1/2 and p38 phosphorylation [114]. In this connection, it was demonstrated that in RAW 264.7 cells CLA isomers regulate LPS-induced inflammatory cytokine gene expression in an isomer-specific manner that likely implies a selective modulation of the PPAR/RXR heterodimer. Among the tested CLA isomers, 9-trans,11-trans-CLA was the most effective, while 9-cis,11-trans-CLA did not significantly affect immune cell activation [115]. Subsequently, CLA was reported to prime mouse bone marrow-derived macrophages to an M2 phenotype secreting IL-10, likely as a consequence of IL-10 receptor overexpression and STAT3 phosphorylation [116].

Futhermore, ω-3 PUFAs give rise to specialized pro-resolving mediators (SPMs), such as E-series resolvins (Rvs) from EPA and D-series Rvs protectins and maresins from DHA; SPMs provide

an additional contribution to M2 phenotyping and to inflammation resolution [63]. Noteworthy, thanks to SPM production, ω-3 PUFAs might direct macrophage activity towards plaque resolution independently from induction of cytokines. For example, RvD1 protects murine macrophages from apoptosis through anti-apoptotic protein up-regulation and also by attenuating oxidative stress through PKA-mediated inactivation of NOX [117].

As regards the ω-6 PUFA arachidonic acid, its role is multifaceted: although its modification by 5-lipoxygenase gives rise to the pro-inflammatory autocoids leukotrienes and PGs, a shift to the 12-lipoxygenase or 15-lipoxygenase enzymatic pathways promotes the synthesis of the SPM lipoxins [118,119]. Among them, lipoxin A_4 inhibited foam cell formation, inflammation, and apoptosis occurrence induced by oxLDL in macrophages [120].

Down-regulation of MMPs and of the extracellular matrix MMP inducer (EMMPRIN), subsequent to NF-κB inhibition, was observed in oxLDL-stimulated macrophages after incubation with the alkaloid berberine [121]. This modulation might depend on miR150-5p increase that leads to the purinergic receptor P2X7 repression and consequently to AMPKα and MAPK inactivation, as newly brought to light in human and murine oxLDL-induced macrophages [122].

In a rat model, crocin, the carotenoid responsible for saffron yellow color, favored the M2 macrophage polarization and balanced the levels of inflammatory cytokines by limiting NF-κB p65 expression and nuclear translocation [123]. Similarly, lycopene and astaxanthin were proven to diminish, in activated M1 macrophages, the secretion of inflammatory mediators such as TNFα or ILs by inhibiting NF-κB [124,125]. In particular, astaxanthin could be effective in preserving Src homology phosphatase 2 (SPH2), a negative regulator of NF-κB activity [125].

NF-κB binding activity has been reported to be inhibited also by the iridoid scropolioside A that reduced PGE_2 and COX-2 production in LPS-stimulated murine RAW264.7 macrophages [126].

Anti-inflammatory properties have been ascribed to the steroidal compound vit D. In LPS-activated macrophages, vit D biologically active form, namely 1,25-dihydroxyvitamin D ($1,25(OH)_2D_3$), up-regulated MAPK phosphatase-1 (MKP-1) turning off the p38 signaling responsible for cytokine production [127]. To further confirm the anti-inflammatory effect of vit D, *in vitro* incubation with $1,25(OH)_2D_3$ decreased TLR4 expression on cell membranes of differentiated M1 macrophages and increased vit D receptor, the latter likely representing a negative feedback loop mechanism to contain the pro-inflammatory M1 response [128]. Of note, vit D receptor has been recently implied in the restoration of functional autophagy and consequently of lipid removal in both mice and human macrophages. The interaction between vit D and its receptor would indeed trigger a protein tyrosine phosphatase non-receptor type (6PTPN6)/SHP-1 dependent signaling underlying autophagy activation [129].

Ajoene isomers and their oxidized sulfonyl derivatives from garlic showed efficacy in attenuating LPS-induced inflammatory response of macrophages in terms of COX-2, PGE_2, and cytokine production. Inhibition of NF-κB transcriptional activity and decreased phosphorylation of p38 and ERK MAPKs accounted for these effects [130].

Among saponins, ginsenoside 20(S)-Rg3 could promote M1 to M2 polarization within atherosclerotic plaques of diabetic mice, a switch which likely results from PPARγ activation [131]; the enhancement of STAT6 phosphorylation could account for the improvement of M2 polarization of RAW264.7 macrophages by ginsenoside Rb1 [132]. In addition, the deactivation of the NOTCH signaling pathway, in particular the prevention of NOTCH intracellular domain nuclear translocation, could account for the suppression of oxLDL-loaded THP1 differentiation by diosgenin, another saponin [133]. Moreover, the last compound was previously reported to reduce the production of ROS and pro-inflammatory mediators by LPS/IFNγ-stimulated macrophages blocking the signaling of NF-κB and activator protein-1 (AP-1), and of their down-stream mediators casein kinase 2 (CK2) and JNK [134].

3.2. Nutraceutical effects on inflammasome and autophagy

Several polyphenols were demonstrated to be effective in hindering autophagy impairment, among which luteolin [135], a flavonoid extract [136], proanthocyanidins, and EGCG [137]. Resveratrol has been recognized as a SIRT1 activator able to sustain macrophagic functional autophagy and ultimately apoptotic cell efferocytosis [138]. Another investigation reported that, in murine macrophages submitted to mitochondrial oxidative stress, autophagy was promoted by resveratrol through a SIRT3/AMPK positive feedback loop [139]. In oxLDL-induced RAW264.7 foam cells, the flavonoid quercetin restored autophagic process, thus reducing lipid accumulation and cell senescence, by abrogation of mammalian Ste20-like kinase 1 (MST1) expression [140]. Similarly, both EGCG and a mixture of oligomeric proanthocyanidins favored lipid disposal in oxLDL-induced foam cells by coordinated activation of autophagy and lysosomal acid lipase, and induction of the cholesterol transporters ATP-binding cassette transporter (ABC) A1 and ABCG1. In this case, autophagosome formation was triggered by activation of the Class PI3K/Beclin1 complex followed by assembly of the Atg12-Atg5-Atg16L and Atg8/LC3 complexes; interestingly, the same results were observed also by treatment with β-sitosterol [137]. Anti-atherogenic and anti-inflammatory properties of curcumin might rely on its capacity to reduce NLRP3 inflammasome expression, caspase-1 cleavage, and IL-1β secretion, as observed in phorbol myristate acetate (PMA)-induced human macrophages. All these actions seem to depend not only on the down-regulation of

TLR4/MyD88/NF-κB signal cascade but also on the deactivation of the purinergic 2X7 receptor (P2X7R), another up-stream factor for NLRP3 assembly induction [141]. To further support that polyphenols are effective in interfering with NLRP3 inflammasome signal switch on, there is the evidence that a red wine extract or, to a lesser extent, resveratrol alone negatively affected LPS-priming of murine macrophages necessary for NLRP3 synthesis and IL-1β secretion; in addition, the wine extract preserved from activation of NLRP3 by complexation with the adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC), whose expression was lessened by wine polyphenols [142]. Similarly, luteolin inhibited the expression of NLRP3, ASC, caspase-1, IL-18, and IL-1β in LPS-stimulated RAW264.7 cells, thus promoting their polarization toward an M2 macrophage type, as confirmed by the induction of the M2 markers arginase-1 and IL-10. In addition, the pholyphenol was also confirmed to limit ROS production [143].

Berberine might be considered for autophagy promotion too. In fact, this alkaloid was proven to reduce the inflammatory response of both human and murine oxLDL-loaded macrophages by stimulation of autophagy through intervention on Akt/mTOR or AMPK/mTOR signaling pathways [144,145].

Futhermore, the saponin araloside promoted M2 polarization of murine macrophages exposed to oxLDL reducing foam cell formation; also in this case, autophagy induction, mediated by SIRT1 up-regulation, was recognized as the driving force [146]. Another saponin, namely ginsenoside Rb1, improved autophagy in macrophage foam cells via AMPK phosphorylation that subsequently led to higher microtubule-associated protein light chain 3 (LC3)II and Atg5 levels [147]. Ginsenosides might also rescue cells from inflammasome activation, and likely from pro-inflammatory IL-1β maturation and secretion, as demonstrated in mouse and human macrophages, in which both NLRP3 and AIM2 inflammasomes were inhibited by a red ginseng extract [148]. Moreover, ginseng is rich in ursolic acid, a triterpene that could additionaly contribute to macrophage autophagy by increasing the expression of Atg5, Atg16l1, and LC3, thereby suppressing IL-1β secretion and promoting cholesterol efflux [149].

Another natural compound acting on autophagy is tanshinone IIA. It resulted to activate KLF4 and to enhance autophagy and M2 polarization of oxLDL-induced macrophages by inhibiting miR-375 [150].

Scropolioside B, an iridoid, decreased expression and synthesis of NLRP3, pro-IL-1β, and IL-1β in LPS-induced THP1 cells [151].

As regards PUFAs, macrophages, isolated from mice fed on a diet supplemented with both fish or botanical ω-3 and ω-6 PUFAs, exhibited NLRP3 inflammasome suppression, and reduced IL-1β secretion as a consequence of improved autophagy and mitochondrial function. Of note, botanical

ω-3 and ω-6 PUFAs action seemed independent of mitochondrial ROS production [152]. Administration of EPA, DHA, and other ω-3 PUFAs to bone-marrow derived macrophages prevented LPS-induced NLRP3 and NLRPb1 inflammasome activation and IL-β1 secretion. At least for NLRP3, ω-3 PUFAs might signal through activation of FFA4 and GPR40 [153].

3.3. Nutraceuticals as modulators of cell redox equilibrium

Micronutrients might be helpful in alleviating disease exacerbation caused by imbalances in the redox equilibrium. According to their chemical structure, many of these substances work as classical antioxidants provided with ROS scavenging, chain-reaction quenching, and metal-chelating activities. Besides that or alternatively, they have been proven to affect the principal signal cascades that rule redox equilibrium inside and outside cells [8,72,75].

Polyphenols seem to act primarily through involvement of the transcription factor Nrf2, critical for the cells to carry out the antioxidant response against oxidative damage. For example, both hydroxytyrosol and resveratrol quenched the oxidative and inflammatory burst triggered by LPS in macrophages, reducing PGE_2 production likely through the negative regulation of the immune response regulator miR-146a and the promotion of Nrf2 nuclear translocation [154]. A polyphenolic extract from Tarocco citrus reduced iNOS and COX-2 expression and ROS/NO release by murine macrophages under inflammatory condition. Inhibition of NF-κB and activation of Nrf2 would account for the extract anti-inflammatory and antioxidant activities, respectively [155]. Protocatechuic acid potentiated the glutathione (GSH) antioxidant system of J774A.1 cells by inducing JNK-mediated Nrf2 phosphorylation [156]. Conversely, an extract of the flavonoids anthocyanins appeared to suppress Nrf2 expression and consequently ROS production and expression of inflammatory cytokines, iNOS, and COX-2 that were induced in RAW264.7 macropohages by LPS [157].

Other micronutrients, besides polyphenols, could improve redox balance in macrophages primarily by Nrf2 modulation. For example, the isothiocyanate sulforaphane from broccoli is a well-established inducer of Nrf2 and, in response to primary oxidative stress, it favors the expression of endogenous phase II and antioxidant enzymes, including GSH related enzymes [158]. Interestingly, Keap1/Nrf2 induction by sulforaphane was proven to promote, at least in non-macrophagic cells, the expression of most of the 20S proteasome subunits involved in the degradation of oxidized proteins, thus representing a strategy to prevent long-term oxidative damage and possibly ER stress [158,159]. As regards macrophages, in RAW264.7 cells sulforaphane inhibited the NLRP1b, NLRP3, NAIP/NLRC4, and AIM2 inflammasomes through an Nrf2-independent pathway. The down-stream

results were the deactivation of caspase-1, together with the repression of IL-1β processing and secretion, and of macrophage pyroptosis [160]. Likely through Nrf2 activation and NF-κB inhibition, sulforaphane elicited the M1 to M2 phenotypic change in PMA-differentiated THP1-derived macrophages, assessed in terms of expression levels of M1 (IL-1β, IL-6, TNF-α, IL-23, CCR7) and M2 (IL-10, PPARγ, MRC1, CCL22) marker genes [161]. Nrf2-mediated anti-inflammatory activity of sulforaphane, including down-regulation of iNOS, was reported also in RAW264.7 cells challenged with LPS [162]. Considering all these evidences, it would be of interest to investigate the possible involvement of Nrf2 and proteasome in the sulforaphane antioxidant activity also in the context of atherosclerosis.

Another isothiocyanate, namely allyl-isothiocyanate from brassica species, counteracted inflammation in LPS-stimulated RAW264.7 macrophages through Nrf2/HO-1 activation. In this case, although not verified, the immune response regulator miR-155 was pointed to as the mediator of the signaling triggered by allyl-isothiocyanate [163].

In addition to Nrf2, other redox sensitive pathways can undergo modulation by natural compounds. Resveratrol counterbalanced PMA-induced intracellular GSH depletion and consequently pro-inflammatory differentiation of THP1 cells via AMPKα activation [164]. Geraniin interrupted, through a SOCS-1/NF-κB-dependent mechanism, the M1 inflammatory response due to ROS and iNOS-derived NO in THP1 cells stimulated with LPS [165]. Myricitrin has been suggested to attenuate the inflammatory activation of murine macrophages by inhibiting the assembly of NOX components. Indeed, the decrease of intracellular ROS resulting by myricitrin administration could account for the abolition of both Janus kinases (JAKs) and STAT1 phosphorylation**,** induced by LPS, and consequently for the suppression of DNA-binding activity of STAT1 [166]. The antioxidant properties of punicalagin and gallic acid, two polyphenols typical of pomegranate juice, could rely on the stimulation of macrophage paraoxonase-2 expression which, in turn, could depend on the activation of PPARγ and AP-1 [167].

Siphonaxanthin, a xanthophyll present in green algae, but not other carotenoids such as lutein and fucoxanthin, attenuated ER stress and the subsequent NF-κB activation, pro-inflammatory cytokine expression, and NO generation induced by the pro-atherogenic advanced glycation end products in RAW264.7 macrophages. In particular, high doses of siphonaxanthin increased the expression of some antioxidant genes that contribute to ER stress mitigation [168].

In oxLDL-treated macrophages, DNA damage, telomere shortening, cell senescence, and apoptosis due to ROS overproduction have been reversed by the iridoid catalpol, acting on the PGC-1α/telomerase reverse transcriptase (TERT) pathway [169]. Alternatively, this iridoid might attenuate M1 polarization, inflammatory response, and oxidative stress elicited by IFNγ in J774.A1

macrophages through induction of estrogen receptor α. The effect could depend on iNOS suppression and on promotion of endothelial NOS instead [170].

Berberine has been shown to reduce macrophage superoxide anion concentration by inhibiting the expression of its source NOX subunit gp91phox, and by recovering superoxide dismutase (SOD) activity [171]. Moreover, β-sitosterol, a molecule which does not show significant ROS scavenger activity, might protect against oxidative stress because of manganese SOD and GSH peroxidase activation in PMA-stimulated RAW264.7 macrophages, likely through mediation of estrogen receptors and PI3K [172].

