Mediterranean Products as Promising Source of Multi-Target Agents in the Treatment of Metabolic Syndrome.

Donatella Bagetta,[a,b]‡ Annalisa Maruca,[a,b]‡ Antonio Lupia,[a,b]‡ Francesco Mesiti,[a,b] Raffaella Catalano,[a,b] Isabella Romeo[b,c] Federica Moraca,[b,d] Francesca Alessandra Ambrosio,[a]* Giosuè Costa,[a,b] Anna Artese,[a,b] Francesco Ortuso,[a,b] Stefano Alcaro,[a,b] Roberta Rocca[b,e]*

[a] Dipartimento di Scienze della Salute, Università "Magna Græcia", Campus Salvatore Venuta, Viale Europa, 88100, Catanzaro, Italy.

[b] Net4Science srl, Università "Magna Græcia", Campus Salvatore Venuta, Viale Europa, 88100, Catanzaro, Italy.

[c] Department of Chemistry and Chemical Technologies, University of Calabria, via Pietro Bucci, 87036, Arcavacata di Rende, Italy.

[d] Department of Pharmacy, University of Naples “Federico II”, via D. Montesano 49, 80131, Naples, Italy

[e] Department of Experimental and Clinical Medicine, "Magna Græcia" University, Campus Salvatore Venuta, Viale Europa, 88100, Catanzaro, Italy.

‡ These authors contributed equally.

ABSTRACT: Alteration of nutritional habits play an essential role on the risk of developing Metabolic Syndrome (MetS). Several epidemiological studies have shown that assuming diets rich of foods included in the Mediterranean diet (MetDiet) pattern like, such as olive oil, nuts, fruit, fiber, vegetables, wine and grain cereals has protective effects on the different risk factors characterizing the MetS. The beneficial effects of the MetDiet in the MetS are mainly due to the antioxidant and anti-inflammatory properties of the most abundant phytochemical components of such foods as polyphenols like resveratrol and oleuropein, allyl sulfides, ellagic acid, mono- and poly-unsaturated fatty acids (MUFA and PUFA), tocopherols and flavonoids like quercetin, which have shown positive results in the prevention of cardiovascular diseases (CVDs), with related risk factors, like hypertension, hypercholesterolemia and obesity. In this review, we highlighted the multi-target activities of the bioactive components contained in some foods typical of the Mediterranean area like olive oil, onion, liquorice, rosemary, oregano, hazelnut, pistachio, "Melannurca" apple, red wine, hot pepper, Citrus sp. fruits, saffron and garlic, with particular focus on their impact on health outcomes in relation to MetS main key factors, such as insulin resistance (IR) and type 2 diabetes mellitus (T2DM), endothelial dysfunctions, inflammatory response, oxidative stress and dyslipidaemic and hypercholesterolemic effects.

KEYWORDS: Metabolic Syndrome (MetS); Mediterranean Diet (MedDiet); Multi-target; Polypharmacology; Prevention; Anti-oxidant; Anti-inflammatory; Polyphenols.

1. INTRODUCTION

Metabolic syndrome (MetS) describes a collection of metabolic abnormalities that are associated with visceral adiposity. This condition is diagnosed by the simultaneous occurrence of at least 3 of these 5 factors: abdominal obesity, atherogenic dyslipidaemia associated with low-density lipoprotein (LDL) and/or high-density lipoprotein (HDL), elevated triglyceride (TG), hypertension, atherosclerotic cardiovascular diseases (CVDs) and fasting plasma glucose of at least 100 mg/dl.[1] Disease patterns associated with MetS can be chronic, debilitating, and lethal. MetS is clearly a multifactorial pathology, in which several pathways are involved in the metabolic disorder. Although the multi-factorial nature is evident, nowadays available drugs individually act on each aspect of the disease. The identification of common pathways as drug targets surely could be useful to figure out molecules with multi-target profile, able to interact with them to contrast the disorder.

In recent decades, the paradigm of "one drug, one activity, one disease" has dominated the drug discovery process in Western Medicine. However, this idea has been changed through the discovery of multi-target bioactive compounds, in which the same drug can simultaneously exert its effects through interactions with multiple targets, by opening new areas for research. In particular, a wide variety of molecules derived from natural products have been evaluated for their multiple biological effects, such as analgesic, anti-proliferative, anti-inflammatory, anti-bacterial and anti-oxidant effects, among others.[2]

This review highlights some of the recent findings regarding different multi-target natural bioactive compounds, with particular attention to the products that characterize the Mediterranean diet (MedDiet). Indeed, emerging evidence underlines the protective effect exerted by the MedDiet on the different factors of MetS.[3] In particular, the anti-oxidant and anti-inflammatory properties

of MedDiet food such as olive oil, nuts, vegetables and wine, have been widely documented and their beneficial properties seem to be connected to their phytochemical components. In this review, we presented a brief background on the isolated natural compounds extracted from Mediterranean products, their structures, their multi-target activities and their postulated mechanism of action. We aim is to highlight the principal evidence linking the effectiveness of the MedDiet in preventing or delaying the physiopathological components accountable for MetS onset. Therefore, the main bioactive compounds contained in typical MedDiet foods are examined, by focusing on their activity in the regulation of mechanisms involved in key MetS features, such as insulin resistance (IR), endothelial dysfunctions, inflammatory response, oxidative stress and dyslipidaemia.

2. POLYPHARMACOLOGY AS INNOVATIVE APPROACH

The observation that several drugs explicate their pharmacological effect through the interaction with multiple targets is shifting the drug discovery paradigm from the one target–one drug model to a more effective multiple-target approach, a phenomenon called polypharmacology. In this context, the development of selective molecules acting specifically on a single molecular target, according to the paradigm ‘single keys for specific locks’, has been overcome and is moving towards the identification of ideal ‘master keys’ which recognize a set of ‘multiple locks’ (Figure 1), usually involved in multi-factorial or complex disease, to gain access to a clinical benefit.[4] Compounds that are rationally designed with a well-defined multi-target profile have been defined as Designed Multiple Ligands (DMLs) that must be distinguished from non-selective (or “dirty”) drugs, which possess activity towards irrelevant targets not involved in the selected disease.

Designing drugs that can simultaneously interact with multiple targets in a synergistic fashion is a promising approach for treating complex diseases like cancer, metabolic disorders, neurodegenerative diseases and others.[5] Thus, there is increasing attention in the identification and validation of targets combination associated with a desired clinical effect, avoiding the off-target effect. In conclusion, polypharmacology is an emerging and promising new paradigm in drug discovery and development. In fact, comparing the use of single-target drug combination with the multi-target approach, this last has different advantages, such as higher efficacy, improved safety profile and simpler administration.[6]

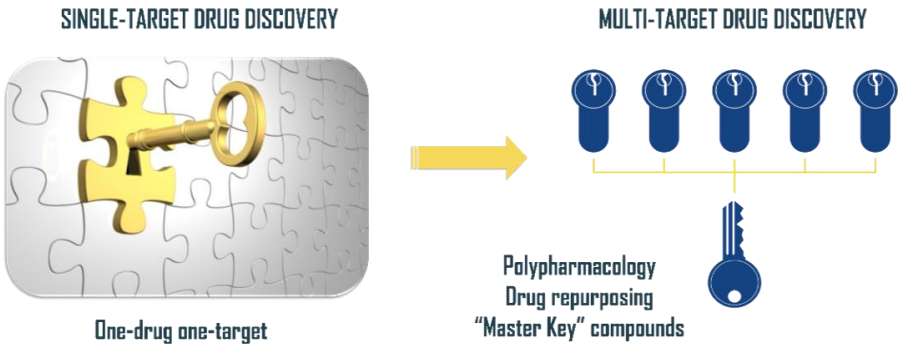


Figure 1. Representation of the concepts: "Single key for a specific lock" and "Master key for multiple locks".

3. MEDITERRANEAN AREA PRODUCTS

The MedDiet is a dietary pattern followed by people living in the Mediterranean Sea basin and it was firstly described by Keys in 1960s[7]. It is characterized by three important features: (a) daily consumption of non-refined cereals and products (e.g., whole grain bread, whole grain pasta, and brown rice), fresh fruits, vegetables, nuts, low-fat dairy products, and olive oil as principal source of lipids; (b) moderate intake of wine (especially red wine); (c) regular physical activity. Moreover,

moderate consumption of fish, poultry, potatoes, eggs, and sweets, and monthly consumption of red meat are also included in the MedDiet.[8] In addition to these characteristics, nutritional scientists identify foods derived from plants (nuts, olives and fruit) as having beneficial effects on human health thanks to their high content of bioactive compounds, including monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs) and polyphenols.[9] Contrary to conventional opinion, the MedDiet is not a low-fat diet, but it is rich in foods containing mostly unsaturated fatty acids[10] and anti-oxidants (olive oil, fish, and nuts), which are associated with a reduced risk of CVD. Moreover, the optimal mix of vitamins, phytochemicals, and anti-oxidants (especially found in grains, fruits, and vegetables) have beneficial impacts, such as preserving the glycaemic index (GI), reducing TG levels and lowering LDL oxidation and inflammation.[6]

4. BIOACTIVE COMPONENTS FROM MEDITERRANEAN PRODUCTS WITH MULTI-TARGET PROFILE

4.1 Olive

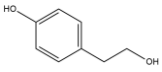
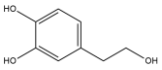
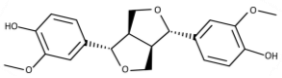
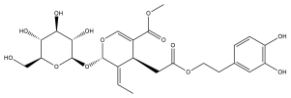
The olive tree (*Olea Europea L.*) is a subtropical species typical of the Mediterranean basin. It concerns an evergreen tree, with narrow silvery leaves and small white flowers.[11] At the begging, the cultivation of olive tree involved the eastern Mediterranean and subsequently, it was expanded in Southern Europe and North Africa.[11] The olive fruit is a drupe, oval shape and consists mainly in two parts: pulp and seed. From the pulp is extracted at least 98% of olive oil.[12] The production and even the chemical composition of olive oil is strongly associated with several factors: cultivar, geographic region, fruit ripeness and storage firmly affect the olive oil composition.[13] Olive oil can be mainly classified in extra-virgin olive oil (EVOO), virgin olive oil (VOO), and refined olive oil, depending on the physical/chemical methodologies practised to obtain it and the relative

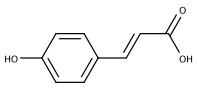
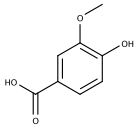
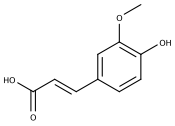
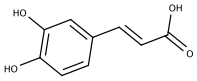
quality. Generally, the main components in olive oil can be divided into a saponifiable and unsaponifiable fraction. The saponifiable fraction represents around 98% of total weight and consists in glycerides, saturated and unsaturated fatty acids (stearic acid, palmitic acid, linoleic acid, meristic acid and oleic acid) while unsaponifiable fraction represents at least 1% of total weight.[14] The former fraction composed by at least more than 200 components that are not chemically related to fatty acids.[15] Hydrocarbons, sterols, triterpenes, tocopherols, pigments, phenols, belong to the unsaponifiable class. Further, phenol compounds can be classified as phenolic acids, phenolic alcohols, flavonoids, and secoiridoids.[16] The latter are present exclusively in *Oleace* family, whereas other derivatives are widely present also in other botanical groups.[16] Among all, phenolic compounds have been extensively studied considering their anti-oxidative profile and the health benefits associated.[17] The content of phenols derivatives in olive oil change according to several factors, but strongly dependent on oil production and storage.[18] Surely, the amount of phenols is higher in EVOO than refined oil.[19] In literature, it has been reported that the total amount of phenols in EVOO could vary between 800 mg/kg and 1 g/kg.[20] Other studies suggest that the total phenols content in EVOO is over than 500 mg/kg[21] or 232 mg/kg.[19] Tyrosol (TY) and hydroxytyrosol (HT) are the major phenols alcohols in olive oil and oleuropein (OL) is the principle secoiridoid in olive fruits. HT is produced by enzymatic cleavage of OL and its amount is strictly correlated with the oxidative stability of olive oil.

Phenols derivatives in olive oil mainly contribute to the quality and organoleptic properties and the beneficial effects of olive oil have been chiefly attributed to its phenols content.[22-24] Then, considering the importance associated with phenols derivatives, studies to assess the number of phenols in olive oil and their anti-oxidant activity have been carried out.[25-27]

Generally, free-radical scavenging capability has been demonstrated by using 2,2-diphenyl-1-picrylhydrazyl (DPPH) test whereas the ability to inhibit lipid peroxidation has been figured out by β-carotene bleaching (BCB) assay.[28] Furthermore, even Ferric Reducing Anti-oxidant Power (FRAP), Trolox Equivalent Anti-oxidant capacity (TEAC) and other assays are also used.[29] Byram *et al.,* have performed an excellent study of 55 EVOO samples in order to assess their phenols content and the anti-oxidant profiles.[30] The analysis of phenols content has been carried out by HPLC-ECD, and their anti-oxidant activity has been evaluated by TEAC and FRAP assays. Finally, the Total Reduction Capacity (TCR) has been derived. TY, HT, pinoresinol (PINO), and OL were the major abundant compounds found, but even other derivatives, p-coumaric, vanillic acid, ferulic acid and caffeic acid have been detected (Table 1).[30]

Table 1. Most representative bioactive compounds with their relative percentage in EVOO.

Classification	Compound	Structure	Concentration in EVOO (%)
Phenol alcohol	Tyrosol		46%
	Hydroxytyrosol		36%
Lignan	Pinoresinol		13%
Secoiridoid	Oleuropein		3%

Phenolic acids	p-coumaric Acid		1%
	Vanillic Acid		1%
	Ferulic Acid		0.5%
	Caffeic Acid		0.4%

The anti-oxidant activity has been studied through FRAP and TEAC assays for all the compounds detected in olive oil, but we focus our attention on the more present derivatives (TY, HT, OL, PINO).[30] Moreover, this study evidences that olive oil differs notably in their TRC. Among all, *Carotina* Italian cultivar showed the highest TRC value whereas *Cayon* French cultivar the lowest anti-oxidant capacity. Furthermore, by calculation of the Spearman's coefficient, it was demonstrated a moderate correlation between the content of TY, HT and OL with the total reducing capacity.[30] Below, we reported the involvement of olive oil and other derivatives in the MetS. The principal biological actions are related to the anti-oxidant capability showed by the main component found in olive derivatives. Olive oil phenols, mainly HT and OL, have shown great biological properties, including among all anti-oxidant[31], anti-inflammatory[32], anti-diabetic[33], and anti-cancer activities[34]. Surely, olive phenols derived from olive oil, olive fruits and/or olive leaf extract (OLE), exert beneficial properties against the main features of MetS.[15, 35] Indeed, a healthy

lifestyle and adherence to the MetDiet could be helpful to control hypertension. The beneficial effect of olive derivatives against hypertension is mainly associated with the content of polyphenols.[36] As reported by Fito *et al.*, by comparing high phenolic oil consumption with low phenolic refined oil, it comes up that the effects to control systolic blood pressure (SBP) and diastolic blood pressure (DBP) can be ascribed to the presence of phenolic compounds.[37] Similar results have been obtained from a study in which it has been compared the effects of polyphenols rich olive oil and high oleic sunflower oil in hypertension patients. It has emerged that polyphenols rich olive oil decrease SBP and DBP.[38] Again, in hypertensive patients that assume virgin olive oil enriched with own phenols have been observed an improvement of endothelium faction during the postprandial phase.[39] Moreover, considering the great ability of olive phenols to control hypertension, different studies have been also conducted to correlate the results obtained by olive phenols with the one derived by anti-hypertensive medications.[40] In particular, it has been observed that the administration of 1,000 mg (correspondent to 199 mg OL) aqueous OLE daily per 8 weeks exerts a similar action of captopril to control hypertension.[41] Different biological mechanisms have been proposed underlying these pharmacological activities. It has been found that the flavonoid derivatives apigenin and luteolin (Figure 2) exert their anti-hypertensive action through the inhibition of the angiotensin converting enzyme 2 (ACE2), with IC_{50} values of 280 μM and 290 μM, respectively.[42] It seems that the ACE2 inhibition mechanism is due to the formation of chelate complexes in the active centre.[42]

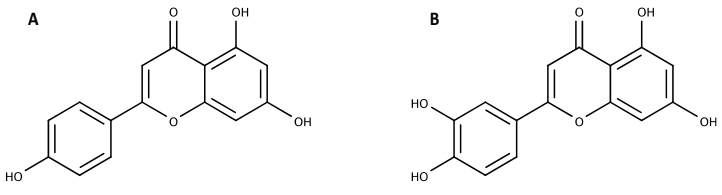


Figure 2. 2D molecular structure of **A**) Apigenin and **B**) Luteolin.