3.4. Nutraceuticals as modulators of cell metabolism: effects on lipid homeostasis and other metabolic routes

A large number of polyphenols has been reported to reduce foam cell development. EGCG restored ABCA1-mediated reverse cholesterol transport by inhibition in macrophages of the NF-κB activity induced by TNFα. The entire process appeared to depend on the Nrf2-Kelch-like ECH-associated protein 1 (Keap1) signaling, which controls NF-κB function [173]. Transformation of human macrophages into foam cells was also prevented by the citrus flavonoids naringenin and hesperitin by up-regulation of LXRα and its target genes ABCA1 and ABCG1 in an AMPK or PPARγ dependent manner, respectively [174,175]. Other polyphenols effective against lipid-laden cell development are quercetin [176], dihydromyricetin [177], kaempferol [178], resveratrol [179], pomegranate ellagic acid and punicalagin, [180], coffee phenolic acids [181], and curcumin [182]; they act by improving LXRα, PPARγ, and/or ABC-transporters, and eventually by regulating scavenger receptor expression. More in detail, in THP-1 cells LXRα/ABCA1 up-regulation by curcumin might derive from AMPK-SIRT1 signaling activation [183]. On the other hand, it was evidenced that curcumin treatment of M1 subtype RAW264.7 cells led to PPARγ overexpression and, in turn, to ABCA1 and CD36 induction. These effects, together with improved intracellular cholesterol esterification, have been deemed as mechanisms efficient to favor noxious lipid handling by atherosclerotic macrophages and to attenuate their inflammatory response [184]. In contrast with the aforementioned data, the flavonoid gossypetin isolated from the flowers of Hibiscus species limited foam cell formation by PPARγ blockage, promoting the PPARα/LXRα/ABCA1 signal with down-regulation of the CD36-dependent oxLDL uptake by J774.A1 murine macrophages [185]. Similarly, resveratrol was reported to down-regulate PPARγ, but also PPARα, without affecting PPARβ/δ, thus reducing the conversion of THP1 PMA-differentiated cells into foam cells, pointing to AMPK and SIRT1 overexpression as the causative mechanism [186]. A novel mechanism has

been recently discovered to explain the protective action of the flavonoid fisetin against lipid accumulation in oxLDL-exposed macrophages. It comprises the induction of CK2-interacting protein-1 (CKIP-1), a protection factor for the cardiovascular system, and of REGγ (11S regulatory particles, 28 kDa proteasome activator, proteasome activator subunit 3), a member of the 11S proteasome activators already recognized as a therapeutic target for lipid metabolism disorders; indeed, REGγ limits organic cation transporter-1 (Oct-1) transcriptional activity, with the subsequent down-regulation of lectin-like LDL receptor-1 (LOX-1), a scavenger receptor responsible for oxLDL uptake [187]. Very recently, fisetin was demonstrated to regulate lipid homeostasis of oxLDL-induced U937 macrophages also by reducing the sterol regulatory element binding protein 1 (SREBP-1)-dependent expression of the liposynthesis genes 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and FA synthase. The process was shown to depend on the antioxidant properties of the flavonoid that, by quenching ROS production, abolished up-stream NLRP3 activation by oxLDLs [188]. In this connection, FA synthase has been recently suggested to be essential for the TLR-mediated macrophage pro-inflammatory activation and its activity was associated to the promotion of cholesterol biosynthesis [189]. The addition of the pomegranate polyphenols punicalagin and/or β-sitosterol to simvastatin raised the drug efficacy against foam cell formation. Punicalagin and/or β-sitosterol appeared to inhibit cholesterol biosynthesis in J774.A1 macrophages and, in combination with simvastatin, significantly reduced ROS production [190].

Phytosterols are well-known to reduce plasma LDL levels by competitive exclusion of cholesterol from micellar space in the intestinal lumen and modulation of enterocyte cholesterol trafficking. In addition, they might have a direct effect on cholesterol homeostasis in macrophage-derived foam cells; stigmasterol, but not campesterol and sitosterol, positively regulated the expression of ABCA1 and ABCG1. Surprisingly, while stigmasterol attenuated the inflammatory response and campesterol was almost inert, sitosterol exacerbated it [191].

A nutritional mixture of flavanol rich cocoa extract and ω-3 PUFA-rich fish oil, with or without phytosterols, increased ApoA-I mediated cholesterol outflow, possibly reversing foam cell formation, and delayed M1 polarization of a monocyte derived THP-1 macrophage model of atherosclerosis [192]. Nevertheless, the potentiality of UFAs to offset against aberrant lipid homeostasis in atherosclerotic macrophages is controversial. Attenuating the ER stress, both the monounsaturated FA oleic acid and the ω-6 PUFA LA were proven to suppress LOX-1 expression, which was induced by palmitic acid in macrophage-like cells [193]. Apparently, this evidence conflicts with a more recent investigation reporting that LA and its natural source soy oil are pro-atherogenic since, by exacerbation of oxidative stress and modulation of the redox-sensitive p38 MAPK, they favor triglyceride biosynthesis and accumulation in J774.A1 cells [194]. In agreement

to that, the UFAs palmitoleate, oleate, linoleate, and arachidonate had been previously implicated in atherogenesis since their supply impaired cholesterol release by macrophages by enhancing ABCA1 degradation [195]. In particular, the action of oleate and linoleate appears to be mediated by their acyl-CoA derivatives and could depend on acyl-CoA synthetase 1 up-regulation [196]. In addition, palmitic, oleic, linoleic, linolenic, or eicosapentaenoic acids significantly reduced both ABCA1 and ABCG1 macrophage content by altering, at a transcriptional level, the LXR/histone deacetylase signaling and possibly, in a LXR-independent manner, by inhibiting post-transcriptional pathways [197]. In human macrophage-derived foam cells also CLA seemed to reduce intracellular cholesterol content by up-regulation of ABCA1 through both PPARγ- and LXRα-dependent pathways. This occurred although the expression of CD36 was increased by CLA [198]. This is consistent with inhibition by CLA of PGC-1α-mediated macrophage transition to foam cells [199], but contrasts with cholesterol accumulation observed in CD36-overexpressing human macrophages exposed to CLA [200]. It is possible that different CLA isomers have distinct features; in fact, trans-9,trans-11-CLA, but not cis-9,trans-11 and trans-10,cis-12-CLA, activated the cholesterol transporter ABCG1 in murine macrophages by a SREBP1c-dependent mechanism [201].

Among carotenoids, lycopene might be helpful against foam cell formation by affecting cholesterol metabolism of human macrophages. The signal machinery triggered by this compound consisted in an initial inhibition of the cholesterol synthesis key enzyme HMG-CoA reductase followed by small GTPase RhoA inactivation, subsequent increase in PPARγ and LXR activities, and final enhancement of ABCA1 expression [202]. Cholesterol efflux from murine macrophages to high density lipoproteins (HDLs) was accelerated by all-trans-retinoic acid and by its precursor 9-cis-β-carotene. Both compounds increased ApoE protein level but only 9-cis-β-carotene was effective in the induction of ABCA1, ABCG1, and ApoE genes [203]. A novel mechanism was recently suggested to underlie ABCA1, ABCG1, and scavenger receptor class B type I (SR-BI) overexpression, as well as cholesterol outflow promoted by astaxanthin in oxLDL-overloaded macrophages. This mechanism identified noncoding circular RNAs as key players of the process induced by the carotenoid [204].

In PMA-differentiated THP-1 monocytes, the steroidal saponin diosgenin was proven to induce ABCA1 protein and ABCA1-mediated cholesterol outflow without affecting LXR but suppressing miR-19b, a post-trascriptional regulator of ABCA1 [205].

PPARα and LXRα are likely the target of the anti-atherogenic action of the garlic derived allicin too, resulting in improved cholesterol exchange by ABCA1 overexpressing macrophages [206].

Cholesterol efflux associated to M2 polarization was favored by $1,25(OH)_2D_3$ in THP-1-derived foam cells. In this case, LXR-dependent ABCA1 and ABCG1 overexpression was the consequence of the induction of CYP27A1, the enzyme responsible for the synthesis of the LXR agonist 27-hydroxycholesterol [207].

Macrophage differentiation into foam cells has been prevented by berberine too, but through other mechanisms: in oxLDL-stimulated THP1 cells this alkaloid down-regulated the expression of CD36 and LOX-1, and increased the expression of adipocyte enhancer-binding protein 1 (AEBP1), a key regulator of genes associated with intracellular cholesterol homeostasis, including PPARγ, LXRα, and ABC-transporters [208]. In addition, cholesterol-lowering effects of berberine were exerted by activation of Nrf2/HO-1, which accounted for ABC-transporter overexpression, and by inhibition of AP-1, which suppressed scavenger receptor expression [209]. Berberine has also been demonstrated to act by up-regulating AMPK and SIRT1 and by down-regulating PPARγ [210]. Berberine as well as ω-3 the PUFAs DHA and EPA were proven to reduce modified LDL uptake by human macrophages, in a scavenger receptor-independent manner, likely as the result of diminished macropinocytosis [211,212].

A preventive effect of tanshinone II on foam cell formation was observed in human monocyte-derived THP-1 cells challenged with oxLDL. This compound markedly down-regulated SR-A and up-regulated ABCA1 and ABCG1 expression. This was the consequence of ERK activation, Nrf2 phosphorylation and nuclear translocation, and final HO-1 overexpression [213].

All these observations point to metabolism and cell homeostasis of lipids, in particular of cholesterol, as the main processes that can be affected by bioactive micronutrients, but other metabolic cycles can be affected as well. A flavonoid-rich cocoa extract has prompted M2 polarization of active THP-1 derived macrophages which was shown by the reduction of inflammatory cytokine secretion and the increase of IL-10 and IL-12 release. The conversion from M1 to M2 phenotype was accompanied with enhanced oxygen consumption and ATP production through the mitochondrial oxidative phosphorylation, suggesting that flavonoids could act principally as antioxidants that favor the switch towards the oxidative metabolism [214].

Rescue of mitochondrial functions and of the anti-inflammatory metabolism and phenotype might be promoted in M1 macrophages also by carnosine. Indeed, this molecule was recently proven to restore ATP/ADP and $NAD(P)^+$/NAD(P)H balance in activated RAW264.7 macrophages, the last effect being indicative of a strong inhibition of the main reactions responsible for cell ROS production. Furthermore, carnosine antioxidant efficacy appeared to be strengthened by its ability to improve the antioxidant defense through up-regulation of Nrf2, HO-1, and ROS scavenger enzymes,

and simultaneously to decrease NOX-2 and COX-2 expression, reactive nitrogen species formation, and lipid peroxidation [215,216].

4. Nutraceutical approaches to the treatment of atherosclerosis: outcomes from human studies

The evidence, at a molecular level, of the antiatherogenic potential of many natural derivatives has prompted to evaluate their efficacy also in humans. Literature in this field, from small observational or interventional studies to larger epidemiological or clinical trials, has been continuosly growing [8, 74,217,218]. In some cases, as exemplified by some relevant studies hereinafter reported, the micronutrient impact on vascular events was assessed together with inflammatory and oxidative state indices; this provides some information about the correlation between nutraceutical intake and the mechanisms that mainly contribute to atherosclerosis progression. Of note, although the last parameters are usually measured in the circulation and not specifically in the lesions or in the atherosclerotic macrophages, it is conceivable that the systemic condition could reflect what occurs in the plaque cells, among which macrophages.

Polyphenols, UFAs, and carotenoids are the bioactive compounds probably most widespread in nature and abundant in food, thus they are the most investigated for nutritional and pharmacological appplications. The PREDIMED trial is undoubtedly one of the most extensive study carried out to analyze the contribute of the Mediterranean nutritional pattern (i.e. increased intake of vegetables, fruits, legumes, fish or seafood, moderate red wine consumption, and reduced intake of red meat), characterized by a high content of polyphenols and PUFAs, on the primary prevention of CVD. Almost 7500 high-risk participants were submitted to two Mediterranean diet regimens supplemented with either virgin olive oil or nuts, or to a control low-fat diet. Intervention with both the enriched diets brought to short-term and long-term decreases in the circulation of inflammatory cytokines, and to an increase of plaque stability markers, together with an improvement of the classical cardiovascular risk factors, including the lipid profile. Of note, the total polyphenol intake, measured as urinary polyphenol excretion, inversely correlated with the levels of inflammatory markers, suggesting a dose-dependent anti-inflammatory efficacy of polyphenols. In spite of that, no significant changes were observed for the expression of genes involved in the atherosclerosis-related inflammation [219-223].

A meta-analysis of human nutrigenomic studies highlighted the capacity of acute or sustained interventions with a Mediterranean dietary regimen to down-regulate, in peripheral blood monocytes (PBMCs), the expression of inflammatory and pro-oxidant mediators involved in atherosclerosis. Olive oil appeared the main responsible for gene modulation, thanks to its high content of MUFAs,

carotenoids and, in particular, of polyphenols; in fact, some genes, such as TNFα and monocyte chemotactic protein 1 (MCP1), have been affected by olive oil and its polyphenols, within and out of the context of the Mediterranean diet [224].

Other dietary sources of polyphenols have been considered for preventive purposes too. Several epidemiological studies have demonstrated the positive association between cocoa and its products and lower CVD risk and mortality, pointing to a pivotal role played by cocoa flavanols. Indeed, systemic levels of inflammatory markers such as ILs and C-reactive protein (CRP) appeared reduced, mainly in studies considering healthy subjects, after short- and medium-term consumption of cocoa derivatives. Nevertheless, a neutral effect on CRP, ILs, and on other inflammatory proteins (TNFα, MCP1) has also been reported, either in healthy subjects and in individuals at cardiovascular risk [225]. Furthermore, cocoa powder supplementation to high-cardiovascular risk volunteers significantly lowered monocyte CD36 expression [226]. As regards polyphenolic compounds present in green and black tea, both case-control studies and meta-analysis data are in support of an inverse association between tea consumption and the risk of coronary artery disease and its fatal outcomes [227].

Resveratrol and its sources grape and wine were taken into consideration for secondary cardiovascular prevention [228,229]. One-year daily consumption of a grape-extract of the phytochemical was able to modulate, in PBMCs of stable coronary artery disease patients, the expression of inflammation-related transcription factors, including KLF2, NF-κB, AP-1, c-Jun, ATF-2, and CREB-binding protein. In the cells the expression of IL-1β and TNF-α was also significantly reduced, but no significant changes of inflammatory markers were observed in the serum, except the reduction of IL-6 levels. Of note, lower expression of the inflammatory cytokines in PBMCs was concomitant with increased levels of miR-21, miR-181b, miR-663, and miR-30c2, and with lower levels of miR-155 and miR-34a, all involved in monocyte and macrophage inflammatory pathways such as TLR and NF-κB signaling. However, the authors could not detect circulating resveratrol or other grape-derived metabolites, thus the direct relation between resveratrol and the effects observed might be only speculative [230,231].

An anti-inflammatory activity was also ascribed to UFAs, which characterize some dietary patterns, such as the Mediterranean and the Greenland ones, proven to be health promoting [228, 229]. In elderly healthy people, consumption of a Mediterranean diet enriched in MUFAs limited the postprandial inflammatory response in mononuclear cells compared to a saturated FA-rich diet, reducing the expression of TNFα, IL-6 and MCP1, and of MMP-9, thus suggesting a plaque stabilizing efficacy. Of note, MUFA-diet appeared able to act directly on the up-stream NF-κB signaling, by lowering p65 subunit expression [232]. Very recently, outcomes from the ongoing

CORDIOPREV randomized trial further suggest the anti-atherogenic potential of a Mediterranean diet at high virgin olive oil content. It emerged that, compared to a low-fat diet, 5 and 7 years adherence to an olive oil-rich pattern reduced the arterial intima-media thickness of subjects with coronary heart disease at baseline. One might presume that MUFAs present in olive oil largely contribute to vascular protection, although no data about the actual intake of bioactive species, in terms of compound concentration in the plasma and/or urine of participants, were provided to confirm that [233,234].

As precursors of the pro-resolving mediators SPMs, ω-3 PUFA have been explored for atherosclerosis treatment as well, but to date observations from clinical trials did not give conclusive results [235]. On one hand, ω-3 PUFAs, including EPA and DHA, did not significantly reduce cardiovascular events in humans [236]. In this connection, ω-3 PUFAs did not seem to affect SPM levels in urine and plasma of healthy volunteers after fish oil dietary consumption [237]. Conversely, in patients with chronic inflammation, high doses of purified EPA and DHA affected plasma levels of intermediates of SPM biosynthesis and attenuated the expression of pro-inflammatory cytokines in LPS-stimulated PBMCs isolated from study's participants [238].

Moreover, EPA, DHA, docosapentaenoic acid (DPA), and monohydroxylated SPM precursors down-regulated M1 and up-regulated M2 genes of LPS-stimulated monocyte-derived macrophages that were isolated from patients with peripheral artery disease after a short-term intake of marine oil enriched with these FAs and SPM precursors. The phenotypic changes strongly correlated with the plasma SPMs/PGs ratio [239].

More generally, ω-3 PUFAs were demonstrated to promote plaque stabilization: the lipid core of coronary plaques of patients under statin therapy was significantly reduced by EPA co-administration, while fibrous cap formation was favored. It decreased also plasma MCP1 [240]. The OCEAN trial, which enrolled patients awaiting carotid endoarterectomy, reported that interventions with ω-3 PUFA ethyl ester capsules decreased plaque foam cell number and mRNA levels of MMP-7, MMP-9, MMP-12, and IL-6, in association with a higher plaque EPA content [241]. These observations are consistent with an earlier study showing that ω-3 PUFAs-enriched fish oil supplementation to patients with advanced lesions were readily incorporated in the carotid plaque, and were able to limit macrophage infiltration and to enhance atheroma stability. By contrast, the same results were not observed for increased consumption of ω-6 PUFAs [242]. Overall, the latest results are consistent with the outcomes of meta-analysis of clinical trials, including the DART, the GISSI-Prevenzione, and the Jelis trials, from which it emerged that marine ω-3 PUFA supplementation lowered the risk for the major vascular diseases [235].

Among carotenoids, most attention was given to β-carotene and lycopene, while other carotenoids were less investigated. In consideration of data variability, employment of β-carotene for the reduction of vascular morbidity is still debated and should be considered carefully [243]. On one hand, a prospective quantification of β-carotene in the serum of more than 29.000 men, enrolled for the ATBC study, provided evidence for an inverse correlation between β-carotene levels and the occurrence of CVD, heart disease, and stroke during the 31-years follow-up period [244]. On the other hand, according to the Cochrane Database review, β-carotene and vitamin A could increase all-cause mortality [245], and in agreement with that β-carotene was not recommended for prevention of CVD by the US Preventive Task Force [246].

As regards lycopene, interventional studies indicated that its consumption by means of tomato-based foods might be vasoprotective and reduce cardiovascular risk [247]. In addition, in subjects with subclinical atherosclerosis, 1-year treatment with lycopene, alone or in combination with luteolin, induced a decrease in the intima-media thickness that was inversely associated to plasma levels of both carotenoids [248] These effects might be ascribed to lycopene antioxidant and anti-inflammatory propertie; indeed, in individuals at high cardiovascular risk, a daily tomato-juice intake led to a plasmatic trans-lycopene increase that correlated with lessening of plasma IL-8 [249]. However, other studies did not sustain lycopene anti-atherogenic activity. In fact, a relatively high daily consumption of tomato-based products or lycopene supplements were ineffective at reducing vascular disease-related inflammatory markers in moderately overweight, healthy, middle-aged individuals, in spite of the lycopene increase in plasma [250], or at lowering CRP serum levels both in healthy volunteers and in CVD patients [251].

A saffron extract and its main carotenoid, crocin, have also been evaluated for the treatment of CVD patients; crocin, in particular, was able to promote SIRT1 and AMPK expression in the PMBCs of patients and to decrease NF-κB. These effects were accompanied to the reduction of MCP1 and oxLDL levels in the serum [251].

As regards other less common natural bioactive compounds, literature is still limited and certainly less exhaustive, also in consideration of the few number of participants included in the studies presently available [8, 218]. Phytosterols have been considered mainly as cholesterol-lowering agents [218], while their application as atherosclerosis-related anti-inflammatory substances was less investigated. It has been reported that orange juice and orange juice fortified with phytosterols lessened IL levels in healthy human volunteers [252]; however, this evidence does not seem furtherly corroborated since a following meta-analyses of trials on humans did not report anti-inflammatory efficacy for phytosterol-enriched foods, at least in terms of CRP content [253]. Also for vit D evidence about benefits of its supplementation for atherosclerosis treatment is still scarce,

although its deficiency is increasingly referred to as a risk factor for vascular diseases, [85]. Of note, a trial is presently going on to explore the anti-inflammatory effects of the injection of a Danshen extract containing tanshinone II in patients with stable coronary artery disease [254].

Conclusions and future perspectives.

Atherosclerosis is a multifaceted pathological process in which macrophages play a pivotal role. Their orientation towards a more or less inflammatory phenotype can affect plaque evolution towards vulnerable lesions, which ultimately leads to fatal adverse outcomes such as ischemic stroke and myocardial infarction, or, conversely, towards atherosclerotic process resolution. In this connection, inflammatory state, redox balance, and metabolic regulation represent a unique complex network that in a coordinated manner drives macrophage polarization and is, in turn, orchestrated by macrophages themselves according to their phenotype. By operating on this network, several substances of natural origin, including extra-nutritional constituents in foods or micronutrients, have shown efficacy to direct macrophage polarization; for this reason, these compounds have been considered as coadjuvants in the prevention and treatment of atherosclerosis

The body of evidence available shows that nutraceutical bioactivity mainly relies upon their capability to operate on the diverse signaling cascades that regulate macrophage functions (Fig. 2). Of note, the most widespread compounds in dietary sources, such as polyphenols, UFAs, and carotenoids, act on several pathways (e.g. NF-κB, MAPKs, TLRs, Nrf2, and PPARs), involved in multiple fundamental macrophage metabolic cycles and immune responses. In some cases, molecules less common in natural sources or present at very low concentrations seem to target more selectively biochemical factors with more specific roles. Examples of that include the modulation of estrogen receptors by β-sitosterol [172], of inflammasomes by saponins [148], of noncoding RNA by berberine, tanshinone II, and diosgenin [122,150,205], or of TERT by the iridoid catalpol [169].

Considering that, the integration of specific compounds through concentrated forms, including non-food matrices like pills, extracts, or powders [255], might represent a promising tool for therapeutical approaches aimed to direct the inflammatory network in atherosclerotic macrophages. In particular, this could be the case of substances such as saponines, iridoids, and berberin, that not only show more peculiar bioactivities but whose uptake through foodstuffs is limited. Noteworthy, administration of molecules targeting machineries with a selective activity might limit perturbations of signaling pathways with a broad impact on important processes shared by vascular and extra-vascular cells, thus avoiding potentially harmful interferences. Other advantages of nutritional

supplements are their less sensitivity to those alterations brought about food storage and cooking that can change molecule biochemical reactivity, and eventually a major bioavailabilty due to the absence of complex foodstuff matrices.

Nevertheless, definitive and unanimous data about the atherosclerosis-related properties of certain nutraceuticals are still few, as well as information about their bioavailability or potential toxicity due to their overconsumption This is likely the result of the great variability of the experimental models utilized for their investigation, especially as regards dose and duration of treatments. In particular, as regards studies on humans, the molecule anti-atherogenic efficacy is usually verified by means of clinical parameters, such as the intima-media thickness or the frequency and seriousness of cerebro- and cardiovascular events, while inflammatory and oxidative markers are less frequently observed. Moreover, only few investigations have evaluated the actual uptake of the administered substances, for example by measuring plasma, urine or other tissue levels of the presumed bioactive principle and of its metabolites. In the absence of these data, it is difficult to infer a conclusive correlation between a defined nutraceutical and the observed outcomes in humans. For this reason, further *in vitro* and *in vivo* studies on animals and humans, including extensive clinical trials, are necessary to confirm the effectiveness of natural compounds to induce anti-atherogenic polarization in macrophages and to establish the most suitable guide lines for their administration [256,257].

Consequently, the application of micronutrients for atherosclerosis treatment in fully replacement of current pharmacological therapies is not reliable yet. In spite of that, a balanced diet which comprises a variety of nutraceutical-containing foods, such as the Mediterranean diet, likely provides bioactive molecules in amounts adequate to counterbalance atheroma formation. Of note, the copresence in the same foodstuff or meal of more micronutrients could ensure even more efficacy, as highlighted by investigations reporting a synergistic action of them in mixtures [111,112,192]. Functional foods enriched with beneficial species could be also considered [255], in particular to enhance provision of essential micronutrients or when the everyday diet is not sufficient for their supplementation.

In conclusion, diets rich in bioactive species, fortified foods, and micronutrient supplements can be employed for early prevention and possibly to improve patient response to drugs [258], as emerged from the study of Rosenblat and collaborators about the combined effect of pomegranate micronutrients and simvastatin [179]. Of note, this could allow lower drug doses reducing their side-effects. For these reasons, nutraceuticals may represent a valid coadjuvant against atherosclerosis evolution and their consumption should become fundamental in daily nutrition.

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Conflict of interest

Authors declare not to have conflicts of interest.

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Fig. 1. Different macrophage subtypes found in atherosclerotic lesion. Stimuli present in atherosclerotic lesions direct macrophage polarization towards different phenotypes charactized by specific expression and function profiles.

Fig. 2. Nutraceutical modulation of the most relevant macrophage signaling pathways and the relative beneficial effects against atheroma progression.

Highlights

- Pro- or anti-inflammatory macrophage polarization drives atheroma development.
- Oxidative stress and lipid dyshomeostasis promote pro-inflammatory polarization.
- Nutraceuticals affect macrophage inflammatory, oxidative and metabolic pathways.
- Nutraceutical use may favor antiinflammatory atherosclerotic macrophage polarization.