Another study suggests that OL increase the production of nitric oxide (NO) by modulating the activity of NADPH-oxidase (NOX) and nitric oxide synthase enzymes (NOs).[43] The high presence of phenolic compounds in MedDiet is responsible for the beneficial effects against obesity. Several studies confirmed the positive role of olive phenols to control obesity as another feature of MetS.[44, 45] In one study, mice have been randomly divided into two classes: high-fat diet (HFD) and 0.15% OLE-supplemented diet groups for 8 weeks. In mice treated with OLE, supplements have been observed a significant reduction of body weight compared to control.[46] Additionally, another study has reported that mice treated with 0.03% OL-supplements for 10 weeks showed a reduction of 55% body weight compared with the control.[47] Moreover, it has been found that HT supplementation (10 mg/kg/day x 17 weeks) prevents HFD-induced obesity.[48] Again, in Wistar rats receiving hypercaloric-chow treated with olive oil extracts (3g/kg x 42 days) it has been observed an increased oxygen consumption, fat-oxidation, myocardial beta-hydroxy acyl coenzyme-A dehydrogenase (OHADH) and lower respiratory-quotient.[49] However, there is not clear evidence about these important biological activities in humans. Several mechanisms have been proposed at the basis of these biological activities. Malliou *et al.*, using theoretical molecular docking simulation, indicated that OL is a ligand of peroxisome proliferator-activated receptor-alpha (PPARα), a nuclear receptor protein mainly involved in the lipid metabolism.[50] It was provided that OL docked in the receptor in a similar manner observed for indeglitazar, a well-known PPARα ligand. Further, it was found that the glucose part of the molecules docked in the entrance of the cavity with M335, L331, N219 and T238. Meanwhile, the methylester moiety of OL interacted with Y464 by forming hydrogen bond. Final, it was demonstrated that OL possesses

all the structural characteristics to fit in the PPARα binding site such as methyl ester, glucose and the hydroxytyrosol moieties.

Moreover, other *in vitro* and *in vivo* studies have suggested that olive phenols could suppress lipogenesis, induce lipolysis, and promote adiponectin secretion, probably through down-regulation of different adipogenic genes.[46, 51] Another study in the experimental model has reported an increase of the Mitochondrial brown fat uncoupling protein 1 (UCP1) expression, which led to the formation of "beige" adipose tissue and a decrease of visceral fat amount.[52]

MedDiet, characterized by a high amount of olive products, and to high intake of MUFAs, exerts a protective action against dyslipidemia[53]. Lockyer *et al.,* have demonstrated a correlation between the consumption of olive derivatives and the decrease of total cholesterol (TC), LDL and TG in humans.[54] Similar results have been obtained by Estruch *et al.*, which have observed an increase of HDL associated with the phenols of olive oil.[55] In order to understand better these biological activities, different mechanisms have been considered. It seems that OL is able to decrease TC and total glycerides by down-regulation of adipogenesis transcription factors.[56] Further, OL inhibits enzymes involved in fatty acid biosynthesis (fatty acid synthase, FAS), triglycerides synthesis (diacylglycerol acyltransferase, DGAT) and cholesterolgenesis (HMG-CoA reductase, HMGCR).[57] In addition, in animal models treated with olive phenols supplementations have been observed a positive anti-hyperglycaemic response.[58, 59] In alloxan-induced diabetic rats, the treatment with phenolic-rich olive extracts, which correspond to 8 mg/kg OL and 16 mg/kg HT per 4 weeks, led to decrease of serum glucose level.[60] Analogous results have obtained in diabetic rats treated with 0.5 mg/kg OLE for 30 days.[61] Important hypoglycaemic effects have been also observed in humans.[33, 62] Actually, in overweight middle-aged men assuming OLE for 12 weeks (51.1 mg OL, 9.7 HT x day), an improvement of 15% in insulin sensitivity has been recognized.[63]

Different mechanisms underlying these biological properties have been proposed. Deckdouck *et al.*, demonstrated that olive phenols are able to inhibit α-amylase and β-glucosidase and IC_{50} (μg/mL) values for both enzymes have been also calculated.[28] HT has shown the lower α-amylase IC_{50} (81.63 μg/mL), whereas luteolin had the best inhibition activity towards β-glucosidase (IC_{50}= 14.12 μg/mL), even better than acarbose as reference compound (IC_{50}= 340 μg/mL)[28]. However, Loizzo *et al.,* also have evaluated the inhibition profile and relative IC_{50} values of phenolic extract from extra virgin olive oil.[42] All samples exhibited lower IC_{50} towards β-glucosidase then α-amylase and a strict correlation between the total phenolic content and enzymatic inhibition activity has been demonstrated.[42] Vaidya *et al.,* also provide an additional proof of the anti-diabetic effect of secoiridoid glycoside OL. [64] In fact, they evaluated the capability of OL to inhibit glycogen phosphorylase-a (GPa) and by molecular docking studies, they have reported that OL can bind GPa in the pyridoxal phosphatase (PLP) binding site with docking energy of -3.82 Kcal/mol. Furthermore, an experimental study reported the improvement of glucose-induced insulin-releasing and an increased glucose peripheral uptake.[65] Moreover, in streptozocin-induced diabetic rat, it has been observed an up-regulation of the insulin receptor substrate-1 (IRS-1) mRNA expression.[66]

4.2 Onion

Onion (*Allium cepa*) represents one of the most ancient vegetables mentioned in several scriptures since the Middle Age and, after potato and tomato, constitutes the third most essential horticultural crop.[67] Indeed, due to its versatility, onion is exploited for consumption, seed production, culinary uses and processed food.[68]

At this aim, after the detailed chemical investigation of the phytocomplex, literature data have shown that onion offers a variety of constituents (Figure 3), such as flavonoids, phenolic acids, organosulfur compounds, anthocyanins, associated with different properties in the biological and pharmacological fields.[69-71]

In particular, onion properties have to be attributed to the presence of quercetin glycosides due to its hydrophobicity, co-planarity structure and reducing activity. In detail, the quercetin shows a significant free radical-scavenging activity because of the presence of the hydroxyl groups at 3' and 4'-positions of the B-ring and the 3-position of the C-ring. It has been also found that quercetin inhibits the xanthine oxidase (XOD), lipoxygenase (LOX) and NOX. The Structure Activity Relationship (SAR) and computational studies revealed important findings on the binding of flavonoid in the active site of XOD enzyme. In detail, molecular modelling showed that the polar C3 hydroxyl of quercetin stretched to the space surrounded by the hydrophobic residues such as F1009, V1011 and L1014 into the binding pocket.[72]

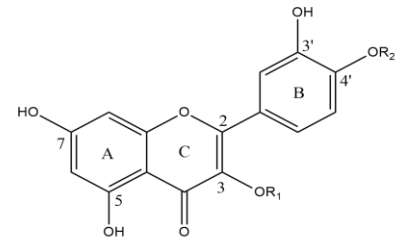


Figure 3. 2D molecular structures of the most bioactive compounds present in the Onion.

Besides, literature data noticed that quercetin can inhibit the nuclear factor kappa-B (NF-κB) inflammation signal cascade and reduce inflammatory cytokine levels, including tumour necrosis

factor (TNF-α) and Interleukins (ILs).[73] As an antidiabetic agent, recent studies have highlighted the capability of quercetin to positive influence glucose and lipid metabolism. This effect could be related to the increase of the glucose uptake by means of mitogen-activated protein kinases (MAPKs) insulin-dependent mechanism, resulting in the translocation of glucose transporter type 4 (GLUT4).[74]

Another study was aimed to investigate the role of quercetin on advanced glycation end products (AGEs) formation and to understand the binding pose of the quercetin with respect to human serum albumin (HSA). Docking results noticed that the quercetin is able to make strong interactions with D121, K174, D173, V120, E119 and D173, highlighting that the quercetin affinity to HSA is due to hydrophobic contacts within the hydrophobic core of the enzyme. These findings suggested that the binding of the compound to free amino group of lysine prevailingly within the core of HSA may be responsible for the inhibition of AGE formation.[75]

Quercetin can enhance the phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) in skeletal muscle cells. It has been also examined that quercetin inhibits the glycogen phosphorylase (GP), which catalyzes the rate-limiting step of glycogenolysis.[76]

Srinivasan *et al.,* studied the antihyperglycemic effect of quercetin in streptozotocin (STZ)-induced diabetic rats and analysed molecular interactions between quercetin and various diabetes mellitus-related protein targets, such as GP and the peroxisome proliferator-activated receptor-gamma (PPARγ). It was found that quercetin established interactions with G177, W173, T85 and T219 residues of GP protein. Concerning PPARγ docking study, the quercetin engaged interactions with PPARγ amino acid residue Y473 and showed a better binding affinity to the enzyme with respect to gallic acid and metformin.[77]

Moreover, many experimental studies have demonstrated that other components of onion, such as S-methlycysteine sulfoxide (SMCS) and S-allylcysteinesulpoxide, are associated to a hypoglycaemic effect due to the direct action on the pancreas and the rise of the insulin levels in the blood. As results, SMCS is able to ameliorate diabetic condition in rats, maintaining the body weight and controlling the blood sugar.[76]

4.3 Glycyrrhiza L.

Glycyrrhiza genus comprises about 20 species of the *Leguminosae* family and it is typical of the temperate climates of most of the continents, with the exception of Southern Africa. In the Mediterranean Sea area, the most typical species are *Glycyrrhiza glabra L.* and *Glycyrrhiza echinata L.,* whose roots are used to obtain liquorice extracts, which possess a wide range of pharmacological properties. Liquorice root is frequently used in traditional medicine particularly for gastric and duodenal ulcers, *Helicobacter pylori* effects and allergenic reactions. Liquorice is a source of proteins, polysaccharides and simple sugars, mineral salts, pectines, starch, coumarins, vitamins, but a large number of other biological compounds have also been isolated.[78] Currently, it has been calculated that more than 300 flavonoids such as isoliquiritigenin, isoangustone A, licoricidin, dehydroglyasperin C, licochalcone A (LCA), licochalcone E (LCE) and 20 triterpenoids have been isolated from liquorice root.[79] In particular, among triterpenoids, the major bioactive components are the saponin Glycyrrhizic acid (or Glycyrrhizin, GC) and its aglycone Glycyrrhetinic acid (GA) (Figure 4B and 4A, respectively) in a percentage range from 5 to 24%.[80] Both compounds are known in the literature for their multiple biological activities and have been employed as scaffolds for the semi-synthesis of several derivatives with interesting pharmacological properties including an anti-diabetic activity.[81]

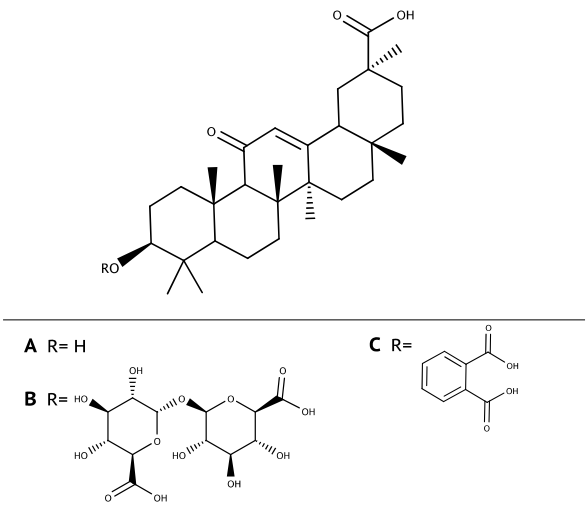


Figure 4. 2D molecular structures of the scaffold of triterpenoids and most bioactive derivatives: **A**) the aglycon GA, **B**) the saponin GC and **C)** GC phthalic ester derivative.

Furthermore, given the association between MetS and hypercoagulation, [82] it was found that the phthalic ester derivative of GC (Figure 4C) presented a more pronounced thrombin inhibition (IC_{50}=114.4 ± 1.3 μM) than the saponin (IC_{50}=235.7 ± 1.4 μM) and molecular docking studies revealed the importance of the phthalic ester moiety to engage hydrogen bonds interactions with A113 and K110, key residues essential for fibrinogen recognition by thrombin.[83] Beyond the semi-synthetic derivatives of GC and GA, multiple pharmacological activities have been demonstrated also for the pure natural compounds extracted from liquorice.[79] In particular, concerning the metabolic diseases, it has been found that liquorice exhibits anti-diabetic effects by inhibiting insulin resistance and oxidative stress/free-radical damage, to delay the development of diabetes. This effect is mainly due to GC, GA and some flavonoids as liquiritigenin, isoliquiritigenin,

glabridin, LCA (Figure 5B) and LCE (Figure 5C) that act with different molecular mechanisms. For instance, GA and GC act on glucose absorption, glucose uptake, insulin secretion and diabetic vascular dysfunction,[84] while flavonoids exhibit significant blood glucose-lowering effect with different mechanisms. Moreover, LCA selectively inhibits the c-Jun N-Terminal Protein Kinase 1 (JNK1) activity, resulting in G1 phase arrest and apoptosis,[79] while LCE increases the levels of PPARγ expression via the stimulation of AKT signals, resulting in improvements in hyperglycaemia and hyperlipidaemia under diabetic conditions.[85] Some studies have further shown that liquorice extract would be a therapeutic agent for the prevention and treatment of diabetes nephropathy led by mesangial fibrosis and glomerulosclerosis.[86] Finally, liquorice extract has a potential therapeutic effect on diabetes due to its anti-oxidant and anti-hyperglycaemic properties.[87, 88] For instance, LCE (Figure 5C) evidenced weak but significant, anti-diabetic effects on type 2 diabetes mellitus (T2DM), due to the PPARγ ligand-binding activity *in vitro*. Indeed, two weeks of LCE (Figure 5C) treatment lowered blood glucose levels and serum triglyceride levels in diabetic mice.[85] Glycyrrhiza flavonoids have been also investigated to figure out their anti-obesity and lipid-lowering effects. These results derived from the inhibition *in vitro* of the pancreatic lipase enzyme (PL). Specifically, flavonoids isolated from *Glycyrrhiza glabra* roots 3,3',4,4'-tetrahydroxy-2-methoxychalcone (Figure 5A), isoliquiritigenin (Figure 5D), liquiritigenin (Figure 5E), licuroside (Figure 5F) and isoliquiritoside (Figure 5G) exhibited the strongest inhibitory activity of PL with IC_{50} values of 7.3μM, 35.5μM, 14.9μM and 37.6μM, respectively. *In vitro* assays against PL have been further explained through molecular docking calculations of such calchones (Figure 5) and it turned out that the most active isoliquiritigenin (Figure 5D) not only showed a high binding potential towards the active site of PL, but also it formed strong hydrogen bonding interactions with the active site amino acid residues H263, R256,

D79 and F215, which are important for the PL activity.[89] Taken together, all these evidences indicate the potential of the chalcone scaffold as a source of PL inhibitors for preventing obesity.

Liquorice flavonoid oil (LFO) significantly decreases hepatic cholesterol and plasma lipoprotein LDL cholesterol levels in HFD rats by suppressing the HMG-CoA synthase (HMGCS) activity thus improving the cholesterol metabolism. Such a mechanism could hypothesize possible implications of liquorice in the prevention of CVDs.[90] Glycyrrhizin has been reported to ameliorate liver dysfunction associated with the MetS, thus suggesting a therapeutic potential against hepatocellular damage in MetS.[91] Extracts of *Glycyrrhiza glabra* as GA, dehydroglyasperin C and especially GC have been reported to possess hepatoprotective effects. Indeed, GC has been widely used in the treatment of a variety of liver diseases, such as hepatitis B, hepatitis C, liver fibrosis, and cirrhosis of the liver. In particular, GC regulates the expression of CYP3A and CYP7A to prevent the toxic accumulation of bile acids,[92] GA protects hepatocytes against TNF-α-induced chronic liver inflammation.[93]

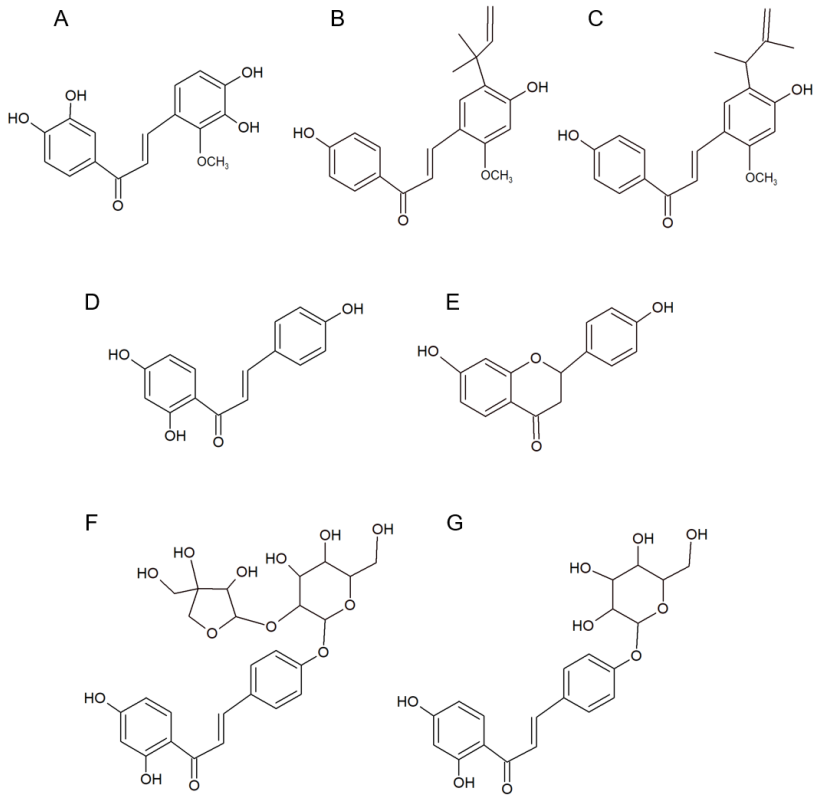


Figure 5. Calchones and flavonoids isolated from *Glycyrrhiza glabra*.

Hepatoprotective effects are exerted also by the bioactive calchone flavonoids including liquiritigenin, isoliquiritigenin and LCA (Figure 5B). Emerging evidence suggested that these natural products relieved liver diseases and prevented drug-induced liver injury through multi-targeting therapeutic mechanisms, including anti-steatosis, anti-oxidative stress, anti-inflammation, immunoregulation, anti-fibrosis, anti-cancer, and drug-drug interactions. Two most

recent clinical trials further demonstrated that liquorice extract, coupled with a low-calorie diet, improved lipid profile in obesity patients and exert potential effects on obesity-related fatty liver.[94] Furthermore, in 2017, Namazi *et al.*, reported the anti-obesity effects of Liquorice.[95] It has been suggested that liquorice can affect obesity and its complications including insulin resistance and lipid profile through various mechanisms[96], most of them including the PPARγ gene, which is expressed exclusively in adipose tissue and is a candidate gene for obesity phenotype and its complications.[97] All these findings the great potential of liquorice bioactive components for the treatment of metabolic diseases.

4.4 Rosemary

Rosemary (*Rosmarinus officinalis L.*) is an aromatic, evergreen shrub plant belonging to the Labiatae family (Lamiaceae) and indigenous to the Mediterranean region. Analysis of the chemical composition of rosemary extract (RE) showed that the most important pharmacologically active components are different classes of polyphenols including phenolic terpenes, flavonoids and phenolic acids. Phenolic terpenes of rosemary include diterpenes such as carnosic acid, carnosol, rosmanol, epirosmanol, isorosmanol, rosemaridiphenol, rosmadial Methoxycarnosol and Methoxycarnosate; triterpenes such as ursolic acid, betulinic acid andoleanolic acid. Flavonoids include both flavones (apigenin, luteolin, hispidulin and genkwanin) and flavonols (rutin, kaempferol, kaempferol-3-*O*-rutinoside, naringenin-*C*-hexoside, hesperetin, apigenin-7-*O*-glucoside, quercetin, isorhamnetin-3-*O*-hexoside, apigenin-acetylglucosidase, isohamnetin-lutelion, and isorhamnetin-luteolin). Phenolic acids found in rosemary are: rosmarinic acid, chlorogenic acid, m-hydroxybenzoic acid, coumaric acid, vanillic acid, caffeic acid and p-hydroxybenzoic acid. Among the phenolic compounds, those found in the highest quantity are

carnosic acid, carnosol and rosmarinic acid (Figure 6),[98] which are endowed with the predominant pharmacological effects of rosemary[99], such as anti-inflammatory[100], anti-oxidant[101], anti-bacterial[102], and anti-viral actions[103].

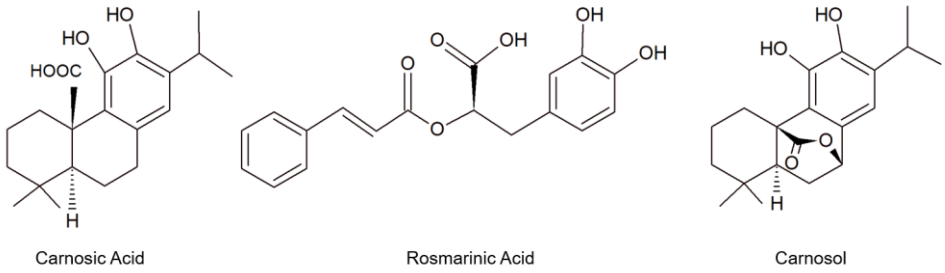


Figure 6. 2D structures of the major polyphenols components of *Rosmarinus officinalis L.*: carnosic acid, carnosol and rosmarinic acid.

They are also able to interact with multiple molecular targets involved in the pathogenesis of metabolic diseases. According to Yu *et al.*, carnosic acid could hinder atherosclerosis by means of a multi-target mechanism. [104] They have demonstrated that carnosic acid inhibits TNF-α-induced migration, ROS production, MPP-9 expression, and down-regulates nuclear translocation of NF-kB subunits p50 and p65 in human aortic smooth muscle cells. The inhibition of nuclear translocation of NF-kB subunits p65 and p50 have been also reported along with the demonstration of carnosic acid effect on the expression of cell adhesion molecules and on the attachment of monocytes to the endothelium.[105] These authors have shown that pre-treatment with carnosic acid at 20 mM reduced the U937 cells adhesion to IL-1 beta-treated human umbilical vein endothelial cells (HUVECs), suppress ROS production and the expression of cell adhesion molecules like the Intercellular Adhesion Molecule 1 (ICAM-1, or CD54), the vascular cell adhesion molecule-1

(VCAM-1, or CD106) and E-selectin (also known as CD62E) through the inhibition of NF-kB. Rosemary components are also promising anti-obesity and anti-diabetic agents. In fact, Takahashi *et al.*, have found that both carnosic acid and carnosol inhibit the *in vitro* differentiation of mouse preadipocytes, 3T3-L1 cells, into adipocytes. These actions seemed to be mediated by activation of the anti-oxidant response element (ARE) and induction of phase2 enzymes, in particular Gsta2, Gclc, Abcc4, and Abcc1, all of which are involved in the metabolism of glutathione (GSH). Furthermore, carnosic acid and carnosol, significantly increase the intracellular level of total GSH. Thus, it has been proposed that the stimulation of GSH metabolism could be a critical step for the inhibition of adipocyte differentiation in 3T3-L1 cells and suggest that pro-electrophilic compounds such as carnosic acid and carnosol may be potential drugs against obesity-related diseases. Specifically, Takahashi *et al.*, have demonstrated that carnosic acid inhibits adipocyte differentiation at very low concentrations ($IC_{50} = 0.86$ µM). In addition, both carnosol and carnosic acid have been found to possess PPARγ transcriptional activities. PPARγ is a ligand-activated transcription factor, belonging to the metazoan family of nuclear hormone receptors. Activation of PPARγ increases the transcription of enzymes involved in primary metabolism, leading to lower blood levels of fatty acids and glucose. Hence, PPARγ represents the major target for the glitazone type of drugs currently used for the treatment of T2DM.[106-107] In addition, *in vitro* studies have shown that RE has an insulin-like effect to inhibit the production of glucose by hepatocytes. RE was shown to significantly suppress gluconeogenesis in hepatocellular liver carcinoma (HepG2)[108] In addition to numerous *in vitro* and *in vivo* studies, the anti-diabetic effect of RE has been recently investigated in humans demonstrating that subjects treated for eight weeks with dried rosemary leaf powder, showed a significant reduction of LDL cholesterol, an increase of HDL cholesterol and a reduction of fasting plasma glucose. [109] In a recent study, new carnosol and carnosic acid-

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related compounds in heated rosemary have been identified. Their structures have been determined by mass spectrometry and nuclear magnetic resonance analyses and their effects on antioxidative stress and PPARγ activation have been examined.

Among the five compounds identified, dehydromiltirone (Figure 7A), miltiodiol (Figure 7B) and miltirone (Figure 7D) were already described. Meanwhile, two compounds reported in Figure 7C and 7E were newly discovered molecules (Figure 7). The anti-oxidant properties of carnosic acid and of compounds depicted in Figure 7 have been tested. It emerged that carnosic acid as well as miltiodiol (Figure 7B) and the newly discovered compound reported in Figure 7C, possess important pharmacological properties, in particular as inhibitors of the lipid peroxidation.

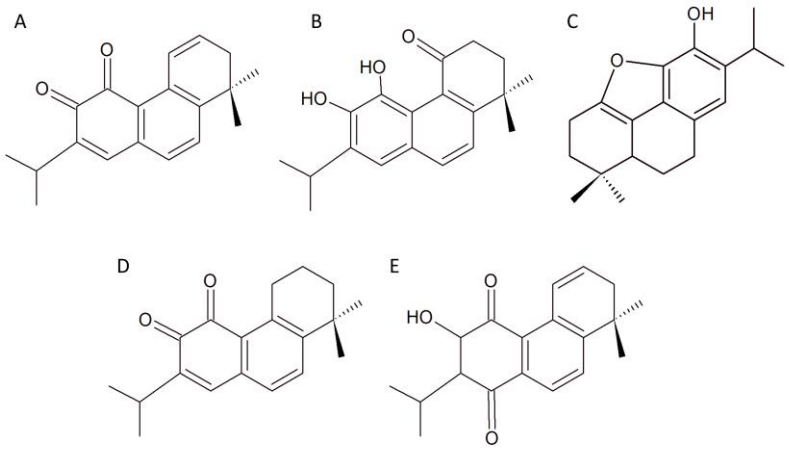


Figure 7. 2D structures of compounds A–E generated by heat treatment of rosemary.

The potent inhibitory activities of carnosic acid (IC_{50}=0.07 µM) (Figure 6) and miltiodiol (IC_{50}=0.11 µM) (Figure 7B) can be explained by the presence of the catechol scaffold. However,

compound reported in Figure 7C despite lacking in the catechol ring, it has shown the most potent inhibitory activity of the lipid peroxidation (IC_{50}=0.03 µM), if compared not only with carnosic acid and miltiodiol, but also with dehydromiltirone (IC_{50}=0.94 µM) (Figure 7A) and miltirone (IC_{50}=0.27 µM) (Figure 7D). The bioactive components reported in Figure7, have been also evaluated for their PPARγ transactivation activity. All five compounds in Figure 7 have shown significant PPARγ transactivation activities in cells at adequate doses of 10 µM and 50 µM. Compounds reported in Figure 7A, 7C and 7E are endowed with more potent PPARγ activities than carnosic acid. Their adipogenic activities have been also examined, demonstrating that compounds reported in Figure 7C and 7E possess adipogenic activities in 3T3-L1 cells at almost the same doses that showed PPARγ transactivation activities.[110]

Rosmarinic acid is a natural ester of 3,4-dihydroxyphenyllactic acid and caffeic acid, belonging to the family of hydroxyl cinnamic acids. Apart from Rosmarinic acid being a potent anti-oxidant, it has a large number of other biological activities such as anti-viral, antibacterial and anti-inflammatory properties and it could also prevent-amyloid aggregation.[111] Moreover, its most relevant pharmacological activity is due to its anti-diabetic property. Indeed, rosmarinic acid (Figure 6) has been found significantly inhibits α-glucosidase, α-amylase, dipeptidyl peptidase-4 (DPP-IV), a serine protease responsible for the degradation of insulinotropic incretin glucagon-like peptide 1, and protein tyrosine phosphatase 1B (PTP1B) responsible for the reversal of insulin receptor autophosphorylation. Rosmarinic acid (Figure 6) is also able to counteract the insulin resistance of T2DM due to excessive triglyceride storage in liver and muscle. The effect of rosmarinic acid on skeletal muscle cells have been studied by Vlavcheski *et al.*, demonstrating that rosmarinic acid stimulates glucose uptake in L6 muscle cells through activation of AMPK phosphorylation.[112] The stimulation achieved the maximum value, using 5µM Rosmarinic acid

without any changes on cell morphology or cell toxicity assessed by microscopic examination. It has been also noted that the maximum stimulation of glucose uptake treated with Rosmarinic acid was comparable to the stimulation of insulin and Metformin. The treatment of L6 myotubes with Rosmarinic acid also significantly increased the AMPK phosphorylation of T172, which was at the same level as with 2 μM Metformin treatment.[113]

4.5 Oregano

Oregano (*Origanum vulgare L.*) is an aromatic perennial herb of the mint family (*Lamiaceae*), known for its flavourful dried leaves and flowering tops. Oregano is native to the hills Mediterranean countries and Western Asia. The Essential Oil of Oregano (EOO), which is composed primarily of carvacrol and thymol, is widely recognized for its curative properties.[114,115, 116,117, 118] Recent investigations have, in fact, demonstrated that these compounds are also potent antioxidant, anti-inflammatory, antidiabetic and cancer suppressor agents. Besides carvacrol and thymol, major constituents of the EOO are γ-terpinene, ρ-cymene, terpinen-4-ol, linalool, β-myrcene, trans-sabinene hydrate and β-caryophyllene (Figure 8). Based on the content of such compounds, it is possible to establish the chemotype of the species. This may depend on several factors such as peculiar climatic and growth conditions, geographical position, soil conditions and harvest season.[119-121] In detail, the phenolic compounds, which carvacrol belong, are characterized by a strong anti-oxidative activity due to their reactivity with peroxyl radicals by hydrogen atom transfer (HAT) mechanism.[122] In particular, carvacrol acts as scavenger of the free radicals comprising superoxide radicals, hydrogen peroxide and NO, thanks to the presence of hydroxyl group linked to aromatic ring. It was observed by Cho *et. al*. that carvacrol prevents obesity in the HFD-fed mice by decreasing body weight and visceral fat-pad weights and lowering plasma lipid

levels. The evidence obtained in this study suggests that carvacrol appears to inhibit visceral adipogenesis possibly by suppressing bone morphogenetic protein receptor (BMPR), fibroblast growth factor receptor 1 (FGFR1) and galanin-mediated signalling cascades and to attenuate the production of pro-inflammatory cytokines in the visceral adipose tissues by inhibiting toll-like receptor 2 (TLR2), toll-like receptor 4 (TLR4)-mediated signalling pathways. These effects on modulating genes associated with adipogenesis and inflammation by carvacrol are considered relatively novel compared with the mechanisms reported for other anti-obesity phytochemicals.[123]

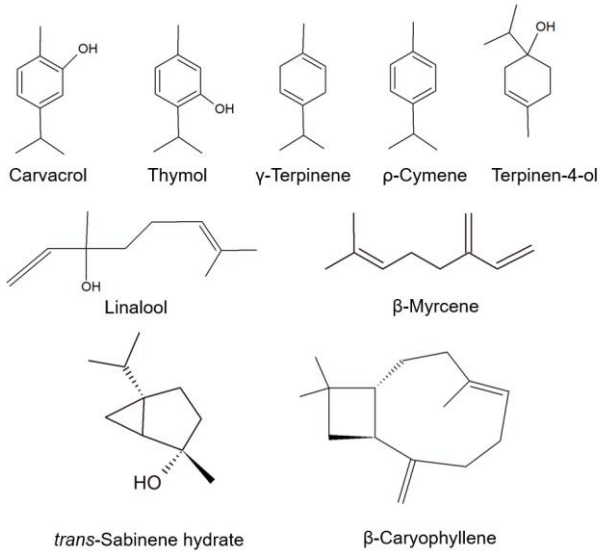


Figure 8. 2D structures of the major constituents of the EOO.