Graphical Abstract

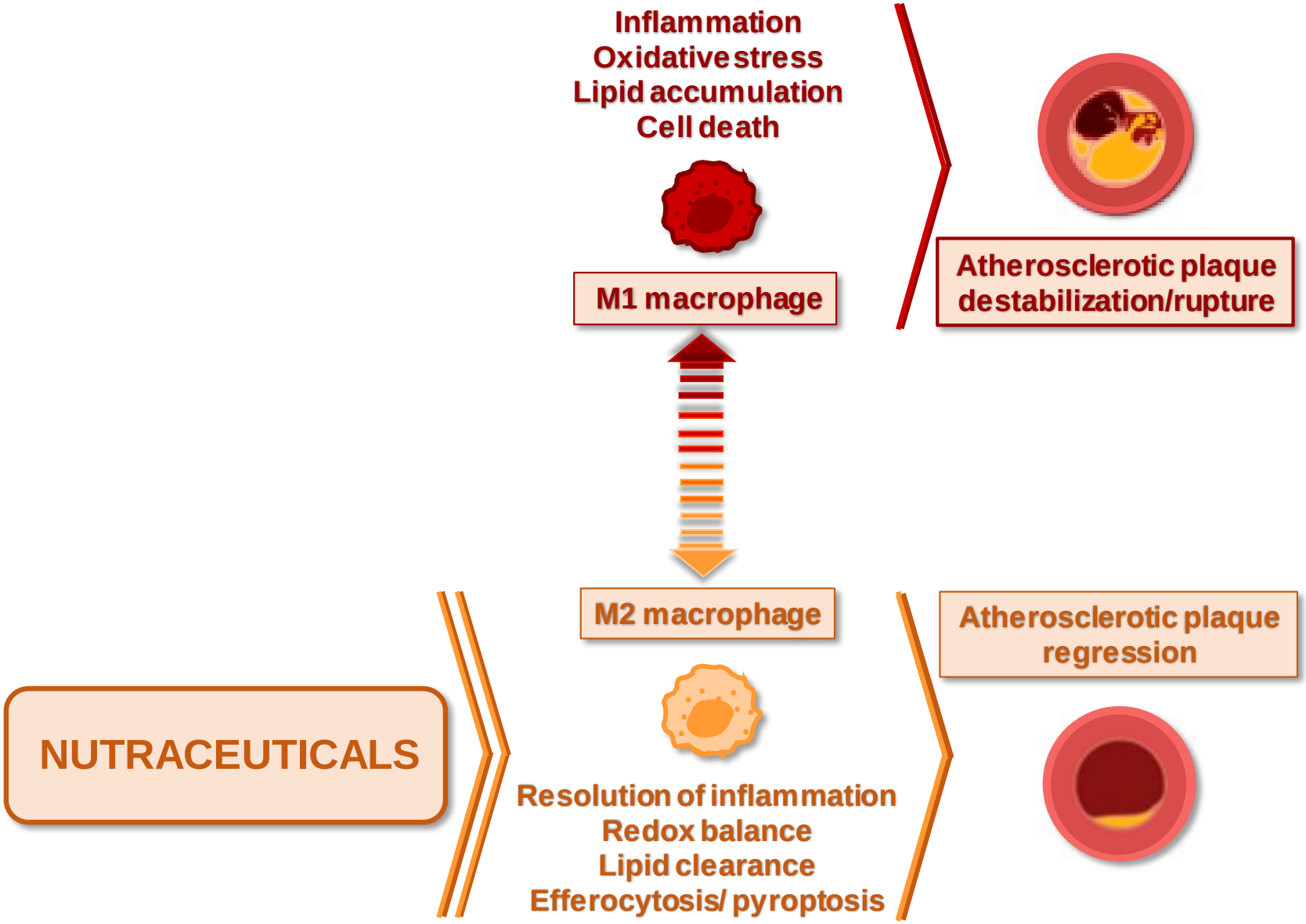

Figure 1

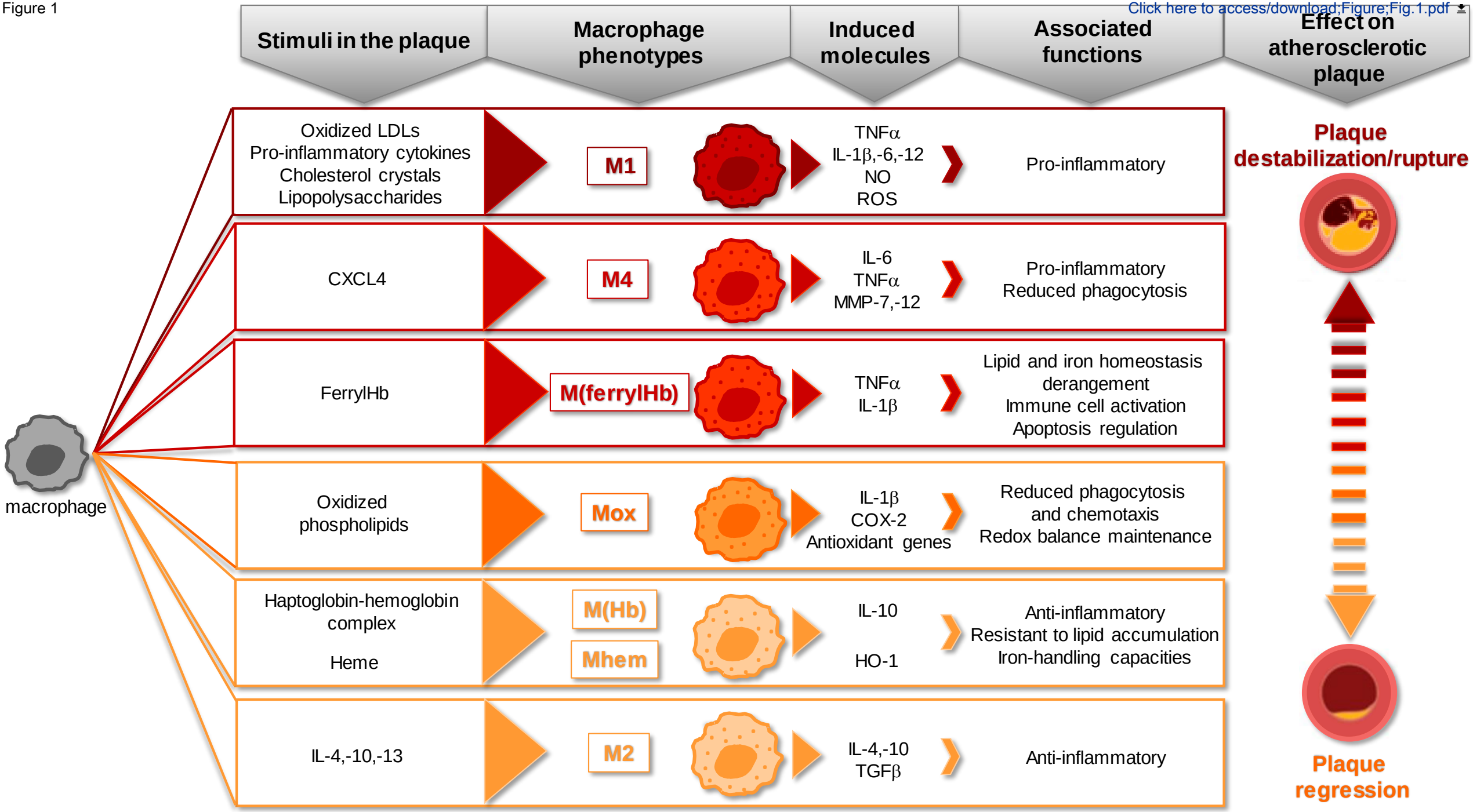

Figure 2

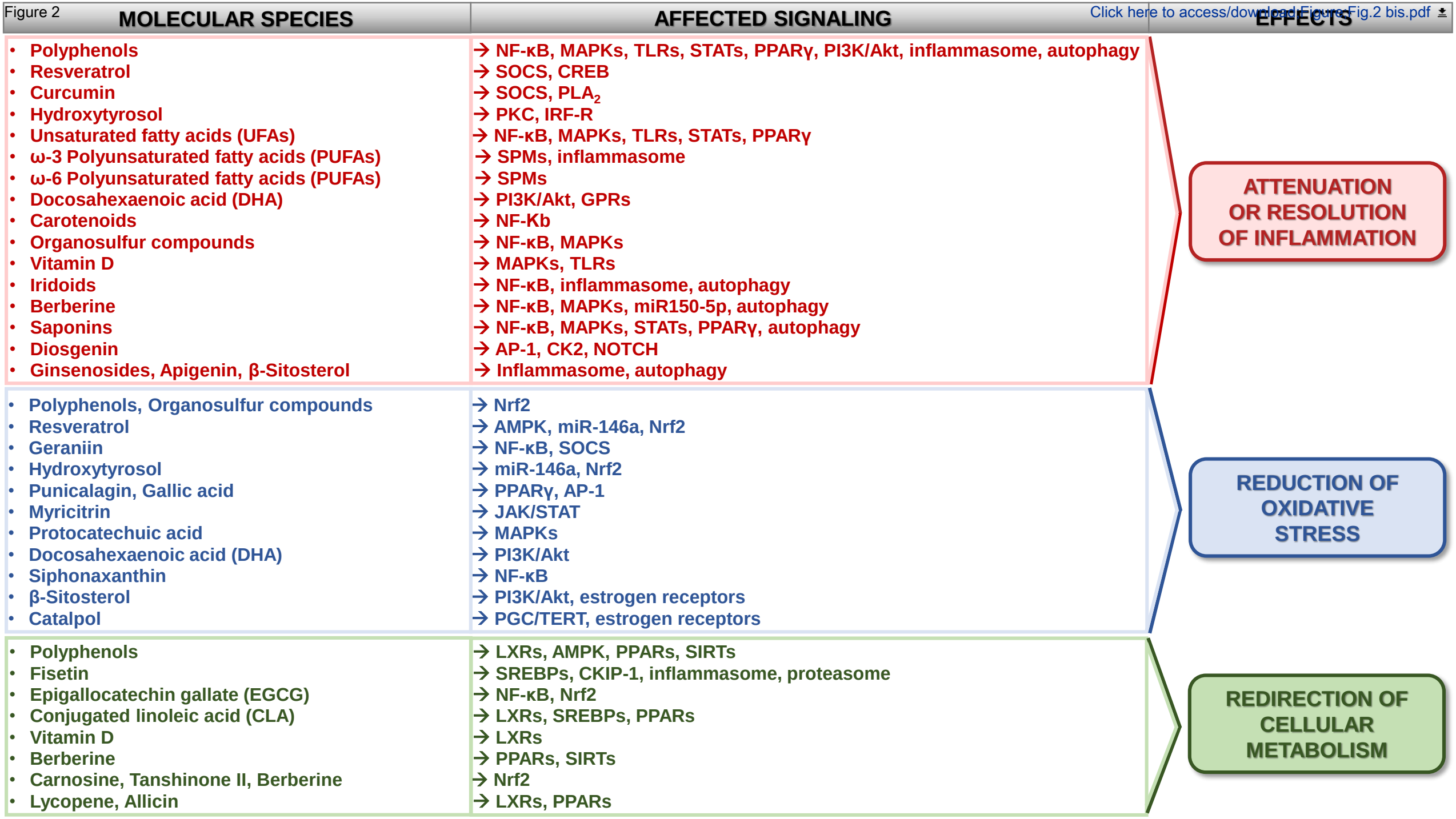

Table 1. Principal nutraceutical compounds and their food sources.

Compounds	Food sources
- **Polyphenols**:	
Resveratrol	Grape and red wine
Curcumin	Turmeric (curcuma)
Epigallocatechin gallate (EGCG)	Green tea, hibiscus
Punicalagin, Gallic acid	Pomegranate juice
Protocatechuic acid	Black olives, mushrooms, chicory
Phenolic acids	Coffee
Hydroxytyrosol	Olive oil
Others	Fruits (citrus), vegetables, cocoa, spices
- **Carotenoids**:	
Carotenes	Green leafy vegetables, crucifers, orange and yellow fruits and vegetables, egg yolk
Xanthophylls	Green algae, salmon, trout, fish eggs, crustaceans
- **Organosulfur compounds:**	
Allicin, Ajoene	Garlic
Sulforaphane, Allyl-isothiocyanate	Crucifers, mustard
- **Saponins**:	
Ginsenosides, Ursolic acid	Ginseng
Diosgenin	Fenugreek seeds, soy beans
- **Iridoids**	Plants
- **Monounsaturated fatty acids (MUFAs)**	Vegetable oils, nuts
- **Polyunsaturated fatty acids (PUFAs)**:	
ω-3 PUFAs, ω-6 PUFAs	Salmon, herring, cod, bluefish
ω-6 Linoleic acid	Milk, dairy products, meat of ruminants
- **Vitamin D**	Eggs, fish, meat, milk
- **Carnosine**	Mammal and poultry meat
- **Berberine**	Goldenseal, Oregon grape, barberry, tree turmeric
- **Phytosterols**	Vegetable oils, fruits, nuts, cereals
- **Tanshinone II**	Root of Danshen (*Salvia miltiorrhiza*)

Macrophage polarization by potential nutraceutical compounds: a strategic approach to counteract inflammation in atherosclerosis.

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ABSTRACT: Chronic inflammation represents a main event in the onset and progression of atherosclerosis and is closely associated with oxidative stress in a sort of vicious circle that amplifies and sustains all stages of the disease. Key players of atherosclerosis are monocytes/macrophages. According to their pro- or anti-inflammatory phenotype and biological function, lesional macrophages can release various mediators and enzymes, which in turn contribute to plaque progression and destabilization or, alternatively, lead to its resolution. Among the factors connected to atherosclerotic disease, lipid species carried by low density lipoproteins and pro-oxidant stimuli strongly promote inflammatory events in the vasculature, also by modulating the macrophage phenotyping. Therapies specifically aimed to balance macrophage inflammatory state are increasingly considered as powerful tools to counteract plaque formation and destabilization. In this connection, several molecules of natural origin have been recognized to be active mediators of diverse metabolic and signaling pathways regulating lipid homeostasis, redox state, and inflammation; they are, thus, considered as promising candidates to modulate macrophage responsiveness to pro-atherogenic stimuli. The current knowledge of the capability of nutriceuticals to target macrophage polarization and to counteract atherosclerotic lesion progression, based mainly on *in vitro* investigation, is summarized in the present review.

KEYWORDS: atherosclerosis, inflammation, oxidative stress, macrophage polarization, nutraceuticals, lipid homeostasis

Abbreviations

ABC: ATP-binding cassette transporter
AMPK: adenosine 5'-monophosphate-activated protein kinase
AP-1: activator protein-1
ASC: apoptosis-associated speck-like protein containing a CARD
ATF: AMP-dependent transcription factor-1
Atg: autophagy-related gene
CLA: conjugated linoleic acid
CK2: casein kinase 2
COX: cyclooxygenase
CREB: cAMP-responsive element-binding
CRP: C-reactive protein
CVD: cardiovascular disease
DHA: docosahexanoic acid
EGCG: epigallocatechin gallate
EPA: eicosapentenoic acid
ER: endoplasmic reticulum
ERK: extracellular signal-regulated kinase
FA: fatty acid
FOX: Forkhead box protein
GPR: G protein-coupled receptor
GSH: glutathione
Hb: hemoglobin
HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A
HIF1α: hypoxia inducible factor 1α
HO-1: heme oxygenase-1
IFN: interferon
IL: interleukin

iNOS: inducible nitric oxide synthase

IRF: interferon regulatory factor

JAK: Janus kinase

JNK: c-Jun N-terminal kinase

KLF: Kruppel-like factor

LA: linoleic acid

0LDL: low density lipoprotein

LOX-1: lectin-like low-density lipoprotein receptor-1

LPS: lipopolysaccharides

LXR: liver X receptor

MAPK: mitogen-activated protein kinase

MCP1: monocyte chemotactic protein 1

miR: microRNA

MKP-1: MAPK phosphatase-1 NOX

MMP: metalloprotease

mTOR: mammalian target of rapamycin

MUFA: monounsaturated fatty acid

MyD88: myeloid differentiation 88

NF-κB: nuclear factor-κB

NLRP3: nucleotide-binding domain (NOD)-like receptor protein 3

NO: nitric oxide

NOX: NADPH oxidase

Nrf2: nuclear factor E2-related factor 2

oxLDL: oxidized LDL

PAMP: pathogen-associated molecular pattern

PBMC: peripheral blood monocyte

PGC: PPARγ-coactivator

PG: prostaglandin

PI3K: phosphoinositide 3-kinase

PMA: phorbol myristate acetate

PPAR: peroxisome proliferator-activated receptor

PPP: pentose phosphate pathway

PRR: pattern recognition receptor

PUFA: polyunsaturated fatty acid

ROS: reactive oxygen species

Rv: resolvin

RXR: retinoid X receptor

SIRT: sirtuin

SOCS: suppressor of the cytokine signaling

SOD: superoxide dismutase

SPM: specialized pro-resolving mediator

SREBP: sterol regulatory element binding protein

STAT: signal transducer and activator of transcription

TCA: tricarboxylic acid

TERT: telomerase reverse transcriptase

TGFβ: transforming growth factor β

Th: T-helper lymphocyte

TLR: Toll-like receptor

TNFα: tumor necrosis factor α

UFA: unsaturated fatty acid

Vit D: vitamin D

Introduction

Atherosclerosis is a chronic inflammatory disorder affecting large and medium-sized arteries and is characterized by the subendothelial accumulation of lipid species carried by low density lipoproteins (LDLs) together with fibrotic tissue and cell debris. The formation of these deposits is the consequence of endothelial cell dysfunction that triggers a cascade of inflammatory reactions characterized by the continuous and uncontrollable transmigration of circulating immune cells into the vessel wall, giving rise to the atherosclerotic plaque. Key players of atherosclerosis are monocytes/macrophages that are provided with several tasks such as lipid and cellular debris clearance, orchestration of inflammatory response, and tissue repairing. As disease progresses, plaque macrophages engulf more and more lipids, transforming themselves into foam cells able to secrete inflammatory molecules and proteolytic factors, and to release reactive oxygen species (ROS). If the insult to the vasculature persists, the inflammatory response becomes chronic and plaque macrophages start displaying perturbed capability to migrate and phagocytize. As a consequence the

number of apoptotic/necrotic cells in the lesion core increases, leading to advanced plaque vulnerability and, eventually, rupture. On the contrary, when noxious materials, including lipids and necrotic debris, are efficiently removed, the inflammatory response can be reversed under the modulation of protective factors and lesion regression occurs. Resident macrophages can, thus, strongly participate to the resolution process by acquiring anti-inflammatory features and functions [1,2].

Lipid accumulation represents a preeminent event in the atheroma development. Hypercholesterolemia associated to high levels of the cholesterol-carrier LDLs is in fact a well-recognized risk factor for atherosclerosis. In particular, oxidative modifications of these lipoproteins favor their uptake by macrophages via specific scavenger receptors (e.g., SR-A, CD-36) and confer pro-inflammatory properties on these particles, contributing significantly to the lesion lipid-rich necrotic core expansion [3].

Macrophages are the most abundant immune cell type in atherosclerotic lesions whose expansion they significantly contribute during all stages of the disease. In fact, they play prominent roles in oxidized LDL (oxLDL) uptake and cholesterol accumulation, lesion matrix remodeling, cytokine release, and clearance of dead cell debris [1,2].

Most recent advances regarding the macrophage dynamics in atherosclerosis point out the complexity of lesional macrophage phenotype: it has been recognized that rather than a few distinct populations, a broad spectrum of cell subsets could be present depending on the environmental signals, including lipid and cholesterol loading, and that the balance among all these cell populations directs plaque evolution [4]. According to this view, a growing consideration is being given to therapeutic strategies specifically aimed at targeting the atherosclerotic macrophage phenotype, thus promoting disease regression [5,6]. In this context, various molecules of natural origin may represent an important opportunity. Thanks to their multiple activities as antioxidants, lipid-lowering agents, and cell signaling modulators, they can likely be effective in counteracting lesion development and, in particular, in regulating the macrophage inflammatory response [7,8].

The purpose of the present review is to provide the major current insights on the applicability of natural compounds in the prevention and treatment of atherosclerosis, taking advantage of their capability to affect macrophage polarization. In particular, we focus on basic research evidence that elucidates the molecular mechanisms in support of beneficial effects of micronutrients as nutraceuticals, principally focusing on macrophage cell models.

1. Macrophage polarization: a general overview

Macrophages are highly versatile cells able to adopt different functional programs in response to the surrounding microenvironmental stimuli, a process known as macrophage polarization. Classically, they are classified into two main cell phenotypes according to their state of activation: in the presence of harmful stimuli they acquire the so-called M1 phenotype, which is able to promote inflammation; conversely, they assume the alternative inflammation suppressing and reparative phenotype M2 when the inflammatory response is no longer needed [9].

Although initially well accepted, more extensive *in vitro* and *ex vivo* studies have shown that this bipolar M1/M2 classification does not accurately represent the macrophage diversity. In fact, M1 and M2 are only the extremes of a broader spectrum of cell subpopulations, overlapping with each other in terms of metabolic adaptation, gene expression, and function associated with a variety of inflammatory, anti-inflammatory, and remodeling gene program. Noteworthy, these phenotypes are transient and reversible consistently with milieu changes [9]. For instance, M2 macrophages have been further classified into M2a, M2b, M2c, and M2d subgroups, according to the different stimuli that activate them and to their protein production. Among them, M2a subgroup contributes to tissue repair, M2b stands out for the production of both pro- and anti-inflammatory cytokines that regulate immune cell functions, M2c exerts the strongest anti-inflammatory activity and is responsible for phagocytosis and apoptotic cell clearance, and finally M2d has angiogenic properties [10].

1.1. Cell signaling involved in macrophage polarization

The inflammatory orientation of macrophages is under strict control by a variety of transcription factors and coregulatory molecules.

Cytokines released by T-helper 1 (Th1) lymphocytes, such as interferon γ (IFNγ), interleukin-1β (IL-1β), and tumor necrosis factor α (TNFα), but also pathogen-associated molecular patterns (PAMPs) detected by pattern recognition receptors (PRRs), lipopolysaccharides (LPS) and lipoproteins activate the M1 phenotype, or classically-activated macrophages, via involvement of the signal transducer and activator of transcription (STAT) family member STAT1/2 [9,11,12]. Among the inflammatory factors pointed to promote M1 differentiation rather than M2 is also included C-reactive protein (CRP) [13]. Conversely, alternatively-activated M2 macrophages are activated by the Th2-derived cytokines IL-4 and IL-13, or by other anti-inflammatory stimuli through STAT3 or STAT6 modulation [9,12]. Nuclear transcription factors involved in lipid homeostasis, namely peroxisome proliferator-activated receptor (PPAR)-γ and liver X receptors (LXRs), are also identified as mediators in M2 anti-inflammatory phenotyping [14]. More in detail, M2a macrophages express high levels of mannose receptors and respond to IL-4 and IL-13, M2b macrophages are activated by

immune complexes and Toll-like receptor (TLR) ligands or IL-1 receptor agonists, M2c macrophages by IL-10 and glucocorticoids [15], and M2d macrophages by TLR-signals through the adenosine receptor [16].

In response to their activation, M1 macrophages release ROS, nitric oxide (NO) via inducible nitric oxide synthase (iNOS), as well as pro-inflammatory cytokines such as TNFα, IL-1β, IL-12, and IL-23, while all types of M2 macrophages produce anti-inflammatory cytokines and growth factors, such as IL-10, IL-4 and transforming growth factor β (TGFβ), and are angiogenic and pro-fibrotic [10,12,17].

1.2. Metabolic requirements associated to macrophage polarization

Macrophages with M1 and M2 phenotypes significantly differ also for the metabolic requirements necessary to sustain their specific activity: while M1 macrophages depend almost on glucose uptake, glycolysis, and pentose phosphate pathway (PPP), bioenergetic supply in M2 macrophages is ensured mainly by oxidative phosphorylation and fatty acid (FA) oxidation [18,19]. On the other hand, metabolic shifts switched on by growth factors and nutrient availability can themselves be the up-stream signals that control macrophage polarization. Overall, polarizing and metabolic cues finely communicate with each other to coordinate the induction of different phenotype activities and the metabolic processes needed to sustain them [17].