It has been found that oregano extract is a good candidate for the treatment of some aspects of MetS, due to the interaction between its components and PPARs. In fact, the extract is constituted by phytochemical components that act as PPARγ antagonists like quercetin (IC_{50}=3.7±0.4 μM),

luteolin (IC_{50}=4.9±0.4 µM), rosmarinic acid (IC_{50}=43.6±4.2 µM) and diosmetin, PPARγ agonists like biochanin A (IC_{50}=23.7±6.2 µM) and PPARγ modulators such as naringenin (IC_{50}=81.0±10.3 µM) and apigenin (IC_{50}=40.9±9.1 µM). However, the agonistic activity which could improve the lipid profile is too low or counter-balanced by the PPAR antagonists. In addition, the oregano extract is able to antagonize the recruitment of the "adipogenic factor" such as rosiglitazone-mediated DRIP205/TRAP220, thus promoting adipogenesis and adipocyte differentiation in cell culture and increase in weight in humans. Moreover, it has been noticed that the oregano extract has a hypoglycaemic activity due to the inhibition of α-glucosidase, α-amylase and pancreatic amylase (PA).[124] However, the bio-accessibility of oregano polyphenols is limited and the mechanism of how the anti-oxidant activity can affect during gastrointestinal digestion is not clear. At this purpose, a study underlines the effect of hydroalcoholic extracts of three different oregano species on the enzymes above mentioned under simulated gastrointestinal digestion conditions that can change the phenolic compositions. Indeed, this analysis revealed that oregano compounds, such as di-O-syringoyl-β-d-glucopyranose, neochlorogenic acid, and dihydroxy methyl coumarin, are increased at expense of other components, during the gastrointestinal digestion due to the pH shifts, which leads to oxidation and racemization of polyphenolic components.[125] Consequently, this biotransformation results in the enhanced inhibition rate of α-amylase, PL, and in the increased anti-oxidant activity at the gastric and intestinal fractions.[114] Similarly, literature data have evidenced the inhibition of the amylase by the components of *Oregano vulgare*, which increases in association to the phenolic compounds of the rosmarinic acid, underlining the different effects due to the variability in the composition from different species of oregano.[126] Furthermore, oregano could be considered as a candidate for the treatment of secondary complications of diabetes. Actually, glitazones (rosiglitazone and pioglitazone), and fibrates, respectively constitute

one of the treatments provided for diabetes and dyslipidaemia. Nevertheless, considering the side effects of these drugs, the research of new compounds is necessary in order to reduce complications in the MetS. For this reason, the components of the oregano may represent a good alternative for the treatment of obesity and diabetes. It has been also found that oregano could activate the endothelial NO synthase (eNOS), playing an important role in the prevention and amelioration of atherosclerosis in the presence of diabetes.[127-129]

4.6 Hazelnut

Hazelnut is the fruit of the hazel tree, belonging to the species *Corylus avellena L.* of the genus *Corylus*, of the *Betulaceae's* family. Hazelnut is widely consumed all over the world, and the common hazel tree is widely distributed along the coast of North Africa, Southern Europe, Asia Minor and the Black Sea region. Italy is the second-largest producer in the world of hazelnuts after Turkey[130]. Hazelnuts are used as an ingredient in the production of a great variety of manufactured food products including baked goods, cereals, snacks, ice creams, various dessert formulations and mainly pastry and chocolates, but only a small part of the annual production of hazelnut is consumed as raw peanuts.[131] Due to their exclusive composition, hazelnuts have a beneficial effect. Epidemiologic studies have, in fact, associated hazelnut consumption with a reduced incidence of the risk of some chronic diseases, such as CVD, T2DM, hypertension and cancer.[132] The nutritional and nutraceutical properties of Hazelnuts are widely recognized because of its special composition of oil, protein, carbohydrate, sugar and fatty acids. Although the lipid fraction is the major component of hazelnuts (60%), predominating in MUFAs,[133] and PUFAs fatty acids[131], the Hazelnuts oil is particularly rich of specific bioactive and phytochemical compounds like thiamine, riboflavin, tocopherols (α-tocopherols) and phytosterols, essential amino acids (Table 2).[134] In

addition, essential minerals (Manganese, Selenium, Copper and Chromium, Iron, Phosphorus, Calcium, and Zinc), vitamins (A, B, C, K), choline, betaine, anti-oxidant phenolics (caffeic acid), dietary soluble fibres, are present.[131] Hazelnut contains Vitamin E, a family of eight lipid-soluble tocochromanols (tocopherols and tocotrienols), involved in several physiological and biochemical functions, mainly due to its action as an anti-oxidant but also by acting as a membrane stabilizer.[133]

Table 2. Bioactive components contained in hazelnut oil.

Nut oil	
Fatty acid composition (MUFAs and PUFAs)	Myristic acid - 14:0 Palmitic acid - 16:0 Palmitoleic acid - 16:1 Stearic acid - 18:0 Oleic acid - 18:1 Linoleic acid - 18:2 Linolenic acid - 18:3 Arachidic acid - 20:0
Triacylglycerol composition	LLLn LLL OLLn OLLn OLnO LLP OLO LOP PLP OOO SLO OOP SOO
Sterol composition	Cholesterol 24-Methylene-cholesterol Campesterol Campestanol Stigmasterol Δ7-Campesterol Δ5,23-Stigmastadienol + Clerosterol β-Sitosterol Sitostanol Δ5-Avenasterol Δ5,24-Stigmastadienol Δ7-Stigamastenol Δ7-Avenasterol

Tocopherol and tocotrienol composition	α-Tocopherol β-Tocopherol γ-Tocopherol δ-Tocopherol α-Tocotrienol

P: palmitic acid; S: stearic acid; O: oleic acid; L: linoleic acid; Ln: linolenic acid.

Vitamin E exerts also a cardioprotective effect as results of the inhibition of LDL oxidation.[131] The ability of hazelnuts to reduce the LDL cholesterol concentrations is also associated with the presence of MUFA and PUFA, phytosterols and soluble dietary fibres. Thus, these components characterized hazelnuts as a potential hypocholesterolaemia 'heart-healthy' diet aliments.[131] In addition, the presence of vitamin E, riboflavin, tocopherols, phytosterols and other anti-oxidant compounds could explain the ability of hazelnuts to reduce the low-density lipoprotein cholesterol (LDL-C) in the blood and the capacity to ameliorate the endothelial function. The anti-oxidant activity of nuts was confirmed in a recent study, where it was demonstrated that after hazelnut consumption there is an upregulation of the two of the major antioxidant enzymes, superoxide dismutase 1 (SOD1) and catalase (CAT), which have the ability to catalyze the reaction that leads from superoxide (O_2^-) to oxygen and water production. [135] Actually, recent studies have shown that higher consumption of hazelnuts is associated with reduced risk of coronary artery disease and hypertension.[136] In 2003, the Food Drug Administration (FDA), on the basis of scientific data documenting the beneficial effect of hazelnuts consumption, issued a qualified health claim stating that easting 43 g/day of specific nuts (almonds, hazelnuts, pecans, pistachios, walnuts, and peanuts) may reduce CVD risk, thanks to the presence, of anti-oxidant compounds, important minerals such as selenium, calcium, zinc and potassium, MUFAs and PUFAs, which are able to interfere with different mechanisms justifying lipid-lowering properties, the ameliorating of the endothelial function and the hypocholesterolaemia effects of hazelnuts.[136] Furthermore, the presence of dietary soluble fibres and anti-oxidant phenolics in the hazelnuts, is

associated with a decreased risk of obesity, T2DM and MetS.[137] Nuts, in fact, may decrease hyperglycaemia by controlling postprandial glycaemic excursions and increasing insulin sensitivity and secretion by several mechanisms.[138] The impact of nuts on glycemic control has been analyzed in several studies conducted in individuals with T2DM. In particular, 117 subjects with T2DM who received dietary advice and a supplement of mixed nuts, showed a modest but significant decrease in glycated hemoglobin concentrations.[139] Further, the dietary soluble fibres have a protective effect against hypertension, cholesterol, colorectal and prostate cancers and intestinal disorders[140]. In this context hazelnut could be useful for the prevention of MetS associated with T2DM and CVD. In conclusion, the good properties of hazelnuts could suggest a future use of hazelnuts in the prevention of these metabolic diseases (Figure 9).

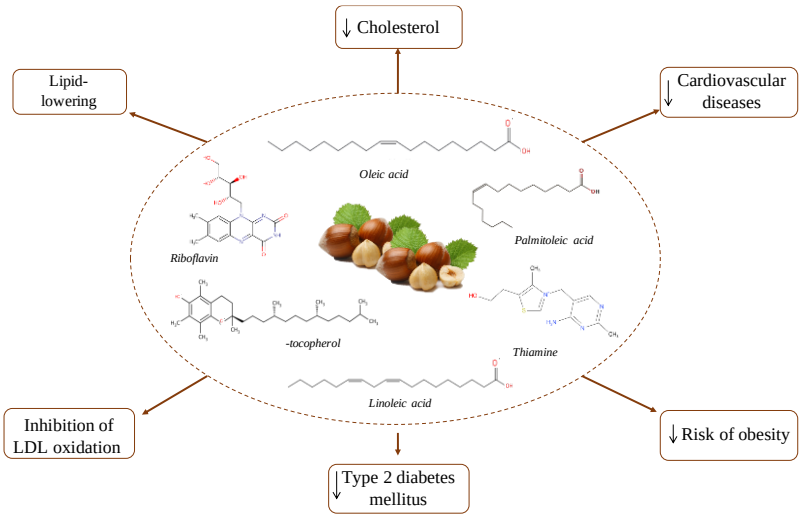


Figure 9. Hazelnuts poly-pharmacological effects in the prevention of MetS.

4.7 Pistachio

Pistachio (*Pistacia vera L.*) is a member of the *Anacardiaceae* family, which is native from the arid zones of Central and West Asia and distributed throughout the Mediterranean basin.[141] Pistachios have a unique nutrient and fatty acid profile; indeed, they are a good source of unsaturated fatty acids (MUFAs and PUFAs), lutein, selenium, flavonoids and phytoestrogen. Pistachios are high in numerous anti-oxidants components such as lutein, β-carotene and γ-tocopherol, relative to other nuts, this explain a good anti-oxidant activity of pistachios .[142] Pistachios are, moreover, the richest source of phytosterols (279 mg total phytosterols/100 g; 210 mg β-sitosterol/100 g, as the predominant phytosterol), potassium (1042 mg/100 g), vitamin B6 (1.3 mg/100 g) and lutein + zeaxanthin (1205 μg/100 g). They are one of the richest sources of protein (21.4 g/100 g), fibres (10.3 g/100 g), selenium (9.3 mcg/100 g), flavonoids and proanthocyanidins.[143] Epidemiologic and clinical studies have consistently demonstrated significant cardiovascular benefits of the pistachios. In fact, the high concentration of lutein, β-carotene and γ-tocopherol in the pistachios are responsible for the important anti-oxidant activity (Figure 10). The presence of these anti-oxidant components justifies the reducing of the inflammatory process and the decreasing concentrations of TG in the plasma correlated with the restoration of endothelial function in adults with T2DM.[144] Due to their anti-oxidant profile, responsible for the anti-diabetic, anti-obesity, and anti-inflammatory effect, the consuming of pistachios should be considered as a supplement in the diet of type 2 diabetic persons.[141] Indeed, the anti-oxidant activity of pistachios related to the presence of lutein, β-carotene and γ-tocopherol, have a beneficial activity on the oxidation of LDL-C and on lipid peroxidation which are components for the formations of atherosclerotic plaques and for the increase of CVD risk[142].

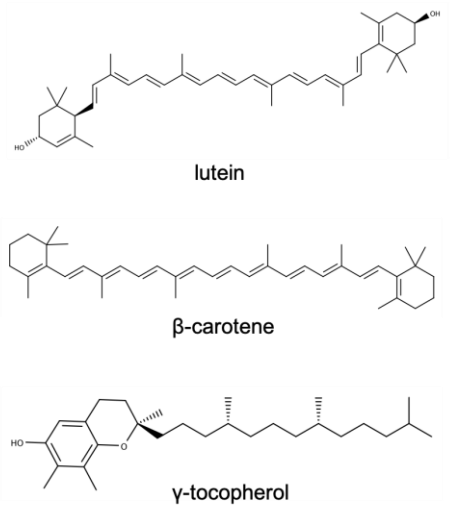


Figure 10. 2D molecular structures of lutein, β-carotene and γ-tocopherol present in pistachios.

This indicates a beneficial effect of pistachios on CVD disease[142,143]. The cardioprotective effects of pistachios have been associated with their favourable fatty acid profiles and to their higher concentrations of anti-oxidants compounds.[142] In fact, as results of the higher concentrations of fatty acid, many studies have shown the beneficial effects of pistachios on lipids and lipoproteins composition which is the primary mechanism for the reducing of the lipid concentrations in the blood.[143] The higher concentration of MUFAs and PUFAs fatty acids, lutein, selenium, flavonoids in the pistachios is correlated with the reducing of blood pressure (BP) and peripheral vascular resistance (Figure 11). Furthermore, the presence in the pistachios of fibres, potassium, selenium and phytosterols contributes to increasing the cardiovascular benefits.

Figure 11. The beneficial effects of Pistachios.

The high concentrations of MUFAs and PUFAs fatty acids, contained in the pistachios, are able to avoid the development of CVD risk due to the action on multiple risk factors of this MetS. In fact, the experimental studies have shown that the daily consumption of pistachios is associated to the decrease of LDL cholesterol, which may reflect effects on plasma stearoyl-CoA desaturase activity (SCD) associated to CVD risk[143]. The beneficial effect of pistachios is attributed to MUFAs and PUFAs, which interfere with two metabolic pathways essential for lipid metabolism. The first action regards the cholesteryl ester transfer protein (CETP), a plasma protein that plays a key role in reverse cholesterol transport by transferring cholesteryl esters (CEs) from HDL to LDL and very low-density lipoprotein (VLDL) particles in exchange for triacylglycerols. The second action concerns SCD which is responsible for the synthesis of monounsaturated fatty acids from saturated fatty acids (SFAS) and plays an important role in cholesterol, triacylglycerol and lipoprotein metabolism[143]. Thus, the anti-oxidant, the lipid- and lipoprotein-lowering regulations mechanisms, and cardiovascular protective effects are due to the multi-target beneficial activity of pistachios.[143,142] These pharmacological properties could justify a possible future use of pistachios as multi-target agents, easily incorporated into a healthy dietary pattern in the prevention of MetS.

4.8 Annurca (or Melannurca) apple

Although apples are the most worldwide-consumed fruits, each cultivated species differ for organoleptic, nutritional characteristics and health benefits. Among the wide apple species, the variety Annurca (also known as "Melannurca"), native from the cultivation areas of the Southern Italy region Campania, owns marked organoleptic qualities such as flavour, excellent taste and scent, for which is defined the 'queen of the apples'[145] and it has been listed as a Protected Geographical Indication (PGI) product (Commission Regulation (EC) No. 417/2006). Several studies have reported the health benefits of Annurca apple that are strictly exerted by its polyphenolic extract (AAE) of which its major bioactive components are chlorogenic acid, catechin, epicatechin, procyanidins B2, rutin, phloridizin (Figure 12).[146]

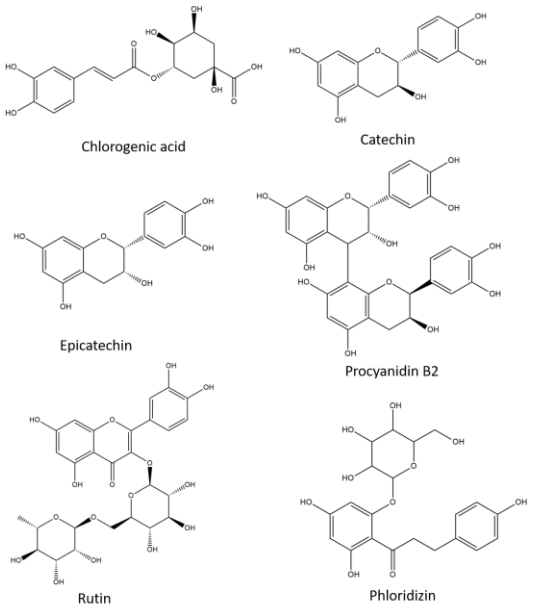


Figure 12. The polyphenol components mostly present in the Annurca apple extract (AAE).

Firstly, *in vitro* studies of Annurca extracts compared by using the following apple cultivars: Red Delicious, Pink Lady, Fuji and Golden Delicious, demonstrated the polyphenolic components found in the extracts of Annurca as the most effective in reducing cholesterol and glucose uptake in HepG2 cell lines[146] and to positively affect lipid metabolism.[147] Subsequently, three clinical trials have been performed: in the first, in 2016, a study published by Tenore and colleagues revealed that, if compared with to other four apple cultivars (Red Delicious, Granny Smith, Fuji, Golden Delicious), a daily consumption of two Annurca apples has the most appreciable hypocholesterolemic effects also *in vivo*, by increasing the HDL levels of 15.2% and decreasing the total and LDL-C levels by 8.3% and 14.5%, respectively. These effects are mainly due to the polyphenolic content of the Annurca flesh, particularly rich of procyanidins (from two to four times more than the other apple samples compared), while the other polyphenolic components, such as dihydrochalcones, flavonols and anthocyanins, are present in an amount close to the average value found for the five apple species considered.[148] In the second clinical trial, revealed that 800 mg/day of Annurca apple polyphenolic extract decreases TC by about 24.9% and the LDL cholesterol of -37,6%, equivalent to the consumption of 10 mg of Atorvastatin or 40 mg of Simvastatin.[149] Results indicate that the most abundant component of the dimeric fraction in Annurca apple (particularly, procyanidin B2), was the most effective in decreasing LDL cholesterol levels. In the third clinical trial, it has been shown that Annurca extracts increase faecal cholesterol excretion.[150] The molecular mechanism of the cholesterol-lowering activity of AAE has been explained using *in vitro* cultured human hepatocytes treated cells and results showed that AAE acts differently than statins, by promoting mitochondrial respiration, lipolysis and fatty acid β-oxidation. Besides, AAE prevents acetyl-CoA from becoming HMG-CoA and, instead, diverts

it to the Krebs cycle to produce ATP and energy for the cell.[151] Taken together, these data indicate Annurca apple as a functional food for the prevention of CVD risk through a normal diet.

4.9 Red Wine

MedDiet is characterized by an adequately balanced combination of fruit and vegetables, and moderate intake of alcohol, primarily wine red.[152] Indeed, this healthy diet pattern involves a "Mediterranean way of drinking", that consists of a regular, moderate wine consumption mainly with food.[153] According to the Dietary Guidelines for Americans 2010 such kind of wine consumption is defined as up to 1 drink per day for women and up to 2 drinks per day for men.[154] Epidemiological studies have found that moderate alcohol intake is associated with a lower risk of CVD and a reduced risk of all-cause mortality among middle-aged and older adults. The interest in the effects of alcohol has further grown since the 1990s thanks to data, which confirms that especially red wine may contain some beneficial compounds. This specific advantage of wine has been supported by the so-called "French paradox".[155] The term French paradox was coined by the epidemiological observation that the French population was affected by a relatively low incidence of cardiovascular mortality despite a quite high dietary intake of saturated fats. This phenomenon, first described by the Irish physician Samuel Black in 1819, was later named French paradox by Dr. Renaud, a scientist from Bordeaux University in France in 1992. In agreement with the observed relationship between moderate alcohol consumption and reduced risk for coronary heart disease (CHD), it has been suggested that France's high red wine consumption could be the primary reason.[156, 157] Wine is a traditional alcoholic beverage obtained by fermentation of grape must, which qualitative and quantitative composition is related to the variety of grape. Moreover, wines can be distinguished by the geographic location of vineyards, variations in the same vineyard, different viticulture practices, and winemaking and aging techniques.[158] According to

the sweetness, alcohol content, carbon dioxide content, colour, grape variety, fermentation, and maturation process or geographic origin, wine may be classified as red, white, and *rosé*.[159] Chemically, wine is a hydroalcoholic solution (~78% water) that comprises a wide variety of chemical components, including aldehydes, esters, ketones, lipids, minerals, organic acids, phenolics, soluble proteins, sugars and vitamins. Flavonoids constitute a major group of polyphenolic compounds which are directly associated with the organoleptic and health-promoting properties of red wine. There are several reports on the health-protective properties of wine phenolics for several diseases such as CVD, cancers, obesity, neurodegenerative diseases, diabetes, allergies and osteoporosis.[160] Phenolic compounds such as resveratrol, quercetin and rutin possess beneficial effects in the MetS through a multi-target mechanism.

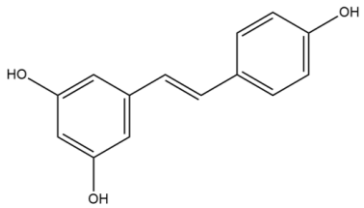


Figure 13. 2D structure of Resveratrol, a polyphenolic compound.

In particular, resveratrol is endowed with cardio-protective and anti-diabetic effects explicated by the involvement of multiple targets (Figure 13). Regarding the cardiovascular effects, resveratrol possesses both anti-atherosclerotic and anti-hypertensive properties. In fact, some studies have shown that resveratrol decreases plasma triglyceride and LDL-C levels increase the high-density lipoprotein cholesterol (HDL-C) [161] and potentiates the liquorice action of pravastatin, by down-regulating the HMGCR. More specifically, Göçmen *et al.,* have found that in Wistar rats the intraperitoneal administration of resveratrol in a daily dose of 20 mg·kg-1 for 20 days lowered the elevated TC, LDL-C, total TG, and VLDL-cholesterol levels compared with the control group.

Additionally, Cho *et al*., have investigated the capability of resveratrol to decrease the activity of hepatic HMGCR. In particular, male Syrian Golden hamsters have been fed a high-fat diet containing 0.025% fenofibrate or 0.025% resveratrol for 8 weeks. Real-time PCR analysis has revealed that HMGCR mRNA expression was significantly lower in the resveratrol group than in the control and fenofibrate group. Resveratrol could also increase the expression of the LDL receptors (LDL-R) in hepatocytes *in vitro*[162] contributing to further abate blood LDL-C levels. In addition, resveratrol possesses anti-atherogenic properties by means of anti-inflammatory effects[163, 164], anti-oxidant mechanism which counteracts the LDL oxidation (process directly involved in atherogenesis);[165] inhibition of smooth muscle cell migration. Accordingly, several potential targets related to these beneficial effects have been highlighted. Resveratrol especially activates the NAD-dependent deacetylase sirtuin-1 (SIRT-1), eNOS, nuclear factor erythroid 2-related factor 2 (NRF2) and ARE; decreases TNFα production;[166] decreases the expression of adhesion molecules (ICAM-1 and VCAM-1) via inhibition of NF-κB pathway activation.[167] A recent study shows that eight weeks of low-dose resveratrol has been able to alleviate some of the cardiovascular defects in hypertensive rats. On the other hand, combination therapy of resveratrol with the hypertensive hydralazine had superior effects in reducing BP. These data demonstrate that the resveratrol in combination with anti-hypertensive agents may provide optimal results in hypertensive patients.[168] The therapeutic action of this compound in relation to diabetes is complex and involves various beneficial effects. SIRT-1 is also an important regulator of many factors influencing T2DM, which activity and expression have been decreased significantly *in vitro* and *in vivo* experimental models of diabetes mellitus.[169] Interestingly, the health benefiting properties of SIRT-1 activation overlap in many ways with those conferred by AMPK activation. In fact, recent studies demonstrate that AMPK and SIRT-1 are core effectors of resveratrol action and that

their activities closely intertwine. Many experimental lines indicate that the metabolic effects of resveratrol are strongly related to AMPK activation. Indeed, resveratrol required AMPK to decrease lipid accumulation in HepG2 cells.[170] Similarly, resveratrol triggered skeletal muscle glucose transport in an AMPK dependent manner. Using an AMPKγ3 knock-out mouse model, it has been demonstrated that faulty AMPK avoids the activation of SIRT-1 upon resveratrol treatment. Consequently, the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) has not been deacetylated in response to resveratrol treatment in AMPKγ3 knock-out mice. A complementary study confirmed that AMPK, is the central target for the metabolic effects of resveratrol since such compound increased the metabolic rate and reduced fat mass in wild-type mice but not in AMPKα1 knock-out deficient mice. In particular, in the absence of either AMPKα1 or AMPKα2, resveratrol failed to increase insulin sensitivity, glucose tolerance, mitochondrial biogenesis, and physical endurance. Consistent with this, the expression of genes important for mitochondrial biogenesis has been not induced by resveratrol in AMPK-deficient mice. In addition, resveratrol increased the NAD-to-NADH ratio in an AMPK-dependent manner, which may explain how resveratrol may activate SIRT-1 indirectly.[171]

Concerning rutin, it has been shown that its hypoglycaemic effects are explicated by reducing glucose absorption from the small intestine. Particularly, rutin is able to inhibit α-glucosidase (IC_{50}=0.196 mmol * L^-1) involved in the digestion of carbohydrates,[172] preventing the excessive increase in the postprandial blood glucose level. The decrease in blood glucose also can be obtained by rutin stimulating the secretion of insulin from β cells and raising glucose uptake by tissues. In fact, it has been demonstrated that in isolated rat pancreatic islets, rutin notably enhances the secretion of insulin.[173] Rutin also has shown an insulin-mimetic role in rat soleus and diaphragm muscles. It has stimulated glucose transport into muscle through activating the

synthesis and translocation of the transporter GLUT-4.[174] Kappel *et al.*, have estimated the in-vitro effect of rutin on glucose uptake in rats soleus muscle after 60 min of incubation, revealing that its stimulatory effect was significant at 500 μM compared with the basal group. Ahmed *et al*., have proved that rutin also increases expression of PPARγ, which thereby improves insulin resistance and glucose uptake in skeletal muscle and adipose. In particular, the oral administration of rutin to diabetic rats (dose of 50 mg/kg body weight/day for 30 days) led to a significant improvement of hyperglycaemia, hyperlipidaemia, serum insulin and concentrations of C peptides, hepatic glycogen content and activity of hexokinase, glucose-6-phosphatase (G6Pase) and GP as well as oxidative stress in diabetic rats.[175] Similarly, Prince and Kama-lakkannan have shown that treatment with rutin decreases the activity of G6Pase in the liver (31%) and kidney (37%) of diabetic rats. Also, rutin decreases the activity of fructose-1,6-bisphosphatase (FBP1), another crucial gluconeogenic enzyme, in the liver (32%), kidney (25%), and muscle (31%). On the other hand, in all these tissues, rutin increases the activity of hexokinase, an enzyme catalysing the glycolysis pathway.[176] Additionally, different studies have evidenced the capability of rutin to counteract the gluconeogenesis, which increased rate is believed to be one of the main causes of hyperglycaemia in diabetic patients.[177] Finally, rutin displays protective effects in preserving the insulin signalling and regulating lipogenesis, manipulating cell cycling, and maintaining mitochondrial function to achieve the integrity of β cells. Thus, rutin could represent a novel strategy for the prevention of T2DM. Specifically, rutin could preserve the insulin secretory machinery and stimulate insulin receptor substrate-2 (IRS-2) signalling in rat pancreatic β cells. These findings further demonstrated the reduced glucolipotoxic effects of rutin through activating AMPK signalling to inhibit the activities of lipogenic enzymes and improving mitochondrial function. Consequently, the cell viability has been retained after attenuating the glucotoxicity

through the broad effect of and rutin.[178]

4.10 Hot pepper

Hot pepper, with the scientific name of *Capsicum annuum*, belongs to the *Solanaceae* family, and it is most commonly consumed as a fruity vegetable. *C. annuum* is well known all over the world to its taste along with characteristic smell and taste. The principal spicy compounds are called capsaicinoids and include capsaicin, dihydrocapsaicin, nordihydrocapsaicin (Figure 14) and others.[179] It is also a promising source of carotenoids, flavonoids, and vitamin precursors. It is also a promising source of carotenoids, flavonoids, and vitamin precursors. This fruit has been proven very effective as anti-oxidant, anticancer, cardioprotective role, oxidative stress prevention, anti-obesity, anti-diabetic, and antimicrobial activities. The medicinal effects of chillies are related to different constituents such as capsaicin, fixed oil, thiamine protein and ascorbic acid.[180]

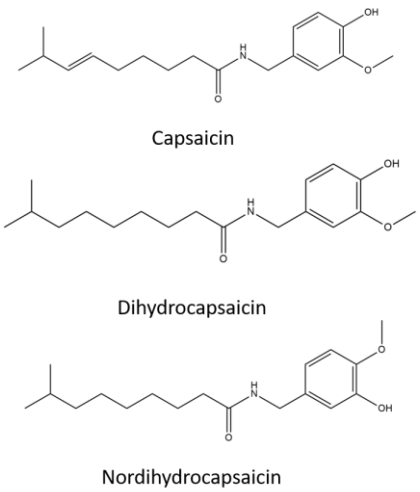


Figure 14. 2D structures of capsaicinoids.

In particular, capsaicin, bioactive compound and water-insoluble derivative of homovanillic acid, is present in higher concentrations in this fruit as compared to other bioactive moieties.[181] The hot pepper and its active constituent have therapeutic potential in different components of MetS. Numerous studies have shown that hot pepper and its constituent, capsaicin, could decrease LDL, cholesterol, TG, and increase the HDL level. The hypolipidemic effect may be related to different factors such as reduction of intestinal absorption of cholesterol and elevation of cholesterol and bile acid excretion in the activation and activation of PPARα.[182,183]

In addition, as shown in Figure 15, *C. annum* shows important anti-diabetic effect correlated to several mechanisms including a) the inhibition of two important enzymes which can hydrolyze polysaccharides into glucose, α-amylase and β-glucosidase;[184,185] b) weight regulation and hypolipidemic effects; c) anti-oxidant activity; d) insulin mimetic or secretagogues;[186] e) activation of transient receptor potential vanilloid subtype 1 (TRPV1), leading to improvement of insulin resistance, suppressive inflammation;[187] f) glucose homeostasis regulation, increasing insulin sensitivity in peripheral tissues; g) stimulation of glucagon-like peptide-1 (GLP-1) secretion; h) protection β cells from apoptosis, improvement in glucose tolerance; i) reduction of fasting insulin/glucose level and expression of adipocytokine genes.[188]

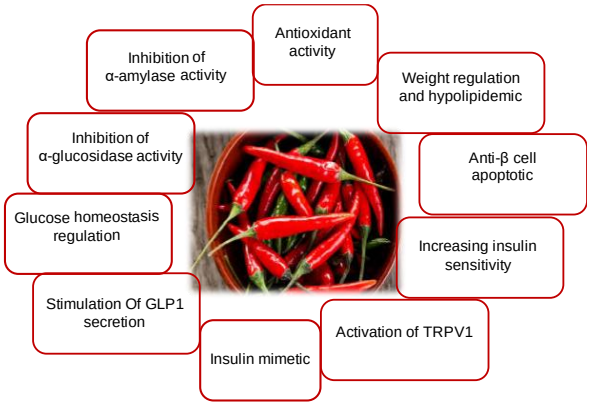


Figure 15. Anti-diabetic mechanisms of *C. annuum*.

Several studies have revealed the anti-obesity effect of *C. annuum* with different mechanisms including satiety, thermogenesis, fat oxidation due to the suppression inflammatory actions of macrophages and release of monocyte chemoattractant protein-1 from adipocytes,[189] rise of energy expenditure,[179] reduction of energy intake,[190] prevention of adipogenesis,[191] restriction the activity of PL and lipoprotein lipase,[192,193] stimulation of lipolytic activity, [194] inhibition of the differentiation of adipocytes and moderating adipokine release from adipose tissue.[195,196] Animal studies have reported that capsaicin possesses anti-obesity effects via limiting the activity of lipoprotein lipase and inhibiting white fat cells generation.[193]

Decreased pre-adipocyte differentiation, proliferation, and lipogenesis are important in the adipogenesis, the critical process of fatty adipose accumulation. Different studies have supported that capsaicin decreases adipogenesis and regulates genes function related to lipid metabolism, and then leads to weight loss. Hsu *et al*., have demonstrated that capsaicin inhibits the expression of PPARγ, leptin and the CCAAT/enhancer-binding protein alpha (C/EBP-α).[197] Furthermore, it efficiently induces apoptosis and inhibits adipogenesis in 3T3-L1 preadipocytes and adipocytes *in*

vitro.[197] Zhang *et al*., have found that capsaicin treatment increased intracellular calcium, preventing the adipogenesis of 3T3-L1-preadipocytes *in vitro*. [198] Male C57BL/6 obese mice, treated with capsaicin, showed decreased fasting glucose, insulin, leptin concentrations, and improved glucose intolerance in obese mice, together with decreased TRPV1 expression in adipose tissue, and improved PGC-1α and PPARα expression in the liver.[199] In another work, Ohnuki *et al*., have demonstrated that mice treated with capsaicin and capsiate, a non-pungent capsaicin analogue, could suppress body fat accumulation and promote energy metabolism. [200, 201]

Experimental studies have associated Brown adipose tissue (BAT) activity, the principal site of adaptive thermogenesis, with protection against metabolic diseases and obesity.[202]

Different literature data have suggested that capsaicin is an important compound to counter diet-induced obesity by enhancing metabolism and energy expenditure.[201, 203]

The activity of BAT can be activated and recruited by cold exposure but also by numerous food ingredients, including capsaicin.[204] Capsinoids in C57BL/6J mice additively have increased whole-body energy expenditure and fat accumulation and decreased body weight gain. The mechanisms may be associated with increased energy expenditure, lipolysis activation in BAT, and increased cyclic adenosine monophosphate (cAMP) levels and PKA activity in BAT.[205]

A rodent experiment has shown that capsaicin could counter the detrimental effects of high-fat diets, such as glucose intolerance, hypercholesterolemia, and suppressed activity in BAT. These effects have been mainly due to increase of the expression of metabolically important thermogenic genes, such as SIRT-1, Mitochondrial brown fat uncoupling protein 1 (UCP1), bone morphogenetic protein 8B (BMP8b), PGC-1α, and positive regulatory domain containing zinc finger protein 16 (PRDM-16) in BAT. Furthermore, capsaicin supplementation has promoted weight loss and the respiratory exchange ratio, post HFD.[206]

Baskaran *et al*., have shown that activation of TRPV1 channels by dietary capsaicin started browning of adipose tissue to contrast obesity.[207]

All these observations provide evidence that capsaicin can activate and recruit BAT, promising strategy to counter obesity. The neuronal circuits in the hypothalamus and brainstem maintain energy balance detects alterations in energy stores and triggers metabolic to maintain energy homeostasis. Energy balance requires the ability of the brain to detect the status of energy stores and match energy intake with expenditure.[208] In individuals with obesity, the hypothalamic endoplasmic reticulum stress induces to low levels of leptin receptor signalling with an increase of leptin resistance.[209]