Metabolic signaling pathways activated by polarizing signals include Akt, mammalian target of rapamycin (mTOR), and adenosine 5'-monophosphate-activated protein kinase (AMPK) [18]. In fact, activation of the TANK-binding kinase/inhibitor of nuclear factor-κB kinase/Akt pathway or of the mTOR/Akt pathway drives to different glucose utilization in LPS- and IL-4-activated macrophages [20,21]. The transcription factor hypoxia-inducible factor 1α (HIF1α) mediates the M1 reprogramming by LPS and hypoxia through up-regulation of genes involved in glycolysis [22], whose metabolites in turn stabilize HIF1α protein itself [23]. Induction of HIF1α by mTOR also can be responsible for shifts towards glycolytic reactions [24]. Conversely, the oxidative metabolism typical for the anti-inflammatory phenotype is prompted by STAT6 and PPARγ-coactivator (PGC)-1β in response to IL-4 [25], and by AMPK in response to IL-10 [26]. The tricarboxylic acid (TCA) cycle and oxidative phosphorylation are enhanced by IL-4 macrophage activation by up-regulation of genes linked to these routes too, as for example the sedoheptulose kinase carbohydrate kinase-like protein (CARKL), which restricts the glucose flux through the PPP [27]. As a consequence, also mitochondrial metabolism adjustment is associated to macrophage polarization [28]. By perturbing the electron transport chain in mitochondria, both NO and ROS affect energetic supply and metabolic

profile of macrophages, accounting for the suppression of the oxidative phosphorylation and for the switching to glycolytic commitments [18,29,30]. In particular, NO regulates the amount of the catalytic Complex I subunits in murine macrophages and, besides that, the balance of succinate and citrate, the key metabolites of TCA cycle [31]. In addition, ROS overproduction is promoted in mitochondria of inflammatory macrophages by excessive glucose utilization and leads to dimerization of the glycolytic enzyme pyruvate kinase M2 (PKM2), further sustaining glycolysis and the PPP pathway [32]. Activation of NOTCH represents another mechanism to reprogram mitochondrial metabolism in favor of glycolysis and glucose flux to the TCA cycle, thus contributing to mitochondrial ROS generation and ROS-dependent induction of nuclear and mitochondrial M1 genes [33].

2. Macrophage polarization in the atherosclerotic plaque

Macrophage heterogeneity has been recognized in the context of atherosclerosis. Different macrophage populations can originate in response to systemic factors circulating in the blood and to local plaque-specific stimuli; the prevalence of some cell subsets on others can drive plaque evolution and atherosclerosis outcome [34,10]. It has been observed that plaques from symptomatic patients suffering from acute ischemic attack have indeed a greater concentration of M1 macrophages, while M2 macrophages prevail in plaques from asymptomatic patients [35]. At least in mice models, M2 cells are more numerous in early lesions but they shift toward a M1 phenotype as lesion progresses [36]. Moreover, pro-inflammatory macrophages are preferentially located on the rupture-prone shoulders of the plaque, while there are no significant differences between cell subsets in the fibrous caps [37].

In addition to the typical M1 and M2 classes, other macrophage subsets have been specifically recognized in the atheroma (Fig. 1), whose proportion and distribution might reflect plaque vulnerability [5,17].

Oxidative stress is undoubtedely one of the main promoter of atherosclerotic macrophage polarization towards more inflammatory phenotypes: overproduction of oxidant species by macrophages is not only a hallmark of their inflammatory adaptation, but it is also responsible for LDL modification in more pro-atherogenic particles that can in turn trigger and sustain the inflammatory response by the cells. Indeed, in mouse models of atherosclerosis, oxidized phospholipids present in oxLDLs have been established to induce a subtype of macrophages with a Mox phenotype. Compared to M1 and M2, Mox macrophages display reduced phagocytic and chemotactic properties but express antioxidative and detoxifying genes, mainly regulated by the

nuclear factor E2-related factor 2 (Nrf2), which are fundamental for intracellular redox balance maintenance [38].

A non-foam cell type of macrophages, termed as hemoglobin (Hb)-stimulated macrophage, or M(Hb), was identified at hemorrhagic sites of human atherosclerotic lesions. Besides an enhanced cholesterol efflux, they are characterized by a decrease in ROS production and by the expression of anti-inflammatory factors such as IL-10 [39]. Heme also polarizes macrophages towards an atheroprotective hemorrhage-mitigating phenotype, the Mhem subtype, which, by expressing heme oxygenase-1 (HO-1), contributes to cholesterol efflux, Hb clearance via erythrocyte phagocytosis, and oxidative stress reduction [40]. Finally, a very recent publication reported the macrophage polarization towards a pro-atherogenic phenotype after cell exposure to ferrylHb, an oxidized form of Hb commonly present in hemorrhagic atheromas as a consequence of damaged erythrocyte accumulation. FerrylHb internalization by macrophages seems to lead to HO-1 up-regulation and iron overloading within lysosomes. The event induces a transcriptome profile, distinct from that of native Hb and overlapping with gene expression found in human complicated lesions; this gene profile is associated with macrophage activation, inflammation, iron metabolism, apoptosis, and lipid transport, and appears to be driven by activation of the phosphoinositide 3-kinase (PI3K)/HIF1α pathway [41].

A further macrophage state, completely distinct from all the other known phenotypes, namely M4, was described to be induced by the platelet chemokine CXCL4 and to lack phagocytosis capacity but to possess pro-atherogenic properties, including the secretion of metalloprotease (MMP)-7 and MMP-12 [42]. This subtype is predominantly present in the tunica adventitia and intima of coronary arteries of patients with severe coronary artery disease [43].

2.1. Cell signaling and metabolic requirements driving atherosclerotic macrophage polarization

Intra-plaque macrophages, in particular macrophage-derived foam cells, express several PRRs, including TLRs and scavenger receptors (e.g. CD36), and the intracellular PRR inflammasomes [44]. As M1-promoters, PRRs are implicated in the onset and progression of lesions: upon their activation by binding to a multitude of ligands, they trigger diverse signaling cascades in macrophages, resulting in the expression of pro-inflammatory proteins. Ligands of PRRs are PAMPs present in atherosclerotic plaques such as bacterial nucleic acids, peptidoglycans, and exogenous heat shock proteins (HSPs). Beside them, damage-associated molecular patterns (DAMPs), which include cholesterol crystals, oxLDLs, necrotic cell debris, and extracellular matrix components accumulating in growing lesions, also interact with PRRs [11,12]. In response to them, myeloid differentiation 88 (MyD88)-dependent and/or TIR-domain-containing adaptor protein inducing IFNβ (TRIF)-

dependent pathways are triggered leading to TLR activation and final induction of transcription factors such as interferon regulatory factors (IRFs), nuclear factor- κB (NF-κB), c-Jun, Forkhead Box (FOX) O3a, and p53 [11,12]. For example, TLR4 is stimulated by saturated FAs and by minimally modified LDLs via either MyD88-dependent or MyD88-independent/ROS-dependent mechanisms, while oxLDLs stimulate TLR4/6 after binding to the scavenger receptor CD36 [11]; macrophage activation by lysosomal damaging cholesterol crystals requires the involvement of the intracellular nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3) inflammasome [45]; other factors able to induce NLRP3 are ROS, oxLDLs, mitochondrial dysfunction, and endoplasmic reticulum (ER) stress [46-48]. Upon NLRP3 activation, both apoptosis and pyroptosis, a caspase-dependent form of cell death characterized by plasma membrane pore formation and intracellular content release [49], occur contributing to the necrotic core formation [50].

Furthermore, the on-off switch of inflammasome can depend on autophagy, a process aimed at eliminating intracellular macromolecules and aged/damaged organelles, and essential to maintain cellular energy balance and nutritional status, including lipid availability. In particular, lipophagy, namely the autophagic clearance of intracellular lipid materials, regulates cholesterol efflux from macrophages by modulating the lysosomal acid lipase, which is responsible for the hydrolysis of cholesteryl esters stored in the lipid droplets [51]. Autophagy is relevant in determining the macrophage inflammatory state; indeed, its loss promotes systemic inflammation by polarizing macrophages towards M1 cells at the expense of M2 cells [52], thus it is reasonable that it acts in the same way in the plaque. In support of this, in ApoE-null mice macrophages autophagy was seen to become dysfunctional with plaque progression, triggering inflammasome hyper-activation and IL-1β overproduction [53]. *In vitro* and *in vivo* studies pointed to the metabolic anti-inflammatory PI3K/Akt/mTOR pathway being critical for autophagy execution by atherosclerotic macrophages and, ultimately, for determining their differentiation [54,55]. Certain sirtuins (SIRTs), a class of deacetylases involved in various physiological processes, including cell metabolism and cellular response to stress, have also been reported to promote autophagy. This occurs through deacetylation of autophagy-related nuclear and cytosolic factors, such as FOXO1, FOXO3, and autophagy-related genes (Atgs), through involvement in rapamycin complex 1 (mTORC1)- and AMPK-dependent signals, counteracting foam cell formation [56].

In addition, dysregulation of lipophagy accounts for inefficient removal of apoptotic cells by efferocytosis, contributing to accumulation of toxic cell debris in the lesion core [57]. One of the main regulators of the efferocytic machinery, which appears to be compromised in the lipid engulfed macrophages, is Mer tyrosine kinase (MerTK). Activation of this kinase depends on NADPH oxidase (NOX)-derived ROS and TLR4, and is promoted by oxidized polyunsaturated fatty acids (PUFAs)

[58,59]. Of note, efferocytosis presumably addresses macrophages to an anti-inflammatory phenotype since its inhibition promotes IL-1β, IL-6, and TNFα expression, but decreases IL-10 and TGFβ levels [60]. In addition, LXR signaling has been shown to be critical for a functional efferocytic process [61]. A close relationship exists also between efferocytosis and the lipid mediators lipoxins, resolvins (Rvs), protectins, and maresins; all these molecules favor a correct efferocytosis execution contributing to pro-resolving macrophage skewing and quelling of inflammation [62]. In this connection, biosynthesis of these lipid mediators appears higher in M2 compared to M1 macrophages, where biosynthesis of pro-inflammatory autocoids prevails, demonstrating that different macrophage subtypes are also characterized by a specific profile of endogenous lipid mediators [63].

Besides PRRs, other signal cascades have been suggested to drive macrophage polarization. For example, NOTCH pathway promotes the activation of M1 macrophages in atherosclerotic plaques [64], whereas its inhibition raises the secretion of IL-10 by M2-like population [65]. Members of the transcription factor Kruppel-like factor (KLF) family can also underlie macrophage differentiation: KLF4 promotes M2 polarization by inhibiting NF-κB signaling, and likely cooperates with STAT6 and PPARγ, constituting an alternative axis for the anti-inflammatory transition [66]. Conversely, exposure to oxLDLs switches M2 macrophages to a pro-inflammatory M1 profile by preventing the expression of KLF2 [67].

As regards the macrophage classes specifically present in the atherosclerotic plaque, Mox differentiation by oxidized phospholipids depends on Nrf2 activation [38], M(Hb) differentiation depends on haptoglobin-Hb complex formation [39], while Mhem differentiation occurs through induction of activating cyclic AMP-dependent transcription factor-1 (ATF-1), which subsequently induces both HO-1 and LXRβ [40].

Moreover, polarization of atherosclerotic macrophages can be affected by dysfunctional metabolism. Limited oxygen supply in the lesion leads to HIF1α-dependent suppression of FA oxidation and favors, instead, glucose metabolism and lipid accumulation, likely contributing to the inflammatory activation of macrophages [68-70]. Furthermore, ROS overproduction through the mitochondrial oxidative metabolism of foam cells causes mitochondrial damage and blockage of oxidative phosphorylation, and consequently directs to M1 polarization [71].

3. Modulation of atherosclerotic macrophage polarization by nutraceuticals

Classical pharmacological approaches for the prevention and treatment of atherosclerosis aim to correct disorders in the lipid profile, mainly in cholesterol metabolism; however, new strategies, able

to counteract the inflammatory boost that drives plaque progression, are gaining increasing consideration by the clinical community.

Given the importance of dietary habits for health, constituents of foods can offer a reliable support. It is well recognized that the consumption of fruits, vegetables, spices, nuts, fish, and olive oil is able to decrease atherosclerosis incidence, not only by regulating lipid levels but likely also by regulating other processes that contribute to atheroma development [8]. Indeed, the majority of these foods have a high content of bioactive compounds with proven antioxidant, cell signaling, and metabolic activity, which are thus strong candidates for the inhibition of the pro-inflammatory activation of immune cells and consequently for plaque stabilization and even regression [8]. Noteworthy, some advantages derive for the long-term use of natural origin molecules compared to synthetic drugs due to their more relative safety, fewer side effects, and greater efficacy. The list of potentially anti-atherogenic micronutrients includes polyphenols, carotenoids, terpenoids, unsaturated fatty acids (UFAs), and vitamins (Table 1).

Polyphenols are undoubtedly the most important and abundant phytochemicals in the human diet. They are classified in different subclasses, among which are flavonoids, phenolic acids, phenolic alcohols, stilbenes, and lignans; they are chemically characterized by the presence of one or more benzene rings joined to hydroxyl groups, which confers them with antioxidant capacity [72]. Among them are curcumin, isolated from the rhizomes of turmeric and present in the spice curcuma, resveratrol, the main polyphenol in wine, and the olive oil derivatives oleuropein, tyrosol and hydroxytyrosol, all of which have been extensively investigated in the contest of vascular pathology [8].

Other antioxidants of plant origin are carotenoids, a class of lipophilic pigments that comprises carotenes and xanthophylls, according to the presence or absence of oxygen groups, respectively. Lycopene, abundant in tomato, and β-carotene, present in green leafy vegetables, and in orange and yellow fruits and vegetables, are the most widespread carotenes in nature, whereas lutein, from crucifers and egg yolk, is the most common xanthophyll; all of them have been considered for their positive health outcomes. Noteworthy, carotenoids cannot be synthesized by most animals where they are substrates of the enzymatic cleavage that gives rise to vitamin A. The latter, in its active form (i.e. retinoic acid), is the ligand of the transcriptional factors retinoid X receptors (RXRs), fundamental for immune system differentiation and function, as well as for energy metabolism [73].

Olive oil and other vegetable oils provide monounsaturated fatty acids (MUFAs), also recognized to be beneficial for cardiovascular health [74].

Certain organosulfur compounds, such as allicin from garlic and sulforaphane from cruciferous vegetables and mustard, appear beneficial against cardiovascular diseases (CVD) by improving lipid metabolism and modulating crucial redox sensitive pathways [8,75].

Phytosterols are steroid compounds found in vegetable sources such as oils, nuts, fruits, and cereals. The family includes β-sitosterol, stigmasterol, campesterol, and brassicasterol. Thanks to their structure similarity to cholesterol, they have been considered to correct aberrations in cholesterol homeostasis [76].

Ginseng is another world-wide used herbal medicine potentially effective in the treatment of cardiovascular and, more generally, of metabolic diseases. Its anti-inflammatory activity relies principally on members of the saponin family, ginsenosides [77]. Another saponin of interest is diosgenin from fenugreek seeds and soy beans [78].

Berberine, an alkaloid extracted from the root, rhizome, and stem bark of many medicinally important plants, such as *Hydrastis canadensis* (goldenseal), *Coptis chinensis Franch* (Coptis orgoldenthread), *Berberis aquifolium* (Oregon grape), *Berberis vulgaris* (barberry), and *Berberis aristata* (tree turmeric), has been found to regulate lipid metabolism and homeostasis **[**79].

More recently, research attention focused on iridoids, which are secondary metabolites of alkaloid biosynthesis occurring in several plants and some animals. These monoterpenes are provided with anti-inflammatory and antioxidant properties [80].

Another promising natural compound is the diterpene tanshinone IIA, the main fat-soluble monomer component of the root of Danshen (*Salvia miltiorrhiza*), extensively used in traditional folk medicine for the treatment of cerebrovascular disease and CVD [81]

Although fruits and vegetables are preferentially recommended for healthy diets, foodstuffs of animal origin can be sources of bioactive molecules as well. Indeed, not only nuts and vegetable oils but also fish, fish oil, and animal fats are supplies of UFAs, which might be taken into account as potential valuable micronutrients. It is worth to be underlined, however, that ω-6 PUFAs also possess pro-inflammatory features, thus their consumption should be carefully considered [8,82]. Dietary intake of ω-3 and ω-6 PUFAs, many of which cannot be synthesized *in vivo* and therefore are called essential FAs, is determinant for the endogenous production of eicosanoid molecules involved in the inflammatory response. The major examples are the ω-3 eicosapentenoic acid (EPA) and its metabolite docosahexanoic acid (DHA). Besides the intake from fish such as salmon, herring, cod, and bluefish, minimal amount of EPA can also be provided by conversion in the body of the other essential ω-3 PUFA α-linolenic acid [82].