In the brain, the adipose tissue-derived hormone leptin acts to regulate energy balance and neuroendocrine function. Leptin resistance gives lack of appetite reduction, causing a inadequately respond of body.[210] Lee *et al*., have found that TRPV1 has a major role in regulating glucose metabolism and hypothalamic leptin's effects in obesity, with hypothalamic STAT-3 activity blunted in the TRPV1 knockout mice (Figure 16). [211] In particular, an IC_{50} of 6±2 nM is reported for capsaicin towards human TRPV1[212] and IC_{50} of 19 ± 4 nM in Rat TRPV1.[213] In a study, Janssens *et al*., have confirmed that the addition of dietary capsaicin increases satiety and the sensation of fullness in energy equilibrium, and reduces the desire to eat after dinner.[214] Although the studies about capsaicin and its role in appetite are limited, it has been demonstrated that another capsaicin's target may be the neuronal circuits in the hypothalamus. Here, we summarize the potential mechanisms underlying the anti-obesity effects of hot pepper and in particular the active compound capsaicin. These mechanisms include: (1) increase lipid oxidation and inhibit adipogenesis. In fact, capsaicin inhibits adipogenesis by up-regulating the expression of PPARγ and UCP1, with stimulation of adiponectin secretion and increase body fat accumulation; (2)

activate BAT and induce thermogenesis; capsaicin, activating BAT activity, increases expression of UCP1 and PGC-1α; (3) reduces appetite and increases satiety regulated by the hypothalamus; (4) modulates the function of gut microbiome and gastrointestinal tract, increasing in population of the gut bacterium *Akkermansia muciniphila* and stimulating of GLP-1 secretion.[199]

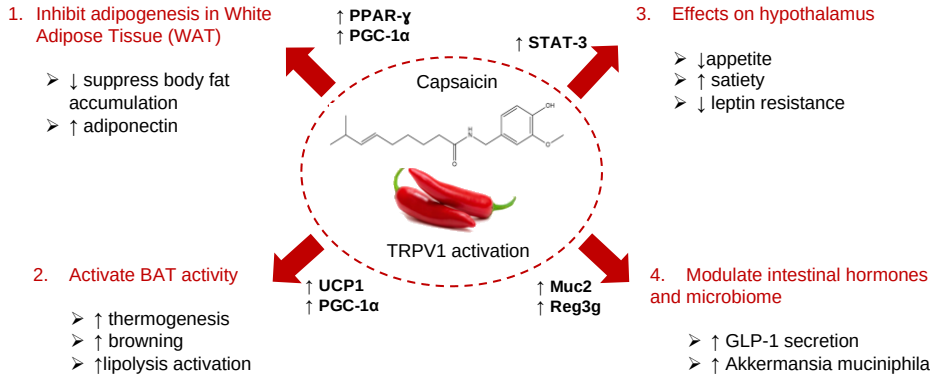


Figure 16. Potential mechanisms underlying the hypolipidemic effects of hot pepper.

In conclusion, all these studies show that hot pepper has a beneficial effect on MetS and could decrease the risk of mortality due to CVD, but in this way, we still need other clinical studies to confirm its efficacy in human.

4.11 Citrus species

The genus *Citrus* (*C.*), family *Rutaceae*, is one of the ancient, most traded, and popular crops. The Mediterranean *C.* fruits have gained high attention since it has been epidemiologically observed an inverse relationship between increased consumption of fruits and reduced risk of different chronic diseases. These activities largely depend upon the diverse chemical constituents of *C.*

fruits, including vitamins, minerals, terpenoids, and flavonoids[215]. *C.* fruits such as oranges, mandarins, grapefruit, and acid citrus fruits, namely lemons, bergamots, and limes, are notably rich in flavonoid [216]. The basic flavonoid structure (Figure 17) consists of 15 carbon atoms and 3 rings of which two are benzene rings connected with a 3-carbon chain. In particular, the A ring originates from resorcinol or phloroglucinol synthesized from the acetate pathway and has a characteristic hydroxylation pattern at the 5 and 7 positions, whereas the B ring originates from the shikimate pathways[217 218]. *C.* flavonoids have received much attention in recent years, for its potential therapeutic qualities, multi-target bioactivities, and relatively low toxicity to animals.

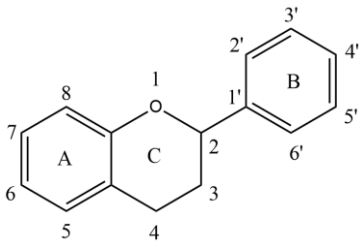
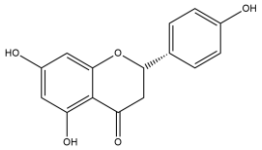
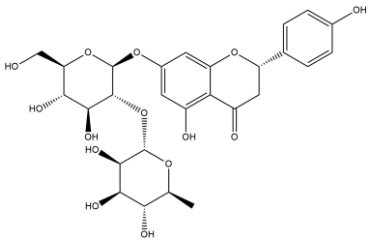
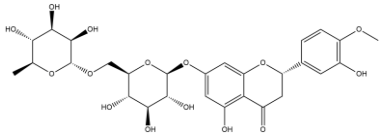
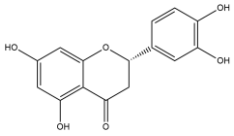
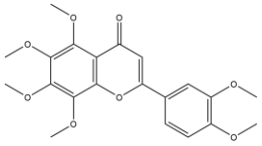
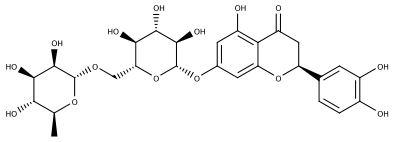


Figure 17. Basic 2D chemical structure of flavonoids

Numerous studies have investigated the chemical composition of the peel, leaf, and flower essential oils of different *C.* species (*sp.*). Naringin, naringenin, nobelitin, narirutin, hesperidin and neohesperidin are the most important flavonoids thus far isolated from citrus fruits (Table 3).

Table 3. 2D structure and class of the most common citrus flavonoids.

Classification	Compound	Structure
Flavanone-aglycone form	Naringenin	
Flavanone	Naringin	
Flavanone	Hesperidin	
Flavanone-aglycone form	Eriodictyol	
Polymethoxylated flavone	Nobiletin	

Flavanone	Eriocitrin	

Naringin is a flavanone glycoside with two rhamnose units attached at the 7-carbon position of the naringenin that represents its aglycon. Naringenin is contained in all citrus species (Table 4) and has shown to possess activity on obesity, hyperlipidaemia, hypertension, diabetes, atherosclerosis and inflammation, thus showing a multi-target mechanism of action on the pathways involved in the MetS.

Table 4. Various *C. sp*. and naringin concentrations found in juice.

Citrus sp.	**Naringin content *(μg/mL)***
Citrus sinensis	21.3
Citrus aurantium	19.7
Citrus reticulata	3383.6
Citrus clementina	8.0
Citrus bergamia	22.3
Citrus paradisi	230.0

Indeed, naringin supplementation has lowered plasma lipids in experimental models of hyperlipidaemia and obesity, has lowered elevated plasma lipid concentrations in high-fat-diet-

fed rats and has decreased plasma lipids and cholesterol in high-cholesterol-diet–fed rats. Hepatic HMGCR activity was significantly reduced in the naringin-supplemented group. C. flavonoids, including naringin, showed an inhibitory action on LDL-cholesterol oxidation.[219] Naringin significantly has reduced fatty streak formation and neointimal macrophage infiltration in vessel walls of cholesterol-fed rabbits. PPARα expression in the liver and the expression of carnitine palmitoyltransferase 1 (CPT1) and mithochondrial uncoupling protein 2 (UCP2), both of which are known to be regulated by PPARα, have been markedly enhanced by naringenin supplementation.[220] [221] The hypoglycaemic effect of naringin is well documented. In particular, it markedly has decreased the activity of hepatic G6Pase and phosphoenolpyruvate carboxykinase (PEPCK). Recent investigations also suggested that the hypoglycaemic activity of naringin is mediated via uptake of glucose in the skeletal muscle by up-regulation of AMPK.[222] The anti-atherogenic activity of naringin in hypercholesterolemic rabbits has been induced by inhibiting ICAM-1 expression in endothelial cells.[223] In MetS, obesity, and related cardiovascular complications, naringin influences AMPK, PPARα, and CPT1-mediated fat utilization and preserves mitochondrial function. Moreover, naringin also prevents the TNF-α-mediated inflammatory process and tissue damage in the liver and vasculature. Figure 18 shows a proposed mechanism for increased mitochondrial biogenesis by naringin.

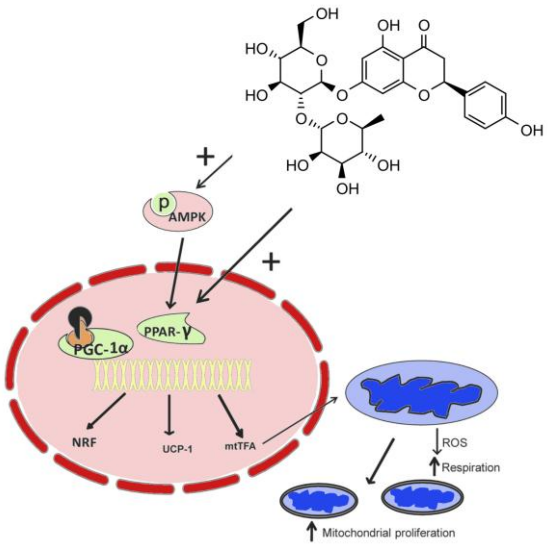


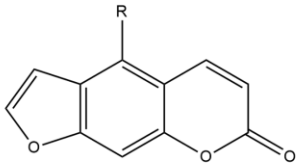
Figure 18. Transcriptional regulation of fat metabolism and mitochondrial biogenesis mediated by AMPK-PGC-1α-pathway.

Docking studies of the ligand citrus flavonoids with four different target proteins have shown that flavonoids are good molecules which dock well with various targets related to diabetes mellitus. The molecular targets, (i.e. glucokinase, glycogen synthase kinases 3β (GSK3B), PPARγ, and DPP-IV have been docked with citrus flavonoids, which provided excellent results as having been seen by the least values of the binding energy. Hesperidin, naringin, neohesperidin have plenty of OH functional groups in the structures, which might promote the formation of hydrogen bonds between flavonoids and protein residues.[224]

Below are explained the mains characteristics of the bioactive compounds of the different *C. sp*. typical of Mediterranean area and in particular, we focused on *C. bergamia, C. sinensis, C. aurantium, C. reticulata, C. clementina, C. paradisi, C. limon.*

C. bergamia Risso et *Poiteau*, commonly named "Bergamot", is a plant belonging to the *Rutaceae* family (subfamily *Esperidea*). It is an endemic plant of the Calabrian region in Southern Italy with a unique profile of flavonoid and flavonoid glycosides present in its juice and albedo such as neoeriocitrin, neohesperidin, naringin, rutin, neodesmin, rhoifolin and poncirin.[225] Bergamot plants grow in a narrow coastal strip of about 150 km, in the area of Reggio Calabria, which presents particularly favourable weather and pedoclimatic conditions for its cultivation.

The herbal preparations obtained from *C. bergamia* are bergamot essential oil (BEO) and bergamot juice.[226] BEO contains up to 93–96% of volatile compounds, such as monoterpenes (25–53% of limonene), as well as discrete quantities of linalool (2–20%) and linalyl acetate (15–40%). BEO also presents a variable percentage (4–7%) of non-volatile compounds, such as pigments, waxes, coumarins, and psoralens. A complete profile of about twenty compounds (furanocoumarins, flavonoids C- and O-glycosides) present in bergamot juice [226] has been obtained. Bergapten and bergamottin (Figure 19) were the primary furanocoumarins in BJ. The beneficial properties of the juice of *C. bergamia* have been investigated in several studies indicating anti-inflammatory, glucose and lipid-lowering properties, anti-obesity activity and some statin-like compounds.[227, 228]



Furanocoumarins

Peak	Name	R
a	Bergapten	OCH_3
b	Bergamottin	$CH_2CHC(CH_3)CH_2C(CH_3)_2$

Figure 19. 2D molecular structures of bergapten and bergamottin.

The 3-hydroxy-3-methyl-glutaryl flavanones enriched fraction (HMGF: brutieridin, melitidin and HMG-neoeriocitrin) (Figure 20), act like statins, having a behaviour similar to simvastatin in a model of hypercholesterolemic rats.[229] Indeed, Leopoldini *et al*., have applied the density functional theory to study the mode of binding of the flavonoid conjugates, brutieridin and melitidin, quantified in bergamot fruit extracts, to the active site of HMGCR This has been compared with that of simvastatin, in order to obtain better insight into the inhibition process of this key enzyme in sterol biosynthesis. Brutieridin and melitidin have been identified to be structural analogues of statins and to partially occupy the site that accepts the part of the CoA substrate, similar to the binding mode of simvastatin. In particular, Leopoldini *et all.*, reported through computational modelling that bergamot's statin-like molecules bind the HMGR at R590, S684, D690, K692 and K735 residues, as well as at the nonpolar amino acids[230]. Regarding clinical trials, Mollace and co-workers have carried out a randomized double-blind placebo-controlled study evaluated a bergamot polyphenol fraction for lowering hyperlipidaemia.

Patients were randomized into three groups as follows: 1) placebo (n=20) 2) bergamot polyphenol fraction (n=20) and 3) bergamot polyphenol fraction phytosomal formulation (n=20). The bergamot polyphenol fraction decreased TC from 262 to 196, LDL-C from 175 to 116, and TG from 252 to 170. Similar results were observed with BPF Phyto: it decreased TC from 261 to 198, LDL-C from 174 to 113, and TG from 252 to 173. The results suggest that both formulations were able to significantly modify cholesterol levels after 30 days. [231]

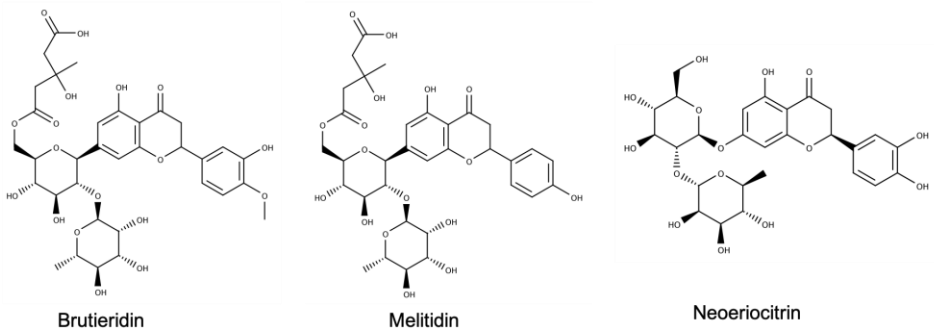


Figure 20. 2D molecular structures of the 3-hydroxy-3-methyl-glutaryl flavanones content in *C. bergamia.*

The bergapten has shown the ability to suppress the activation of the NF-κB, JNK and AKT/mTOR signalling pathways, preventing trabecular bone injury and suppressing the loss of collagen that are the main complications in the diabetes-related osteoporosis, a general metabolic disorder of diabetes mellitus affecting the skeletal system.[232]

Moreover, it was reported that some Bergamot flavonoids may inhibit a mitochondrial carbonic anhydrase VA (CA-VA) isoform with a competitive mechanism of action, coordinating the enzymatic Zinc and establishing other non-covalent interactions, mainly via H-bonds. In particular, virtual screening techniques seems to confirm that Eriocitrin and Apigenin, due to their inhibition profile against the CA-VA isoform, could be potential hit candidates for anti-obesity treatment and prevention. Indeed, the docking simulations carried out with apigenin and eriocitrin show that the C2 phenolic group and the C2 catechol group, respectively, are involved in the zinc coordination into the mitochondrial CA-VA active site.[233]

In addition to the hypolipidemic effect, bergamot has shown radical scavenging activity in the rat model, while histopathological observations showed a protective role on hepatic parenchyma.[234]

Antioxidant activity was evaluated based on its ability to scavenge DPPH•, OH• and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid (ABTS•+) radicals. The antioxidant potential of C. bergamia juice has been previously investigated by Trovato *et al.,* that found a noticeable effect on scavenging DPPH radicals with IC_{50} value of 25.01 µL[235].