The carotenoid astaxanthin too is commonly found in seafood such as salmon, trout, fish eggs, and crustaceans, to which it confers the typical pink or red color [83].

In addition, eggs, fish, meat, and milk fat are sources of the lipophilic cholesterol-based vitamin D (vit D). Of note, although vit D is commonly considered an essential micronutrient, its content in foods is very low; thus, additional provision by means of supplements might be necessary to reach the effective dose. Vit D, initially identified as a crucial hormone in the metabolism of bone calcium, is now gaining growing consideration for its role in other physiopathological processes, including lipid metabolism, oxidative stress, immune and inflammatory responses. For this reason, it has been suggested as a coadjuvant in atherosclerosis treatment, but its real benefit is still questionable, since pro-atherogenic consequences have also been reported for oral vit D intake over time, at least in animal models [84,85].

The nervous system and skeletal muscles of mammals and poultry also store carnosine, a natural histidine-containing dipeptide known as a metal chelator as well as scavenger of ROS and reactive aldehydes [86]. Thanks to these properties, carnosine is recognized to be beneficial against atherogenesis, in particular against foam cell formation [87,88].

3.1. Nutraceuticals as modulators of inflammation: direct effects on inflammatory pathways

Almost all the transcription factors and up/down-stream effectors of the signaling pathways, accounted for macrophage pro- or anti-inflammatory polarization, appeared sensitive to the intervention of micronutrients.

In human peripheral blood mononuclear cells, quercetin lessened the oxLDL-induced TLR2 and TLR4 mRNA levels and modulated the TLR/NF-κB signaling pathway, thereby inhibiting cell inflammatory response [89]. In both murine and human macrophages, the flavonoid apigenin counterbalanced the LPS-induced increase of crucial pro-inflammatory cytokines, partly through mRNA destabilization, thus favoring IL-10 expression. Apigenin was also found to block NF-κB and extracellular signal-regulated kinase (ERK)1/2 activation, as well as to interfere with inflammasome assembly [90]. Hydroxytyrosol, a main polyphenol of olive oil, attenuated the expression of pro-inflammatory molecules, including various cytokines and MMPs, in different macrophage models, principally interfering with NF-κB and protein kinase C (PKC) α and PKCβ1 signaling [91,92], but also with STAT1α and IRF-2, through ROS generation [93]. Epigallocatechin gallate (EGCG), the most abundant flavonoid in green tea, markedly attenuated the cyclooxygenase-2 (COX-2)/membrane-bound prostaglandin (PG) E synthases-1 (PGES-1)/PGE_2 pathway in U937 cells activated by oxidized lipids; also in this case, the flavonoid reduced secretion of inflammatory cytokines and MMP-9, which are responsible for plaque instability [94]. Alternative M2 polarization was promoted by a bacterial metabolite of antocyanins, namely protocathecuic acid, which is present

in black olives, mushrooms, and chicory; in J774 macrophages the protocathecuic acid was able to abolish the PI3K/Akt/NF-κB cascade in favor of the STAT6/PPARγ pathway [95]. Deep consideration has been paid to curcumin as an agent employable to polarize macrophage inflammatory state. Originally recognized as an NF-κB suppressor in myeloid cells [96], this polyphenol has been further demonstrated to abolish NF-κB/mitogen-activated protein kinase (MAPK) activation and to contrast M1 polarization of LPS/IFNγ-primed THP1 differentiated cells by inhibiting TLR4 expression [97]. It appears to switch M0 non-activated and RAW264.7 M1 activated macrophages to M2 phenotype too, via activation of the inhibitor of NF-κBα (IκBα) and PPARγ, respectively [98]. Nevertheless, whether curcumin can act as a natural agonist of PPARγ [99] or not [100], regulating it indirectly by other mechanisms, is still debated. In addition, in RAW264.7 macrophages curcumin appeared to inhibit LPS-induced IL-6, TNFα, and COX-2 expression, as well as p38 MAPK activity, and to restore, instead, the expression and synthesis of two members of the suppressor of the cytokine signaling (SOCS) family, namely SOCS-1 and SOCS-3 [101]. Of note, curcumin ability to affect arachidonic acid metabolism in the same cell model has already been reported: it inhibited the formation of PGE_2 by blocking cytosolic phospholipase A2 (cPLA2) phosphorylation, decreasing COX-2 expression, and inhibiting the catalytic activities of 5-lipoxygenase [102]. Resveratrol was able to prevent the NF-κB-dependent macrophage switching to M1 phenotype limiting the production of inflammatory cytokines and MMPs [103]. In murine macrophages, resveratrol was able down-regulated LPS-induced TNFα and IL-6 production by limiting p38 MAPK phosphorylation and, through inhibition of the small noncoding microRNA (miR) immune response regulator miR-155, by promoting the expression of SOCS-1, a STAT inhibitor [104]. Previously, in the same cells resveratrol has demonstrated to reverse LPS effects in terms of inflammatory species' generation, by negatively regulating the cAMP-responsive element-binding protein (CREB) and MAPK pathways, and by activating the PI3K/Akt signaling [105].

Incubation with the ω-3 PUFA DHA was proven to elicit, in the murine macrophage-like lineage RAW264.7, the activation of PPARγ and, consequently, M2 macrophage polarization and efferocytosis of apoptotic cells [106]. Moreover, DHA diminished the responsiveness of human monocytic THP1 cells to TNFα in terms of ROS production and foam cell formation, in a PI3K-dependent manner [107]. To further support the pleiotropic activity of PUFAs as signaling modulators, LPS-stimulated RAW264.7 macrophages exhibited a lower expression of inflammatory cytokines after supplementation with high doses of DHA alone or DHA plus EPA. In this case, suppression of LPS-induced TLR4 expression in the lipid rafts of cell membrane has been suggested to underlie, at least in part, ω-3 PUFAs action, which resulted in the decrease and stabilization of aorta plaques of Western-diet fed ApoE-deficient mice [108]. Anti-inflammatory activity of DHA

might also rely on its interaction with the free fatty acid receptor 4 (FFA4). Acting as an FFA4 agonist, DHA limited COX-2 expression and thereby prostanoid synthesis by LPS-stimulated RAW264.7 cells, independently of COX-1 regulation. Presumably, activation by DHA would promote FFA4 coupling to β-arrestin 2; as a consequence, it would suppress TLR4-dependent Akt/c-Jun N-terminal kinase (JNK) phosphorylation and, finally, p65 nuclear translocation and binding to NF-κB response elements in the COX-2 promoter [109]. An *in vitro* model consisting of human THP-1-derived macrophages treated with chylomicron remnants was used to elucidate the properties of diverse dietary fats. The chylomicron remnants were enriched in saturated FA, MUFAs, ω-6 PUFAs, or ω-3 PUFAs, respectively derived from palm, olive, corn or fish oil. All FAs suppressed NF-κB transcriptional activity, with fish oil FAs causing the strongest inhibition followed by corn oil, palm oil, and then olive oil FAs. With a similar trend, they also enhanced cholesterol removal by the cells, suggesting that NF-κB inhibition might play a role in this modulation [110].

Interestingly, DHA and the flavonoid quercetin used in combination potentiated the anti-inflammatory effects of the single compounds, as observed in LPS-stimulated RAW264.7 cells. Indeed, they synergistically inhibited the expression and activity of NF-κB/MAPK signaling mediators [111]. In human macrophages, DHA, the flavonoid procyanidins B1, B2 and C1, and the combination of DHA with any of the procyanidins, at concentrations typical of the Mediterranean diet, all attenuated NF-κB signaling. These compounds inhibited IκBα phosphorylation, induced the cytoplasmic retention of NF-κB complex through p105 (NF-κB1) overexpression, and inhibited p65 nuclear translocation and DNA binding [112].

Naturally occurring isomers of ω-6 linoleic acid (LA), identified in milk, dairy products, and meat of ruminants, and named conjugated LA (CLA), were originally recognized as ligands for PPARγ and thus able to exert anti-inflammatory effects on murine macrophages [113]; but more recent data indicated a PPARγ suppressive regulation by these compounds, at least in human macrophages, due to diminished ERK1/2 and p38 phosphorylation [114]. In this connection, it was demonstrated that in RAW 264.7 cells CLA isomers regulate LPS-induced inflammatory cytokine gene expression in an isomer-specific manner that likely implies a selective modulation of the PPAR/RXR heterodimer. Among the tested CLA isomers, 9-trans,11-trans-CLA was the most effective, while 9-cis,11-trans-CLA did not significantly affect immune cell activation [115]. Subsequently, CLA was reported to prime mouse bone marrow-derived macrophages to an M2 phenotype secreting IL-10, likely as a consequence of IL-10 receptor overexpression and STAT3 phosphorylation [116].

Futhermore, ω-3 PUFAs give rise to specialized pro-resolving mediators (SPMs), such as E-series resolvins (Rvs) from EPA and D-series Rvs protectins and maresins from DHA; SPMs provide

an additional contribution to M2 phenotyping and to inflammation resolution [63]. Noteworthy, thanks to SPM production, ω-3 PUFAs might direct macrophage activity towards plaque resolution independently from induction of cytokines. For example, RvD1 protects murine macrophages from apoptosis through anti-apoptotic protein up-regulation and also by attenuating oxidative stress through PKA-mediated inactivation of NOX [117].

As regards the ω-6 PUFA arachidonic acid, its role is multifaceted: although its modification by 5-lipoxygenase gives rise to the pro-inflammatory autocoids leukotrienes and PGs, a shift to the 12-lipoxygenase or 15-lipoxygenase enzymatic pathways promotes the synthesis of the SPM lipoxins [118,119]. Among them, lipoxin A_4 inhibited foam cell formation, inflammation, and apoptosis occurrence induced by oxLDL in macrophages [120].

Down-regulation of MMPs and of the extracellular matrix MMP inducer (EMMPRIN), subsequent to NF-κB inhibition, was observed in oxLDL-stimulated macrophages after incubation with the alkaloid berberine [121]. This modulation might depend on miR150-5p increase that leads to the purinergic receptor P2X7 repression and consequently to AMPKα and MAPK inactivation, as newly brought to light in human and murine oxLDL-induced macrophages [122].

In a rat model, crocin, the carotenoid responsible for saffron yellow color, favored the M2 macrophage polarization and balanced the levels of inflammatory cytokines by limiting NF-κB p65 expression and nuclear translocation [123]. Similarly, lycopene and astaxanthin were proven to diminish, in activated M1 macrophages, the secretion of inflammatory mediators such as TNFα or ILs by inhibiting NF-κB [124,125]. In particular, astaxanthin could be effective in preserving Src homology phosphatase 2 (SPH2), a negative regulator of NF-κB activity [125].

NF-κB binding activity has been reported to be inhibited also by the iridoid scropolioside A that reduced PGE_2 and COX-2 production in LPS-stimulated murine RAW264.7 macrophages [126].

Anti-inflammatory properties have been ascribed to the steroidal compound vit D. In LPS-activated macrophages, vit D biologically active form, namely 1,25-dihydroxyvitamin D ($1,25(OH)_2D_3$), up-regulated MAPK phosphatase-1 (MKP-1) turning off the p38 signaling responsible for cytokine production [127]. To further confirm the anti-inflammatory effect of vit D, *in vitro* incubation with $1,25(OH)_2D_3$ decreased TLR4 expression on cell membranes of differentiated M1 macrophages and increased vit D receptor, the latter likely representing a negative feedback loop mechanism to contain the pro-inflammatory M1 response [128]. Of note, vit D receptor has been recently implied in the restoration of functional autophagy and consequently of lipid removal in both mice and human macrophages. The interaction between vit D and its receptor would indeed trigger a protein tyrosine phosphatase non-receptor type (6PTPN6)/SHP-1 dependent signaling underlying autophagy activation [129].

Ajoene isomers and their oxidized sulfonyl derivatives from garlic showed efficacy in attenuating LPS-induced inflammatory response of macrophages in terms of COX-2, PGE_2, and cytokine production. Inhibition of NF-κB transcriptional activity and decreased phosphorylation of p38 and ERK MAPKs accounted for these effects [130].

Among saponins, ginsenoside 20(S)-Rg3 could promote M1 to M2 polarization within atherosclerotic plaques of diabetic mice, a switch which likely results from PPARγ activation [131]; the enhancement of STAT6 phosphorylation could account for the improvement of M2 polarization of RAW264.7 macrophages by ginsenoside Rb1 [132]. In addition, the deactivation of the NOTCH signaling pathway, in particular the prevention of NOTCH intracellular domain nuclear translocation, could account for the suppression of oxLDL-loaded THP1 differentiation by diosgenin, another saponin [133]. Moreover, the last compound was previously reported to reduce the production of ROS and pro-inflammatory mediators by LPS/IFNγ-stimulated macrophages blocking the signaling of NF-κB and activator protein-1 (AP-1), and of their down-stream mediators casein kinase 2 (CK2) and JNK [134].

3.2. Nutraceutical effects on inflammasome and autophagy

Several polyphenols were demonstrated to be effective in hindering autophagy impairment, among which luteolin [135], a flavonoid extract [136], proanthocyanidins, and EGCG [137]. Resveratrol has been recognized as a SIRT1 activator able to sustain macrophagic functional autophagy and ultimately apoptotic cell efferocytosis [138]. Another investigation reported that, in murine macrophages submitted to mitochondrial oxidative stress, autophagy was promoted by resveratrol through a SIRT3/AMPK positive feedback loop [139]. In oxLDL-induced RAW264.7 foam cells, the flavonoid quercetin restored autophagic process, thus reducing lipid accumulation and cell senescence, by abrogation of mammalian Ste20-like kinase 1 (MST1) expression [140]. Similarly, both EGCG and a mixture of oligomeric proanthocyanidins favored lipid disposal in oxLDL-induced foam cells by coordinated activation of autophagy and lysosomal acid lipase, and induction of the cholesterol transporters ATP-binding cassette transporter (ABC) A1 and ABCG1. In this case, autophagosome formation was triggered by activation of the Class PI3K/Beclin1 complex followed by assembly of the Atg12-Atg5-Atg16L and Atg8/LC3 complexes; interestingly, the same results were observed also by treatment with β-sitosterol [137]. Anti-atherogenic and anti-inflammatory properties of curcumin might rely on its capacity to reduce NLRP3 inflammasome expression, caspase-1 cleavage, and IL-1β secretion, as observed in phorbol myristate acetate (PMA)-induced human macrophages. All these actions seem to depend not only on the down-regulation of

TLR4/MyD88/NF-κB signal cascade but also on the deactivation of the purinergic 2X7 receptor (P2X7R), another up-stream factor for NLRP3 assembly induction [141]. To further support that polyphenols are effective in interfering with NLRP3 inflammasome signal switch on, there is the evidence that a red wine extract or, to a lesser extent, resveratrol alone negatively affected LPS-priming of murine macrophages necessary for NLRP3 synthesis and IL-1β secretion; in addition, the wine extract preserved from activation of NLRP3 by complexation with the adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC), whose expression was lessened by wine polyphenols [142]. Similarly, luteolin inhibited the expression of NLRP3, ASC, caspase-1, IL-18, and IL-1β in LPS-stimulated RAW264.7 cells, thus promoting their polarization toward an M2 macrophage type, as confirmed by the induction of the M2 markers arginase-1 and IL-10. In addition, the pholyphenol was also confirmed to limit ROS production [143].

Berberine might be considered for autophagy promotion too. In fact, this alkaloid was proven to reduce the inflammatory response of both human and murine oxLDL-loaded macrophages by stimulation of autophagy through intervention on Akt/mTOR or AMPK/mTOR signaling pathways [144,145].

Futhermore, the saponin araloside promoted M2 polarization of murine macrophages exposed to oxLDL reducing foam cell formation; also in this case, autophagy induction, mediated by SIRT1 up-regulation, was recognized as the driving force [146]. Another saponin, namely ginsenoside Rb1, improved autophagy in macrophage foam cells via AMPK phosphorylation that subsequently led to higher microtubule-associated protein light chain 3 (LC3)II and Atg5 levels [147]. Ginsenosides might also rescue cells from inflammasome activation, and likely from pro-inflammatory IL-1β maturation and secretion, as demonstrated in mouse and human macrophages, in which both NLRP3 and AIM2 inflammasomes were inhibited by a red ginseng extract [148]. Moreover, ginseng is rich in ursolic acid, a triterpene that could additionaly contribute to macrophage autophagy by increasing the expression of Atg5, Atg16l1, and LC3, thereby suppressing IL-1β secretion and promoting cholesterol efflux [149].

Another natural compound acting on autophagy is tanshinone IIA. It resulted to activate KLF4 and to enhance autophagy and M2 polarization of oxLDL-induced macrophages by inhibiting miR-375 [150].

Scropolioside B, an iridoid, decreased expression and synthesis of NLRP3, pro-IL-1β, and IL-1β in LPS-induced THP1 cells [151].

As regards PUFAs, macrophages, isolated from mice fed on a diet supplemented with both fish or botanical ω-3 and ω-6 PUFAs, exhibited NLRP3 inflammasome suppression, and reduced IL-1β secretion as a consequence of improved autophagy and mitochondrial function. Of note, botanical

ω-3 and ω-6 PUFAs action seemed independent of mitochondrial ROS production [152]. Administration of EPA, DHA, and other ω-3 PUFAs to bone-marrow derived macrophages prevented LPS-induced NLRP3 and NLRPb1 inflammasome activation and IL-β1 secretion. At least for NLRP3, ω-3 PUFAs might signal through activation of FFA4 and GPR40 [153].

3.3. Nutraceuticals as modulators of cell redox equilibrium

Micronutrients might be helpful in alleviating disease exacerbation caused by imbalances in the redox equilibrium. According to their chemical structure, many of these substances work as classical antioxidants provided with ROS scavenging, chain-reaction quenching, and metal-chelating activities. Besides that or alternatively, they have been proven to affect the principal signal cascades that rule redox equilibrium inside and outside cells [8,72,75].

Polyphenols seem to act primarily through involvement of the transcription factor Nrf2, critical for the cells to carry out the antioxidant response against oxidative damage. For example, both hydroxytyrosol and resveratrol quenched the oxidative and inflammatory burst triggered by LPS in macrophages, reducing PGE_2 production likely through the negative regulation of the immune response regulator miR-146a and the promotion of Nrf2 nuclear translocation [154]. A polyphenolic extract from Tarocco citrus reduced iNOS and COX-2 expression and ROS/NO release by murine macrophages under inflammatory condition. Inhibition of NF-κB and activation of Nrf2 would account for the extract anti-inflammatory and antioxidant activities, respectively [155]. Protocatechuic acid potentiated the glutathione (GSH) antioxidant system of J774A.1 cells by inducing JNK-mediated Nrf2 phosphorylation [156]. Conversely, an extract of the flavonoids anthocyanins appeared to suppress Nrf2 expression and consequently ROS production and expression of inflammatory cytokines, iNOS, and COX-2 that were induced in RAW264.7 macropohages by LPS [157].

Other micronutrients, besides polyphenols, could improve redox balance in macrophages primarily by Nrf2 modulation. For example, the isothiocyanate sulforaphane from broccoli is a well-established inducer of Nrf2 and, in response to primary oxidative stress, it favors the expression of endogenous phase II and antioxidant enzymes, including GSH related enzymes [158]. Interestingly, Keap1/Nrf2 induction by sulforaphane was proven to promote, at least in non-macrophagic cells, the expression of most of the 20S proteasome subunits involved in the degradation of oxidized proteins, thus representing a strategy to prevent long-term oxidative damage and possibly ER stress [158,159]. As regards macrophages, in RAW264.7 cells sulforaphane inhibited the NLRP1b, NLRP3, NAIP/NLRC4, and AIM2 inflammasomes through an Nrf2-independent pathway. The down-stream

results were the deactivation of caspase-1, together with the repression of IL-1β processing and secretion, and of macrophage pyroptosis [160]. Likely through Nrf2 activation and NF-κB inhibition, sulforaphane elicited the M1 to M2 phenotypic change in PMA-differentiated THP1-derived macrophages, assessed in terms of expression levels of M1 (IL-1β, IL-6, TNF-α, IL-23, CCR7) and M2 (IL-10, PPARγ, MRC1, CCL22) marker genes [161]. Nrf2-mediated anti-inflammatory activity of sulforaphane, including down-regulation of iNOS, was reported also in RAW264.7 cells challenged with LPS [162]. Considering all these evidences, it would be of interest to investigate the possible involvement of Nrf2 and proteasome in the sulforaphane antioxidant activity also in the context of atherosclerosis.

Another isothiocyanate, namely allyl-isothiocyanate from brassica species, counteracted inflammation in LPS-stimulated RAW264.7 macrophages through Nrf2/HO-1 activation. In this case, although not verified, the immune response regulator miR-155 was pointed to as the mediator of the signaling triggered by allyl-isothiocyanate [163].

In addition to Nrf2, other redox sensitive pathways can undergo modulation by natural compounds. Resveratrol counterbalanced PMA-induced intracellular GSH depletion and consequently pro-inflammatory differentiation of THP1 cells via AMPKα activation [164]. Geraniin interrupted, through a SOCS-1/NF-κB-dependent mechanism, the M1 inflammatory response due to ROS and iNOS-derived NO in THP1 cells stimulated with LPS [165]. Myricitrin has been suggested to attenuate the inflammatory activation of murine macrophages by inhibiting the assembly of NOX components. Indeed, the decrease of intracellular ROS resulting by myricitrin administration could account for the abolition of both Janus kinases (JAKs) and STAT1 phosphorylation**,** induced by LPS, and consequently for the suppression of DNA-binding activity of STAT1 [166]. The antioxidant properties of punicalagin and gallic acid, two polyphenols typical of pomegranate juice, could rely on the stimulation of macrophage paraoxonase-2 expression which, in turn, could depend on the activation of PPARγ and AP-1 [167].

Siphonaxanthin, a xanthophyll present in green algae, but not other carotenoids such as lutein and fucoxanthin, attenuated ER stress and the subsequent NF-κB activation, pro-inflammatory cytokine expression, and NO generation induced by the pro-atherogenic advanced glycation end products in RAW264.7 macrophages. In particular, high doses of siphonaxanthin increased the expression of some antioxidant genes that contribute to ER stress mitigation [168].

In oxLDL-treated macrophages, DNA damage, telomere shortening, cell senescence, and apoptosis due to ROS overproduction have been reversed by the iridoid catalpol, acting on the PGC-1α/telomerase reverse transcriptase (TERT) pathway [169]. Alternatively, this iridoid might attenuate M1 polarization, inflammatory response, and oxidative stress elicited by IFNγ in J774.A1

macrophages through induction of estrogen receptor α. The effect could depend on iNOS suppression and on promotion of endothelial NOS instead [170].

Berberine has been shown to reduce macrophage superoxide anion concentration by inhibiting the expression of its source NOX subunit gp91phox, and by recovering superoxide dismutase (SOD) activity [171]. Moreover, β-sitosterol, a molecule which does not show significant ROS scavenger activity, might protect against oxidative stress because of manganese SOD and GSH peroxidase activation in PMA-stimulated RAW264.7 macrophages, likely through mediation of estrogen receptors and PI3K [172].

3.4. Nutraceuticals as modulators of cell metabolism: effects on lipid homeostasis and other metabolic routes

A large number of polyphenols has been reported to reduce foam cell development. EGCG restored ABCA1-mediated reverse cholesterol transport by inhibition in macrophages of the NF-κB activity induced by TNFα. The entire process appeared to depend on the Nrf2-Kelch-like ECH-associated protein 1 (Keap1) signaling, which controls NF-κB function [173]. Transformation of human macrophages into foam cells was also prevented by the citrus flavonoids naringenin and hesperitin by up-regulation of LXRα and its target genes ABCA1 and ABCG1 in an AMPK or PPARγ dependent manner, respectively [174,175]. Other polyphenols effective against lipid-laden cell development are quercetin [176], dihydromyricetin [177], kaempferol [178], resveratrol [179], pomegranate ellagic acid and punicalagin, [180], coffee phenolic acids [181], and curcumin [182]; they act by improving LXRα, PPARγ, and/or ABC-transporters, and eventually by regulating scavenger receptor expression. More in detail, in THP-1 cells LXRα/ABCA1 up-regulation by curcumin might derive from AMPK-SIRT1 signaling activation [183]. On the other hand, it was evidenced that curcumin treatment of M1 subtype RAW264.7 cells led to PPARγ overexpression and, in turn, to ABCA1 and CD36 induction. These effects, together with improved intracellular cholesterol esterification, have been deemed as mechanisms efficient to favor noxious lipid handling by atherosclerotic macrophages and to attenuate their inflammatory response [184]. In contrast with the aforementioned data, the flavonoid gossypetin isolated from the flowers of Hibiscus species limited foam cell formation by PPARγ blockage, promoting the PPARα/LXRα/ABCA1 signal with down-regulation of the CD36-dependent oxLDL uptake by J774.A1 murine macrophages [185]. Similarly, resveratrol was reported to down-regulate PPARγ, but also PPARα, without affecting PPARβ/δ, thus reducing the conversion of THP1 PMA-differentiated cells into foam cells, pointing to AMPK and SIRT1 overexpression as the causative mechanism [186]. A novel mechanism has

been recently discovered to explain the protective action of the flavonoid fisetin against lipid accumulation in oxLDL-exposed macrophages. It comprises the induction of CK2-interacting protein-1 (CKIP-1), a protection factor for the cardiovascular system, and of REGγ (11S regulatory particles, 28 kDa proteasome activator, proteasome activator subunit 3), a member of the 11S proteasome activators already recognized as a therapeutic target for lipid metabolism disorders; indeed, REGγ limits organic cation transporter-1 (Oct-1) transcriptional activity, with the subsequent down-regulation of lectin-like LDL receptor-1 (LOX-1), a scavenger receptor responsible for oxLDL uptake [187]. Very recently, fisetin was demonstrated to regulate lipid homeostasis of oxLDL-induced U937 macrophages also by reducing the sterol regulatory element binding protein 1 (SREBP-1)-dependent expression of the liposynthesis genes 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and FA synthase. The process was shown to depend on the antioxidant properties of the flavonoid that, by quenching ROS production, abolished up-stream NLRP3 activation by oxLDLs [188]. In this connection, FA synthase has been recently suggested to be essential for the TLR-mediated macrophage pro-inflammatory activation and its activity was associated to the promotion of cholesterol biosynthesis [189]. The addition of the pomegranate polyphenols punicalagin and/or β-sitosterol to simvastatin raised the drug efficacy against foam cell formation. Punicalagin and/or β-sitosterol appeared to inhibit cholesterol biosynthesis in J774.A1 macrophages and, in combination with simvastatin, significantly reduced ROS production [190].

Phytosterols are well-known to reduce plasma LDL levels by competitive exclusion of cholesterol from micellar space in the intestinal lumen and modulation of enterocyte cholesterol trafficking. In addition, they might have a direct effect on cholesterol homeostasis in macrophage-derived foam cells; stigmasterol, but not campesterol and sitosterol, positively regulated the expression of ABCA1 and ABCG1. Surprisingly, while stigmasterol attenuated the inflammatory response and campesterol was almost inert, sitosterol exacerbated it [191].

A nutritional mixture of flavanol rich cocoa extract and ω-3 PUFA-rich fish oil, with or without phytosterols, increased ApoA-I mediated cholesterol outflow, possibly reversing foam cell formation, and delayed M1 polarization of a monocyte derived THP-1 macrophage model of atherosclerosis [192]. Nevertheless, the potentiality of UFAs to offset against aberrant lipid homeostasis in atherosclerotic macrophages is controversial. Attenuating the ER stress, both the monounsaturated FA oleic acid and the ω-6 PUFA LA were proven to suppress LOX-1 expression, which was induced by palmitic acid in macrophage-like cells [193]. Apparently, this evidence conflicts with a more recent investigation reporting that LA and its natural source soy oil are pro-atherogenic since, by exacerbation of oxidative stress and modulation of the redox-sensitive p38 MAPK, they favor triglyceride biosynthesis and accumulation in J774.A1 cells [194]. In agreement

to that, the UFAs palmitoleate, oleate, linoleate, and arachidonate had been previously implicated in atherogenesis since their supply impaired cholesterol release by macrophages by enhancing ABCA1 degradation [195]. In particular, the action of oleate and linoleate appears to be mediated by their acyl-CoA derivatives and could depend on acyl-CoA synthetase 1 up-regulation [196]. In addition, palmitic, oleic, linoleic, linolenic, or eicosapentaenoic acids significantly reduced both ABCA1 and ABCG1 macrophage content by altering, at a transcriptional level, the LXR/histone deacetylase signaling and possibly, in a LXR-independent manner, by inhibiting post-transcriptional pathways [197]. In human macrophage-derived foam cells also CLA seemed to reduce intracellular cholesterol content by up-regulation of ABCA1 through both PPARγ- and LXRα-dependent pathways. This occurred although the expression of CD36 was increased by CLA [198]. This is consistent with inhibition by CLA of PGC-1α-mediated macrophage transition to foam cells [199], but contrasts with cholesterol accumulation observed in CD36-overexpressing human macrophages exposed to CLA [200]. It is possible that different CLA isomers have distinct features; in fact, trans-9,trans-11-CLA, but not cis-9,trans-11 and trans-10,cis-12-CLA, activated the cholesterol transporter ABCG1 in murine macrophages by a SREBP1c-dependent mechanism [201].

Among carotenoids, lycopene might be helpful against foam cell formation by affecting cholesterol metabolism of human macrophages. The signal machinery triggered by this compound consisted in an initial inhibition of the cholesterol synthesis key enzyme HMG-CoA reductase followed by small GTPase RhoA inactivation, subsequent increase in PPARγ and LXR activities, and final enhancement of ABCA1 expression [202]. Cholesterol efflux from murine macrophages to high density lipoproteins (HDLs) was accelerated by all-trans-retinoic acid and by its precursor 9-cis-β-carotene. Both compounds increased ApoE protein level but only 9-cis-β-carotene was effective in the induction of ABCA1, ABCG1, and ApoE genes [203]. A novel mechanism was recently suggested to underlie ABCA1, ABCG1, and scavenger receptor class B type I (SR-BI) overexpression, as well as cholesterol outflow promoted by astaxanthin in oxLDL-overloaded macrophages. This mechanism identified noncoding circular RNAs as key players of the process induced by the carotenoid [204].

In PMA-differentiated THP-1 monocytes, the steroidal saponin diosgenin was proven to induce ABCA1 protein and ABCA1-mediated cholesterol outflow without affecting LXR but suppressing miR-19b, a post-trascriptional regulator of ABCA1 [205].

PPARα and LXRα are likely the target of the anti-atherogenic action of the garlic derived allicin too, resulting in improved cholesterol exchange by ABCA1 overexpressing macrophages [206].

Cholesterol efflux associated to M2 polarization was favored by $1,25(OH)_2D_3$ in THP-1-derived foam cells. In this case, LXR-dependent ABCA1 and ABCG1 overexpression was the consequence of the induction of CYP27A1, the enzyme responsible for the synthesis of the LXR agonist 27-hydroxycholesterol [207].

Macrophage differentiation into foam cells has been prevented by berberine too, but through other mechanisms: in oxLDL-stimulated THP1 cells this alkaloid down-regulated the expression of CD36 and LOX-1, and increased the expression of adipocyte enhancer-binding protein 1 (AEBP1), a key regulator of genes associated with intracellular cholesterol homeostasis, including PPARγ, LXRα, and ABC-transporters [208]. In addition, cholesterol-lowering effects of berberine were exerted by activation of Nrf2/HO-1, which accounted for ABC-transporter overexpression, and by inhibition of AP-1, which suppressed scavenger receptor expression [209]. Berberine has also been demonstrated to act by up-regulating AMPK and SIRT1 and by down-regulating PPARγ [210]. Berberine as well as ω-3 the PUFAs DHA and EPA were proven to reduce modified LDL uptake by human macrophages, in a scavenger receptor-independent manner, likely as the result of diminished macropinocytosis [211,212].

A preventive effect of tanshinone II on foam cell formation was observed in human monocyte-derived THP-1 cells challenged with oxLDL. This compound markedly down-regulated SR-A and up-regulated ABCA1 and ABCG1 expression. This was the consequence of ERK activation, Nrf2 phosphorylation and nuclear translocation, and final HO-1 overexpression [213].