However, bergamot juice administration significantly decreased malondialdehyde levels, a good biomarker of oxidative stress, one of the major aldehydes formed during lipid peroxidation. These findings suggest that a protective role of bergamot in hypercholesterolemic diet-induced renal damage may be attributed to its anti-oxidant properties.[235]

C. sinensis represents the largest citrus groups grown around the world, accounting for about 70% of the total annual production of *C. sp*. "Tarocco", "Moro" and "Sanguinello" are the most widely cultivated sweet orange varieties in Italy. They have unique flesh and peel colour, due to the red pigments belonging to the anthocyanin class, and a higher concentration of vitamin C, flavanones and hydroxycinnamic acids than blond oranges.[236]

Anthocyanins have been associated with potentially beneficial effects on various diseases such as capillary fragility, diabetic retinopathy, and human platelet aggregation. The main anthocyanins in the blood (pigmented) orange juices are cyanidin-3-glucoside (Cy3G) and cyanidin- 3-(6″-malonyl)-glucoside (Cy3MG). They have been reported for having higher anti-oxidant activity than other more common anthocyanins.[237]

The total antioxidant activity of Moro C. sinensis crude juice was evaluated on the basis of its ability to scavenge DPPH•, ABTS•+ radicals and to reduce iron. The acetone-water extract obtained from the fresh edible part of red oranges fruits (C. sinensis, Torocco) displayed an intracellular antioxidant activity of 85% in Caco-2 cells at 50 mg/mL. Positive standard drugs (gallic acid and vitamin C) were used. The extract obtained from red oranges exhibited

significantly higher antioxidant activity than positive controls.[238]Literature data showed that C. sinensis exerts positive effects in the regulation of cholesterol levels. The administration of lyophilized *C. sinensis* juice has shown decreased plasma levels of cholesterol (31%), LDL (44%) and TG (33%).[239] In particular, micronized insoluble fibres from *C. sinensis* fruits lowered the concentrations of serum TG (15.6%–17.8%) and serum TC (15.7%–17.0%) by means of enhancing the excretion of cholesterol (123%–126%) and bile acids (129%–133%) in faeces.[240] The effects of *C. sinensis* fruit extract in high-fatdiet-induced obesity mice have been studied [241]. In particular, Lu Y., *et al.,* conducted studies in liver tissue, in which Female C57BL/6 mice were fed respectively a chow diet (control), an HF diet, HF diet supplemented with 1% w/w citrange peel extract (CPE) or 1% w/w citrange flesh and seed extract (CFSE) for 8 weeks. Observations showed that the expression level of PPARγ and its target genes have been down-regulated by CPE and in addition, both CPE and CFSE decreased the expression level of liver X receptor (LXR) α and β, both involved in lipid and glucose metabolism. Results have suggested that CPE and CFSE administration could ameliorate obesity and metabolic disorders in HF diet-induced obesity mice probably through the inhibition of PPARγ and LXRs gene expressions.[242] [236]

C. aurantium is the Latin name of a plant commonly named bitter orange, sour orange or Seville orange. Components of the fruit are sometimes used as a food, but the plant is more widely used as a medicinal or dietary supplement. Similar to ephedra, it contains synephrine alkaloids (SAs) which as adrenergic agonist can be helpful for weight loss.[243] *p-Synephrine* (Figure 21) is the most abundant active component of extracts from *C. aurantium*, structurally related to endogenous neurotransmitters (epinephrine and norepinephrine). This abundant compound has gained significant popularity for the treatment of obesity as an alternative to ephedra alkaloids, which have been banned from dietary supplements by the United States Food and FDA considering the

associated serious side effects.[244, 245] *p-Synephrine* also presents sympathomimetic activity, which has been associated with oxidation of fats through an increase in thermogenesis and stimulated lipolysis, presumably by means of β-3-adrenoceptors. As a sympathomimetic agent with both α- and β-adrenergic receptor agonist, SAs would be expected to potentially increase energy expenditure and decrease food intake.[246] Several studies indicate that SAs can reduce body weight in rodents, showing the ability to promote lipolysis in adipocytes through β-adrenergic stimulation. These data suggest the ability to selectively reduce body fat without compromising lean tissue.[245]

A limited number of well-designed and controlled human studies have been conducted with bitter orange extracts assessing efficacy and safety. The results of over 20 studies involving a total of approximately 360 subjects that consumed p-synephrine alone or in combination with other ingredients are reviewed and critiqued. Over 50 % of the subjects involved in these studies were overweight/obese, Bitter orange/p-synephrine containing products were consumed for up to 12 weeks. Approximately 44 % of the subjects consumed a bitter orange/p-synephrine only product, while the remainder consumed a complex product that contained multiple ingredients in addition to p-synephrine. p-Synephrine alone as well as in combination products were shown to increase resting metabolic rate and energy expenditure, and modest increases in weight loss were observed with bitter orange extract/p-synephrine-containing products when given for six to 12 weeks. However, a need exists for additional well-controlled, long term human efficacy and safety studies involving p-synephrine/bitter orange extract.[247]

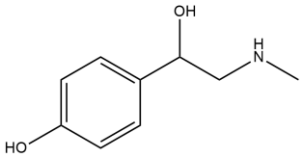


Figure 21. 2D Chemical structure of p-synephrine.

C. reticulata Blanco is commonly known as mandarin fruit. Mandarins are cultivated in countries with temperate summers and mild winters, particularly in Mediterranean countries.

C. clementina is a hybrid between a mandarin orange and a sweet orange and is typical in Calabria (Southern Italy), Plain of Sybaris [107]. Mandarin and clementine are a rich source of essential nutrients. The health benefits associated with their consumption are related to the bioactive molecules present in such fruits such as limonoids, polymethoxy flavones and flavones glycosylates. The total anti-oxidant activity can be correlated with concentrations of, hesperidin, nariutin, and an interest of tangeretin (Figure 22). Among all, Tangeretin (5, 6, 7, 8, 40-pentamethoxyflavone) is effective for the prevention of various disease-related states.[248] A recent study investigating the anti-inflammatory effects of citrus fruit peels have shown that tangeretin had a beneficial effect on lipopolysaccharide (LPS)-induced NO production in macrophage cells, which may provide protection against disease resulting from excessive NO production.[249]

Tangeretin has increased the activation of AMPK pathways in myotubes and in the muscles of mice, leading to increased glucose uptake as well as improvement of obesity-induced glucose intolerance. In obese mice, tangeretin has reduced fat accumulation, adipocytokine production, and insulin resistance, followed by a reduction of circulating lipid mediators, including TC in obese mice on the tangeretin diet. Tangeretin supplementation has reduced adipokines, such as leptin and resistin, which were increased in obese mice.[250]

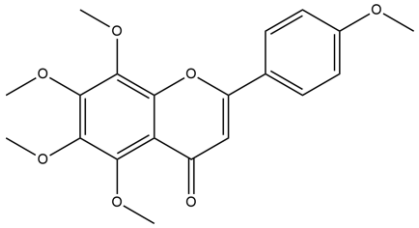


Figure 22. 2D Molecular structures of the tangeretin contained in *Citrus reticulata Blanco* and *Citrus clementina*.

The grapefruit, *C. paradisi* is a subtropical citrus tree, that is cultivated today in the citrus groves of the Plain of Catania, and of the Conca d'Oro in Sicily, in Southern Italy. The varieties of grapefruit differ in colour between red/pink and white depending on the presence or not of lycopene. The fleshy part of the fruit is edible, and the seed extracts have been used as a food supplement and in the cosmetic industry. Active compounds reported for *C. paradise* including flavonoids (naringin and hesperidin, lycopene, among others) and furanocoumarins (bergamottin and 6',7'-dihydroxybergamottin), β-carotene, and *d*-limonene have been also reported. [251]

In HepG2 cell lines, principal flavanones from grapefruit, hesperetin and naringenin both reduced the medium content of apolipoprotein B (ApoB), the main protein component of LDL, with IC_{50} concentrations 43.0 and 48.5 mg/mL medium, respectively. A more pronounced reduction of medium ApoB in HepG2 cells has been observed for a principal polymethoxyflavones (PMFs) from tangerines, tangeretin (IC_{50} 2.5 mg/mL). Roza and co-workers reported a clinical study on the cholesterol-reducing effects of a combination of PMFs (270 mg/d) and tocotrienols (30 mg/d) or placebo in 3 groups of hypercholesterolemic subjects, daily for a period of 4 weeks (group 1 and group 2) or 12 weeks (group 3). The selection of this combination was based on previous in vitro and in vivo research that demonstrated its effectiveness in improving lipid profiles. Daily treatment significantly improved cardiovascular parameters compared to placebo in all groups.

Significant reductions were shown in TC (20%-30%), LDL (19%-27%) ApoB (21%), and TG (24%- 34%).[252]

Animal studies have shown that the active flavonoids in grapefruits, naringin and hesperidin, appear to improve glycaemic control by potentiating insulin secretion, enhancing the transport of blood glucose to peripheral tissues, or by inhibiting endogenous glucose production.[253] Grapefruit has also been reported to stimulate AMP-activated protein kinase, with resulting enhancement of fatty acid oxidation and inhibition of cholesterol and triglyceride synthesis.[254] Regarding the BP reduction, *in vitro* and *in vivo* models have demonstrated that grapefruit extracts decrease coronary vascular resistance and mean arterial pressure possibly by increasing NO synthesis or potentiating the NO-cGMP pathway to induce vascular dilatation.[255] Gamboa-Gómez et al., have reported that treatment with C. paradisi infusion on obese rats fed with a high-saturated-fat-diet led to a reduction in adipocyte size and volume. As a possible anti-obesity mechanism of *C. paradisi,* it has been described that it is able to induce relative expression of carnitine palmitoyl-transferase 1a (CPT1a) that is responsible for the transportation of long-chain fatty acids into the mitochondria through binding to carnitine. The fragrance of grapefruit EO causes activation of the sympathetic nerve activity innervating, which facilitates lipolysis, then results in a suppression of body weight gain.[256]

The lemon plant belongs to the *Rutaceae* family and is the third most important Citrus species after orange and mandarin *C. limon* contains many important phytochemicals, including phenolic compounds (mainly flavonoids) and other nutrients and non-nutrients (vitamins, minerals, dietary fibre, essential oils and carotenoids).[257] These compounds are distributed in different parts of the fruit. Indeed, hesperidin and eriocitrin are present mainly in lemon juice, as well as two isomers of hesperidin, neohesperidin and homoeriodictyol 7-O-rutinoside.[258] Lemon seeds are rich in

eriocitrin, hesperidin and in fewer amounts in naringin; whereas, the peel is rich in neoeriocitrin, neohesperidin and naringin and has minor amounts of narirutin.[259]

Crude extracts of different parts of lemon (leaves, stem, root and flower) have shown many [216] activities on different disorders related to MetS. Indeed, on obesity research, Fukuchi *et al.*, have reported that dietary lemon polyphenols extracted from the lemon peel (0.5 % w/w) on high-fat-diet-induced obesity in mice for 12 weeks suppressed body weight gain (44 %) and body fat accumulation (36 %). One anti-obesity mechanism reported for lemon is by up-regulation of peroxisomal β-oxidation through the increased mRNA level of Acyl-CoA oxidase (ACO) in the liver and white adipose tissues, which was likely mediated via up-regulation of the mRNA levels of PPARα.[260] Additionally, it has been reported that *C. limon* has effects on metabolic alterations caused by obesity. It has been described that supplementation with lemon polyphenols on high-fat-diet-induced obesity in mice significantly improved hyperlipidaemia (serum TG -18 %, TC -26 %, and serum-free fatty acids -5 %), hyperglycaemia (insulin -65 % and faster glucose -26 %), and insulin resistance (-75 %) than obese controls.[251]

4.12 Saffron

Saffron is a spice obtained from the flower of *Crocus sativus*, commonly known as the "saffron crocus". In particular, “threads”, that are vivid red stigmas and styles, are collected and dried to be used mainly as a seasoning and colouring agent in food. One of the most renowned saffron crops in Italy to be cited is the saffron of Aquila (Protected Denomination of Origin, DOP), the best in the world for quality.

In traditional medicine, saffron is often used for the treatment of several disorders as anti-depressant, sedative, anti-spasmodic, respiratory decongestant, expectorant, diaphoretic,

aphrodisiac, and emmenagogue.[261] The three major saffron components responsible of these effects are crocin, picrocrocin, and safranal (Figure 23) and they can be considered potential therapeutic candidates for reducing MetS complications, including hypertension, hyperglycaemia, obesity, and dyslipidemia.[262] In particular, both animal and human studies have been performed in order to define the effects of saffron extracts on various kinds of diseases.[263, 264] Anti-diabetic and hypoglycaemic effects consequent to the intake of saffron and its constituents are obtained by different mechanisms: 1) the control of the expression of adiponectin, TNF-α and leptin in white adipose tissue; [265] 2) the stimulation of glucose uptake and the increase of insulin sensitivity in skeletal muscle cells through both of insulin-dependent, such as, Phosphatidylinositol 3(PI3)-kinase/AKT and mTOR; and insulin-independent (AMPK)/acetyl-CoA carboxylase (ACC); mitogen-activated protein kinases (MAPKs) pathways; [266] 3) the stimulation of insulin release and the increase of the GLUT4 and AMPK expression; [267] 4) the increase in the number of immunoreactive β-cells in the pancreas; 5) the inhibition of PTP1B, a negative regulator of insulin signalling.[268]

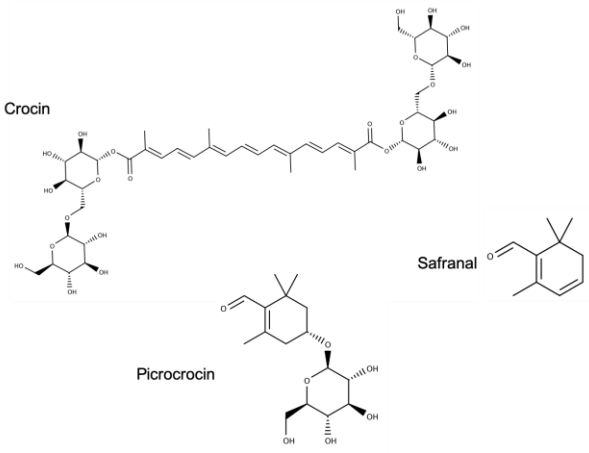


Figure 23. 2D molecular structure of the major saffron components.

Regarding the anti-hypertensive effects of saffron and its constituents, several studies in chemically induced hypertensive rats confirm their activity.[269] The precise mechanisms of their anti-hypertensive and vasomodulatory effects are not yet clear. For instance, it has been shown that saffron and its constituents increase the levels of anti-oxidant NO by enhancing eNOS activity.[270, 271] Moreover, these molecules activate the vasorelaxant functions on smooth muscle cells through the blockage of calcium channels[272] or inhibiting sarcoplasmic reticulum Ca^{2+} release into the cytosol.[273]

Also, the anti-obesity and weight-loss promoting effects of saffron and its constituents have been demonstrated in several studies.[274, 275] *Sheng et al.,* have shown by *in vivo* study that crocin owns several anti-obesity mechanisms similar to those of orlistat, such as the selective inhibition of the pancreatic and gastric lipases activity.[276] However, some differences between the inhibitory functions of crocin with orlistat can be found. Firstly, the dietary fat absorption is reduced more effectively by orlistat than crocin. In particular, orlistat reduces the dietary fat absorption by approximately 30% at a dose of 40 μmol/kg while crocin reduces the dietary fat absorption by 12% at a higher dose, that is 102 μmol/kg.[277] Then, orlistat has an irreversible inhibitory effect on lipase, whereas crocin reversibly inhibits the lipase, since no covalent modification of lipase by crocin occurs.[276] Moreover, while crocin has a more potent inhibitory effect on PL, orlistat strongly inhibits both pancreatic and gastric lipases. Another difference is that orlistat can be minimally absorbed and consequently leads to hepatotoxicity, but crocin is not absorbable.[278] Finally, the orlistat intake causes some adverse gastrointestinal effects including fatty/oily stool, faecal urgency, diarrhoea, system flatulence and abdominal pain.[279] These side effects are not observed during crocin treatment. It has been observed also a protective role of saffron on dyslipidaemia. Indeed, He *et al.,* have reported that crocin has a potent hypotriglyceridaemic and

hypocholesterolaemia activity in atherosclerotic quails.[273] Moreover, it has been demonstrated by Asdaq *et al.*, that anti-hyperlipidaemic and anti-oxidant function of saffron is more effective than crocin, suggesting the presence of other constituents in saffron extracts with anti-oxidant and hypolipidemic properties.[280] A crocin dose of 100 mg showed beneficial effects in patients with metabolic syndrome. After 6 weeks of crocin treatment, a significant reduction from baseline measurements in the levels of TC ($P < 0.001$) and TG ($P = 0.003$) were reported. However, these effects were not significant when compared with placebo group. Several mechanisms have been proposed to explain saffron hypolipidemic effects, such as the inhibition of pancreatic and gastric lipases as a competitive inhibitor,[276] the stimulation of serum adiponectin levels and modulatory effects on the oxidant-antioxidant system.[281] In light of these studies, saffron can be considered as a promising agent in treating dyslipidaemia.

4.13 Garlic

Garlic (*Allium sativum*) is a species of the *Alliaceae* family and it is widely used as a precious spice and a popular remedy for various diseases and disorders.[282] It is native to Central Asia but it is rapidly spread in the Mediterranean basin, becoming an important player of the MedDiet. Some of the most renowned garlic cultivars in Italy are the garlic of Caraglio (Slow Flood praesidium), the white garlic Polesano DOP and the red garlic of Sulmona, which has obtained the recognition of the Ministry of Agriculture, Food and Forestry which has included it in the national list of Traditional Agri-Foodstuffs (PAT).