All these observations point to metabolism and cell homeostasis of lipids, in particular of cholesterol, as the main processes that can be affected by bioactive micronutrients, but other metabolic cycles can be affected as well. A flavonoid-rich cocoa extract has prompted M2 polarization of active THP-1 derived macrophages which was shown by the reduction of inflammatory cytokine secretion and the increase of IL-10 and IL-12 release. The conversion from M1 to M2 phenotype was accompanied with enhanced oxygen consumption and ATP production through the mitochondrial oxidative phosphorylation, suggesting that flavonoids could act principally as antioxidants that favor the switch towards the oxidative metabolism [214].

Rescue of mitochondrial functions and of the anti-inflammatory metabolism and phenotype might be promoted in M1 macrophages also by carnosine. Indeed, this molecule was recently proven to restore ATP/ADP and $NAD(P)^+$/NAD(P)H balance in activated RAW264.7 macrophages, the last effect being indicative of a strong inhibition of the main reactions responsible for cell ROS production. Furthermore, carnosine antioxidant efficacy appeared to be strengthened by its ability to improve the antioxidant defense through up-regulation of Nrf2, HO-1, and ROS scavenger enzymes,

and simultaneously to decrease NOX-2 and COX-2 expression, reactive nitrogen species formation, and lipid peroxidation [215,216].

4. Nutraceutical approaches to the treatment of atherosclerosis: outcomes from human studies

The evidence, at a molecular level, of the antiatherogenic potential of many natural derivatives has prompted to evaluate their efficacy also in humans. Literature in this field, from small observational or interventional studies to larger epidemiological or clinical trials, has been continuosly growing [8, 74,217,218]. In some cases, as exemplified by some relevant studies hereinafter reported, the micronutrient impact on vascular events was assessed together with inflammatory and oxidative state indices; this provides some information about the correlation between nutraceutical intake and the mechanisms that mainly contribute to atherosclerosis progression. Of note, although the last parameters are usually measured in the circulation and not specifically in the lesions or in the atherosclerotic macrophages, it is conceivable that the systemic condition could reflect what occurs in the plaque cells, among which macrophages.

Polyphenols, UFAs, and carotenoids are the bioactive compounds probably most widespread in nature and abundant in food, thus they are the most investigated for nutritional and pharmacological appplications. The PREDIMED trial is undoubtedly one of the most extensive study carried out to analyze the contribute of the Mediterranean nutritional pattern (i.e. increased intake of vegetables, fruits, legumes, fish or seafood, moderate red wine consumption, and reduced intake of red meat), characterized by a high content of polyphenols and PUFAs, on the primary prevention of CVD. Almost 7500 high-risk participants were submitted to two Mediterranean diet regimens supplemented with either virgin olive oil or nuts, or to a control low-fat diet. Intervention with both the enriched diets brought to short-term and long-term decreases in the circulation of inflammatory cytokines, and to an increase of plaque stability markers, together with an improvement of the classical cardiovascular risk factors, including the lipid profile. Of note, the total polyphenol intake, measured as urinary polyphenol excretion, inversely correlated with the levels of inflammatory markers, suggesting a dose-dependent anti-inflammatory efficacy of polyphenols. In spite of that, no significant changes were observed for the expression of genes involved in the atherosclerosis-related inflammation [219-223].

A meta-analysis of human nutrigenomic studies highlighted the capacity of acute or sustained interventions with a Mediterranean dietary regimen to down-regulate, in peripheral blood monocytes (PBMCs), the expression of inflammatory and pro-oxidant mediators involved in atherosclerosis. Olive oil appeared the main responsible for gene modulation, thanks to its high content of MUFAs,

carotenoids and, in particular, of polyphenols; in fact, some genes, such as TNFα and monocyte chemotactic protein 1 (MCP1), have been affected by olive oil and its polyphenols, within and out of the context of the Mediterranean diet [224].

Other dietary sources of polyphenols have been considered for preventive purposes too. Several epidemiological studies have demonstrated the positive association between cocoa and its products and lower CVD risk and mortality, pointing to a pivotal role played by cocoa flavanols. Indeed, systemic levels of inflammatory markers such as ILs and C-reactive protein (CRP) appeared reduced, mainly in studies considering healthy subjects, after short- and medium-term consumption of cocoa derivatives. Nevertheless, a neutral effect on CRP, ILs, and on other inflammatory proteins (TNFα, MCP1) has also been reported, either in healthy subjects and in individuals at cardiovascular risk [225]. Furthermore, cocoa powder supplementation to high-cardiovascular risk volunteers significantly lowered monocyte CD36 expression [226]. As regards polyphenolic compounds present in green and black tea, both case-control studies and meta-analysis data are in support of an inverse association between tea consumption and the risk of coronary artery disease and its fatal outcomes [227].

Resveratrol and its sources grape and wine were taken into consideration for secondary cardiovascular prevention [228,229]. One-year daily consumption of a grape-extract of the phytochemical was able to modulate, in PBMCs of stable coronary artery disease patients, the expression of inflammation-related transcription factors, including KLF2, NF-κB, AP-1, c-Jun, ATF-2, and CREB-binding protein. In the cells the expression of IL-1β and TNF-α was also significantly reduced, but no significant changes of inflammatory markers were observed in the serum, except the reduction of IL-6 levels. Of note, lower expression of the inflammatory cytokines in PBMCs was concomitant with increased levels of miR-21, miR-181b, miR-663, and miR-30c2, and with lower levels of miR-155 and miR-34a, all involved in monocyte and macrophage inflammatory pathways such as TLR and NF-κB signaling. However, the authors could not detect circulating resveratrol or other grape-derived metabolites, thus the direct relation between resveratrol and the effects observed might be only speculative [230,231].

An anti-inflammatory activity was also ascribed to UFAs, which characterize some dietary patterns, such as the Mediterranean and the Greenland ones, proven to be health promoting [228, 229]. In elderly healthy people, consumption of a Mediterranean diet enriched in MUFAs limited the postprandial inflammatory response in mononuclear cells compared to a saturated FA-rich diet, reducing the expression of TNFα, IL-6 and MCP1, and of MMP-9, thus suggesting a plaque stabilizing efficacy. Of note, MUFA-diet appeared able to act directly on the up-stream NF-κB signaling, by lowering p65 subunit expression [232]. Very recently, outcomes from the ongoing

CORDIOPREV randomized trial further suggest the anti-atherogenic potential of a Mediterranean diet at high virgin olive oil content. It emerged that, compared to a low-fat diet, 5 and 7 years adherence to an olive oil-rich pattern reduced the arterial intima-media thickness of subjects with coronary heart disease at baseline. One might presume that MUFAs present in olive oil largely contribute to vascular protection, although no data about the actual intake of bioactive species, in terms of compound concentration in the plasma and/or urine of participants, were provided to confirm that [233,234].

As precursors of the pro-resolving mediators SPMs, ω-3 PUFA have been explored for atherosclerosis treatment as well, but to date observations from clinical trials did not give conclusive results [235]. On one hand, ω-3 PUFAs, including EPA and DHA, did not significantly reduce cardiovascular events in humans [236]. In this connection, ω-3 PUFAs did not seem to affect SPM levels in urine and plasma of healthy volunteers after fish oil dietary consumption [237]. Conversely, in patients with chronic inflammation, high doses of purified EPA and DHA affected plasma levels of intermediates of SPM biosynthesis and attenuated the expression of pro-inflammatory cytokines in LPS-stimulated PBMCs isolated from study's participants [238].

Moreover, EPA, DHA, docosapentaenoic acid (DPA), and monohydroxylated SPM precursors down-regulated M1 and up-regulated M2 genes of LPS-stimulated monocyte-derived macrophages that were isolated from patients with peripheral artery disease after a short-term intake of marine oil enriched with these FAs and SPM precursors. The phenotypic changes strongly correlated with the plasma SPMs/PGs ratio [239].

More generally, ω-3 PUFAs were demonstrated to promote plaque stabilization: the lipid core of coronary plaques of patients under statin therapy was significantly reduced by EPA co-administration, while fibrous cap formation was favored. It decreased also plasma MCP1 [240]. The OCEAN trial, which enrolled patients awaiting carotid endoarterectomy, reported that interventions with ω-3 PUFA ethyl ester capsules decreased plaque foam cell number and mRNA levels of MMP-7, MMP-9, MMP-12, and IL-6, in association with a higher plaque EPA content [241]. These observations are consistent with an earlier study showing that ω-3 PUFAs-enriched fish oil supplementation to patients with advanced lesions were readily incorporated in the carotid plaque, and were able to limit macrophage infiltration and to enhance atheroma stability. By contrast, the same results were not observed for increased consumption of ω-6 PUFAs [242]. Overall, the latest results are consistent with the outcomes of meta-analysis of clinical trials, including the DART, the GISSI-Prevenzione, and the Jelis trials, from which it emerged that marine ω-3 PUFA supplementation lowered the risk for the major vascular diseases [235].

Among carotenoids, most attention was given to β-carotene and lycopene, while other carotenoids were less investigated. In consideration of data variability, employment of β-carotene for the reduction of vascular morbidity is still debated and should be considered carefully [243]. On one hand, a prospective quantification of β-carotene in the serum of more than 29.000 men, enrolled for the ATBC study, provided evidence for an inverse correlation between β-carotene levels and the occurrence of CVD, heart disease, and stroke during the 31-years follow-up period [244]. On the other hand, according to the Cochrane Database review, β-carotene and vitamin A could increase all-cause mortality [245], and in agreement with that β-carotene was not recommended for prevention of CVD by the US Preventive Task Force [246].

As regards lycopene, interventional studies indicated that its consumption by means of tomato-based foods might be vasoprotective and reduce cardiovascular risk [247]. In addition, in subjects with subclinical atherosclerosis, 1-year treatment with lycopene, alone or in combination with luteolin, induced a decrease in the intima-media thickness that was inversely associated to plasma levels of both carotenoids [248] These effects might be ascribed to lycopene antioxidant and anti-inflammatory propertie; indeed, in individuals at high cardiovascular risk, a daily tomato-juice intake led to a plasmatic trans-lycopene increase that correlated with lessening of plasma IL-8 [249]. However, other studies did not sustain lycopene anti-atherogenic activity. In fact, a relatively high daily consumption of tomato-based products or lycopene supplements were ineffective at reducing vascular disease-related inflammatory markers in moderately overweight, healthy, middle-aged individuals, in spite of the lycopene increase in plasma [250], or at lowering CRP serum levels both in healthy volunteers and in CVD patients [251].

A saffron extract and its main carotenoid, crocin, have also been evaluated for the treatment of CVD patients; crocin, in particular, was able to promote SIRT1 and AMPK expression in the PMBCs of patients and to decrease NF-κB. These effects were accompanied to the reduction of MCP1 and oxLDL levels in the serum [251].

As regards other less common natural bioactive compounds, literature is still limited and certainly less exhaustive, also in consideration of the few number of participants included in the studies presently available [8, 218]. Phytosterols have been considered mainly as cholesterol-lowering agents [218], while their application as atherosclerosis-related anti-inflammatory substances was less investigated. It has been reported that orange juice and orange juice fortified with phytosterols lessened IL levels in healthy human volunteers [252]; however, this evidence does not seem furtherly corroborated since a following meta-analyses of trials on humans did not report anti-inflammatory efficacy for phytosterol-enriched foods, at least in terms of CRP content [253]. Also for vit D evidence about benefits of its supplementation for atherosclerosis treatment is still scarce,

although its deficiency is increasingly referred to as a risk factor for vascular diseases, [85]. Of note, a trial is presently going on to explore the anti-inflammatory effects of the injection of a Danshen extract containing tanshinone II in patients with stable coronary artery disease [254].

Conclusions and future perspectives.

Atherosclerosis is a multifaceted pathological process in which macrophages play a pivotal role. Their orientation towards a more or less inflammatory phenotype can affect plaque evolution towards vulnerable lesions, which ultimately leads to fatal adverse outcomes such as ischemic stroke and myocardial infarction, or, conversely, towards atherosclerotic process resolution. In this connection, inflammatory state, redox balance, and metabolic regulation represent a unique complex network that in a coordinated manner drives macrophage polarization and is, in turn, orchestrated by macrophages themselves according to their phenotype. By operating on this network, several substances of natural origin, including extra-nutritional constituents in foods or micronutrients, have shown efficacy to direct macrophage polarization; for this reason, these compounds have been considered as coadjuvants in the prevention and treatment of atherosclerosis

The body of evidence available shows that nutraceutical bioactivity mainly relies upon their capability to operate on the diverse signaling cascades that regulate macrophage functions (Fig. 2). Of note, the most widespread compounds in dietary sources, such as polyphenols, UFAs, and carotenoids, act on several pathways (e.g. NF-κB, MAPKs, TLRs, Nrf2, and PPARs), involved in multiple fundamental macrophage metabolic cycles and immune responses. In some cases, molecules less common in natural sources or present at very low concentrations seem to target more selectively biochemical factors with more specific roles. Examples of that include the modulation of estrogen receptors by β-sitosterol [172], of inflammasomes by saponins [148], of noncoding RNA by berberine, tanshinone II, and diosgenin [122,150,205], or of TERT by the iridoid catalpol [169].

Considering that, the integration of specific compounds through concentrated forms, including non-food matrices like pills, extracts, or powders [255], might represent a promising tool for therapeutical approaches aimed to direct the inflammatory network in atherosclerotic macrophages. In particular, this could be the case of substances such as saponines, iridoids, and berberin, that not only show more peculiar bioactivities but whose uptake through foodstuffs is limited. Noteworthy, administration of molecules targeting machineries with a selective activity might limit perturbations of signaling pathways with a broad impact on important processes shared by vascular and extra-vascular cells, thus avoiding potentially harmful interferences. Other advantages of nutritional

supplements are their less sensitivity to those alterations brought about food storage and cooking that can change molecule biochemical reactivity, and eventually a major bioavailabilty due to the absence of complex foodstuff matrices.

Nevertheless, definitive and unanimous data about the atherosclerosis-related properties of certain nutraceuticals are still few, as well as information about their bioavailability or potential toxicity due to their overconsumption This is likely the result of the great variability of the experimental models utilized for their investigation, especially as regards dose and duration of treatments. In particular, as regards studies on humans, the molecule anti-atherogenic efficacy is usually verified by means of clinical parameters, such as the intima-media thickness or the frequency and seriousness of cerebro- and cardiovascular events, while inflammatory and oxidative markers are less frequently observed. Moreover, only few investigations have evaluated the actual uptake of the administered substances, for example by measuring plasma, urine or other tissue levels of the presumed bioactive principle and of its metabolites. In the absence of these data, it is difficult to infer a conclusive correlation between a defined nutraceutical and the observed outcomes in humans. For this reason, further *in vitro* and *in vivo* studies on animals and humans, including extensive clinical trials, are necessary to confirm the effectiveness of natural compounds to induce anti-atherogenic polarization in macrophages and to establish the most suitable guide lines for their administration [256,257].

Consequently, the application of micronutrients for atherosclerosis treatment in fully replacement of current pharmacological therapies is not reliable yet. In spite of that, a balanced diet which comprises a variety of nutraceutical-containing foods, such as the Mediterranean diet, likely provides bioactive molecules in amounts adequate to counterbalance atheroma formation. Of note, the copresence in the same foodstuff or meal of more micronutrients could ensure even more efficacy, as highlighted by investigations reporting a synergistic action of them in mixtures [111,112,192]. Functional foods enriched with beneficial species could be also considered [255], in particular to enhance provision of essential micronutrients or when the everyday diet is not sufficient for their supplementation.

In conclusion, diets rich in bioactive species, fortified foods, and micronutrient supplements can be employed for early prevention and possibly to improve patient response to drugs [258], as emerged from the study of Rosenblat and collaborators about the combined effect of pomegranate micronutrients and simvastatin [179]. Of note, this could allow lower drug doses reducing their side-effects. For these reasons, nutraceuticals may represent a valid coadjuvant against atherosclerosis evolution and their consumption should become fundamental in daily nutrition.

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Conflict of interest

Authors declare not to have conflicts of interest.

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Fig. 1. Different macrophage subtypes found in atherosclerotic lesion. Stimuli present in atherosclerotic lesions direct macrophage polarization towards different phenotypes charactized by specific expression and function profiles.

Fig. 2. Nutraceutical modulation of the most relevant macrophage signaling pathways and the relative beneficial effects against atheroma progression.