Garlic is widely appreciated as a cholesterol-lowering functional food ingredient since animal and human trials support this notion. Specifically, in humans, a meta-analysis study showed that garlic can reduce lipid profile as well as glucose parameters and be therapeutically effective in patients

suffering from cardiovascular diseases and diabetes. [283] In particular, allicin is evaluated as the most important compound responsible for the cholesterol-lowering effect of garlic.[284] In order to understand the underlying mechanisms to this effect, garlic and its active components have been investigated in cell culture and in animals, showing the inhibition of HMGCR as principal one. Also, S-allylcysteine, S-ethylcysteine, and S-propylcysteine, the water-soluble organosulfur compounds, have been shown to reduce cholesterol synthesis by deactivating HMGCR through enhanced phosphorylation, but they did not change the levels of mRNA or the amount of the enzyme in cultured rat hepatocytes (Figure 24).[285]

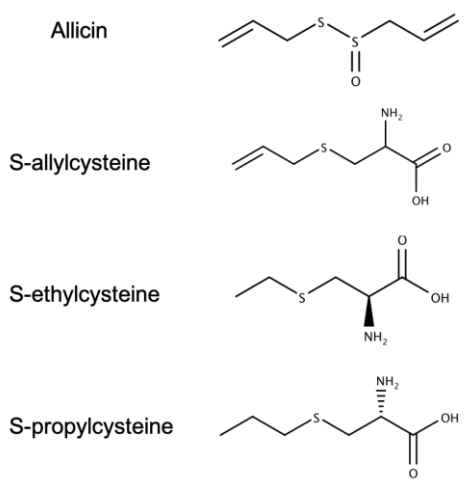


Figure 24. 2D molecular structures of Allicin and other water-soluble organosulfur compounds present in Garlic.

In hepatocyte cells, allyl mercaptan, a major metabolite of garlic compounds, inhibited cholesterol synthesis through a concentration-dependent mechanism.[286] Moreover, although to a lesser extent, garlic and its components inhibit CETP activity and modify the LDL-C/HDL-C ratio. In particular, the CETP activity and antiatherosclerotic effect of garlic, have been studied in cholesterol-fed

rabbits, and it has been found that CETP activity has been significantly reduced in the garlic-supplemented group compared to the control group. Thus, it is possible to conclude that garlic not only reduced atherosclerosis lesions but also altered the ratio of LDL-C/ HDL-C.[287]

Mediterranean Products	Major bioactive chemicals	Major effects	Targets	References
Olive	*Tyrosol*	*Anti-diabetic effect* *Anti-obesity effect* *Anti-hypertensive effect* *Lipolytic agent* *↑ Adiponectin secretion* *↓ [LDL]* *↑ [HDL]* *↓ [Triglycerides]*	*α-amylase* *β-glucosidase* *GPa* *FAS* *DGAT* *HMGCR* *PPARα* *UCP1* *NADPH-oxidase* *ACE2*	28, 37-40, 42-45, 49, 50, 52, 57-59, 64-66
	Hydroxytyrosol			
	Pinoresinol			
	Oleuropein			
	Apigenin			
	Luteolin			
Onion	*Quercetin*	*↑ Glucose uptake*	*MAPK* *GLUT4*	*74, 76, 77*
		Hypoglycaemic effect	*GP* *PPARγ* *AMPK*	
Glycyrrhiza L.	*Glycyrrhizic acid*	*Anti-diabetic effect* *↑ Glucose uptake* *Insulin Secretion* *Hepatoprotective effect*	*Regulation of the expression of CYP3A and CYP7A* *Inhibition of NF-κB pathway activation*	*92, 93*
	Glycyrrhetinic acid			
	Licochalcones-A	*Anti-diabetic effect* *Hepatoprotective effect*	*JNK1*	*79*
	Licochalcones-E		*PPARγ*	85
	Isoliquiritigenin	*Obesity prevention* *Lipid-lowering effects*	*Inhibition of the pancreatic lipase enzyme*	89
	Liquiritigenin			
	Licuroside			
	Isoliquiritoside			

Rosemary	*Rosmarinic acid* *Carnosic acid* *Carnosol*	*Anti-diabetic effect* *Anti-obesity effect* *Anti-hypertensive effect* *↓ [LDL]* *↑ [HDL]*	*α-glucosidase* *α-amylase* *DPP-IV* *PTP1B* *PPARγ* *GSH* *AMPK*	104, 106, 107, 109, 112, 113
Oregano	*Carvacrol* *Thymol*	*Anti-diabetic effect* *Anti-obesity effect* *Hypoglycaemic effect*	*BMPR* *FGFR1* *TLR2* *TLR4* *α-glucosidase* *α-amylase* *PA*	123, 124, 127-129
	Quercetin *Luteolin* *Rosmarinic Acid* *Diosmetin*		*PPARγ antagonist* *α-glucosidase* *α-amylase* *PA*	
	Biochanin A		*PPARγ agonist*	
	Naringenin *Apigenin*		*PPARγ modulator*	
Hazelnut	*Riboflavin* *Oleic Acid* *Palmitoleic Acid* *Thiamine* *Linoleic Acid* *Tocopherol*	*Anti-diabetic effect* *T2DM* *↓ [LDL]*	*Up-regulation of the anti-oxidant enzymes SOD1 and CAT*	*131, 132, 135-139*
Pistachio	*lutein* *β-carotene* *γ-tocopherol*	*Anti-diabetic effect* *Anti-obesity effect* *Anti-inflammatory effect* *Cardiovascular benefits* *↓ [Triglycerides]*		141-143

Melannurca	*Chlorogenic acid*	*Anti-diabetic effect* *Hypocholesterolemic effect* *↓ [LDL]* *↑ [HDL]*	*Promoting mitochondrial respiration*	*146, 147, 150, 151*
	Catechin		*Lipolysis*	
	Epicatechin		*Fatty Acid β-oxidation*	
	Procyanidins B2		*Prevents acetyl-CoA from becoming HMG-CoA and, instead, diverts it to the Krebs cycle to produce ATP and energy for the cell*	
	Rutin			
	Phloridizin			
Red wine	*Resveratrol*	*Anti-diabetic effect* *Cardio-protective effect* *↓ [LDL]* *↑ [HDL]* *↓ [Triglycerides]* *T2DM*	*LDL-R* *HMGCR* *SIRT-1* *eNOS* *NRF2* *ARE* *AMPK* *Inhibition of NF-κB pathway activation*	*161-167, 169-171*
	Rutin	*Anti-diabetic effect* *Hypoglycaemic effect* *Protective effect* *T2DM*	*α-glucosidase* *GLUT4* *PPARγ* *G6Pase* *GP* *IRS2* *AMPK* *FBP1*	*172-176, 178*
Hot pepper	*Capsaicin*	*Anti-diabetic effect* *Anti-obesity effect* *Hypolipidemic effect* *↓ [LDL]* *↑ [HDL]* *↓ [Triglycerides]* *↑ GLP-1 Secretion*	*α-amylase* *β-glucosidase* *PPARα* *PPARγ* *TRPV1* *GLP* *Leptin* *C/EBP-α* *SIRT1* *UCP1* *BMP8b* *PGC-1α* *PRDM-16*	*182-188, 192, 193, 197, 199, 202, 205-207, 211*
	Dihydrocapsaicin			
	Nordihydrocapsaicin			

*Citrus species**		*Naringin*	*Anti-diabetic effect* *↓ [LDL]* *Hypoglycaemic effect*	*G6Pase* *PEPCK* *AMPK* *HMGCR* *PPARα* *CPT1*	*219, 221-224*
		Naringenin	*Anti-diabetic effect*	*PPARα* *UCP2* *CPT1*	
Mediterranean Citrus fruits	*C. bergamia*	*Bergapten*	*Anti-obesity effect* *Hypolipidemic effect* *↓ [LDL]* *↑ [HDL]* *↓ [Triglycerides]*	*HMGCR* *Inhibition of NF-κB pathway activation* *JNK* *AKT/mTOR*	229-232
		Bergamottin			
		Eriocitrin	*Anti-obesity effect*	*CA-VA*	233
		Apigenin			
	C. sinensis	*Anthocyanin*	*Anti-diabetic effect* *↓ [LDL]* *↑ [HDL]* *↓ [Triglycerides]*	*PPARγ* *LXR*	236, 237, 241, 242
	C. aurantium	*p-Synephrine*	*Lipolytic agent*	*α- and β-adrenergic receptor*	245
	C. clementina	*Clementia Tangeretin*	*Anti-diabetic effect* *↑ Glucose uptake*	*AMPK*	249, 250
	C. paradise	*Naringin*	*Anti-diabetic effect* *Anti-obesity effect*	*↓ ApoB* *AMPK* *CPT1a*	252, 254-256
		Hesperidin			
	C.Limon	*Hesperidin*	*Anti-obesity effect*	*ACO* *PPARα*	251, 260
		Eriocitrin			

Saffron	*Crocin* *Picrocrocin* *Safranal*	*Anti-diabetic effect* *Anti-obesity effect* *Hypoglycaemic effect* *↑ Glucose uptake*	*TNF-α* *PI3-kinase/AKT signalling* *AMPK/ACC signalling* *MAPK* *AMPK* *GLUT4* *PTP1B*	*175, 265-268*
Garlic	*Allicin* *S-allylcysteine* *S-ethylcysteine* *S-propylcysteine*	*Anti-diabetic effect* *↓ [LDL]* *↑ [HDL]*	*HMGCR*	285-287

Table X

CONCLUSION

The MetS is a pathological state identified by the coexistence of different dysmetabolic events including T2DM, obesity, hypertension, dyslipidaemia and cardiovascular complications, thus it represents one of the major health risks of the modern age. In fact, even the MetS initially have appeared in the Western world, due to the diffusion of the Western lifestyle across the globe, now it has developed into a now worldwide problem. Once diagnosed, it is crucial to intervene promptly through the adoption of a healthier lifestyle and pharmacologic therapy. Nowadays, the pharmacologic approach requires the administration of drugs able to separately target each dysmetabolic process (statins, ACE inhibitors or angiotensin receptor blockers (ARB), ezetimibe, metformin, etc.). So, in order to ameliorate the compliance of the patients and to increase the therapy effectiveness, a useful and innovative approach is represented by the identification of bioactive compounds interacting with multiple targets. Therefore, since the use of natural compounds for medicine and health has been huge and efficacious during the whole human evolution, in this review we have focused our attention on natural bioactive components characteristic of the Mediterranean area derived from plant extracts, spices, herbs, and essential oils have demonstrated their beneficial role in the management of patients with MetS.The introduction of such dietary supplements could represent a therapeutic resource with considerable potential in the treatment of MetS and protection against the onset of various types of complex multi-factorial pathologies, such as CVD, diabetes, obesity and cancer.

ASSOCIATED CONTENT

Author Contributions

The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

Donatella Bagetta, Annalisa Maruca and Antonio Lupia contributed equally.

AUTHOR INFORMATION

Corresponding Authors:

*E-mail: Federica Moraca: federica.moraca@unina.it; fmoraca@unicz.it;

Francesca Alessandra Ambrosio: ambrosio@unicz.it

Founding Source

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ABBREVIATIONS

AAE, Annurca polyphenolic extracts; ABTS•+, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid; ACE2, Angiotensin converting enzyme 2; ACO, Acyl-CoA oxidase; AGEs, Advanced glycation end products; AMPK, Adenosine monophosphate-activated protein kinase; ARB, Angiotensin receptor blockers; ARE, Anti-oxidant response element; ApoB, Apolipoprotein B; BAT, Brown adipose tissue; BCB, β-carotene bleaching; BEO, Bergamot essential oil; BMP8b, Bone morphogenetic protein 8B; BMPR, Bone morphogenetic protein receptor; BP, Blood pressure; cAMP, Cyclic Adenosine Monophosphate; CA-VA, Carbonic anhydrase VA (CA-VA); CAT, Catalase; CD62E, E-selectin; CETP, Cholesteryl ester transfer protein; CEs, Cholesteryl esters; CFSE, Citrange flesh and seed extract; CHD, Coronary heart disease; CPE, Citrange peel extract; CPT-1, Carnitine palmitoyltransferase 1; CPT1a, Carnitine palmitoyl-transferase 1a; CVDs, Cardiovascular diseases; Cy3G, Cyanidin-3-glucoside; Cy3MG, Cyanidin-3-(6''-malonyl)-glucoside; C/EBP-α, CCAAT/enhancer-binding protein alpha; DBP, Diastolic blood pressure; DGAT, Diacylglycerol acyltransferase; DMLs, Designed Multiple Ligands; DOP, Protected Denomination of Origin; DPP-IV, Dipeptidyl peptidase-4; DPPH•, 2,2-diphenyl-1-picrylhydrazyl (DPPH•); eNOS, Endothelial NO Synthase; EOO, Essential Oil of Oregano; EVOO, Extra-virgin olive oil; FAS, Fatty acid synthase; FBP1, Fructose-1,6-bisphosphatase; FDA, Food Drug Administration; FGFR1, Fibroblast growth factor receptor 1; FRAP, Ferric Reducing Anti-oxidant Power; G6Pase, Glucose-6-phosphatase; GA, Glycyrrhetinic acid; GC, Glycyrrhizin; GI, Glycaemic index; GLP-1, Glucagon-like peptide-1; GLUT4, Glucose transporter type 4; GP, Glycogen phosphorylase; GP, Glycogen phosphorylase; GPa, Glycogen phosphorylase-a; GSH, Glutathione; GSK3B, Glycogen synthase kinases 3 β; HAT, Hydrogen atom transfer; HDL, High-density lipoproteins; HDL-C, High-density lipoprotein cholesterol; HFD, High-fat diet; HMGCR, HMG-CoA reductase; HMGCS, HMG-CoA synthase; HMGF, 3-hydroxy-3-methyl-glutaryl flavanones enriched fraction; HSA, Human serum albumin; HT, Hydroxytyrosol; HUVEC, Human umbilical vein endothelial cells; HepG2, Hepatocellular liver carcinoma; ICAM-1, or CD54Intercellular Adhesion Molecule 1; ILs, Interleukins; IR, Insulin resistance; IRS-1, Insulin receptor substrate-1; IRS-2, Isulin receptor substrate-2; JNK1, c-Jun N-Terminal Protein Kinase 1; LCA, Licochalcone A; LCE, Licochalcone E; LDL, Low density lipoprotein; LDL-C, Low-density lipoprotein cholesterol; LDL-R, LDL receptors; LFO, Liquorice flavonoid oil; LOX, Lipoxygenase; LPS, Lipopolysaccharide; LXR, Liver X receptor; MAPK, Mitogen-activated protein kinase; MUFAs, Monounsaturated fatty acids; MetDiet, Mediterranean diet; MetS, Metabolic Syndrome; NADPH-oxidase, Nicotinamide adenine dinucleotide phosphate-oxidase; NF- κB, Nuclear factor kappa-B; NO, Nitric oxide; NOX, NADPH-oxidase; NOs, Nitric oxide synthase enzymes; NRF2, nuclear factor erythroid 2-related factor 2; OHADH, Beta-Hydroxyacyl-coenzyme A dehydrogenase; OL, Oleuropein; OLE, Olive leaf extract; PA, Pancreatic amylase; PAT, Traditional Agri-Foodstuffs; PEPCK, Phospho-enolpyruvate carboxy kinase; PGC-1α, Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PGI, Protected Geographical Indication; PI3, Phosphatidylinositol 3; PINO, Pinoresinol; PL, Pancreatic lipase; PLP, Pyridoxal phosphatase; PMFs, Polymethoxyflavones; PPARγ, Peroxisome proliferator-activated receptor-gamma; PPARα, Peroxisome proliferator-activated receptor-alpha; PRDM-16, PR-Domain Zinc Finger Protein 16; PTP1B, Protein tyrosine phosphatase 1B; PUFAs, Polyunsaturated fatty acids; RE, Rosemary extract; SAR, Structure Activity Relationship; SAs, Synephrine alkaloids; SBP, Systolic blood pressure; SCD, Stearoyl-CoA desaturase activity; SFAS, Saturated fatty acids; SIRT-1, NAD-dependent deacetylase sirtuin-1; SMCS, S-methlycysteine sulfoxide; SOD1, Superoxide dismutase 1; STZ, Streptozotocin; T2DM,

Type 2 diabets mellitus; TC, Total cholesterol; TCR, Total Reducing Capacity; TEAC, Trolox Equivalent Anti-oxidant capacity; TG, Triglycerides; TLR2, Toll-like receptor 2; TLR4, Toll-like receptor 4; TRPV1, Transient receptor potential vanilloid subtype 1; TY, Tyrosol; UCP1, Mitochondrial brown fat uncoupling protein 1; UCP2, Mithochondrial uncoupling protein 2; VCAM-1 or CD106, Vascular cell adhesion molecule-1; VLDL, Very Low-density Lipoprotein; VOO, Virgin olive oil; XOD, Xanthine oxidase;

Conflict of interest

The authors declare no conflicts of interest

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