

Recent advances in basic and clinical research on the prevention and treatment of the metabolic syndrome and related disorders by the use of olive polyphenols

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Type 2 diabetes mellitus (T2DM) has been defined, together with obesity, the XXI century epidemic and, together with cardiovascular disease, concurs to define a pathological condition known as metabolic syndrome. T2DM can be prevented by an adequate lifestyle and treated, in the preclinical stage and at the onset of the clinical signs, by a diet rich in olive tree polyphenols, in addition to the pharmacological therapy. Studies on animals and humans suggest that olive tree and other plant polyphenols contribute significantly to most of the beneficial effects associated with the Mediterranean diet including reduced cardiovascular disease, T2DM, cancer and aging-associated neurodegeneration. These studies suggest the possible use of plant polyphenols in dietary supplements as nutraceuticals useful against the metabolic syndrome and related conditions, particularly T2DM. The present review summarizes the scientific data on the healthy virtues of the olive polyphenols that support such conclusion.

Key words: Oleuropein, Olive leaf extract, Olive tree polyphenols, Metabolic syndrome, Age-related dysmetabolism, Type 2 diabetes

INTRODUCTION

In the last two decades, the concept of metabolic syndrome has gained widespread consensus as a powerful hypothesis that unifies the metabolic factors underlying the development of both cardiovascular disease, fatty liver disease and type 2 diabetes mellitus (T2DM). In recent years, the incidence of these pathological conditions has involved an increasing number of young people, even though, together with cancer, they represent the main clinical emergence in aged people. However, in addition to age, the relevance of lifestyle, including physical exercise and alimentation, in the etio-pathogenesis of these diseases has gained momentum in the medical community. In particular, T2DM, defined together with obesity (Diabesity) as the XXI Century epidemic, is a so-called wellness disease that can be

prevented by an adequate lifestyle and treated, in the preclinical stage and at the onset of the clinical signs with the pharmacological therapy possibly implemented with a diet rich in plant polyphenols.

T2DM accounts for about 90% of diabetes cases worldwide and in the past 50 years its incidence in the world has increased significantly, and in parallel with the growth of obesity, from 30 million in 1985 to 135 million in 1995 and 217 million in 2005. It has been calculated that in 2013 there were approximately 368 million people diagnosed with the disease compared to around 30 million in 1985¹. Therefore, the World Health Organization has recognized this disease as a global epidemic. In Italy, T2DM has been calculated to affect about 5 million people, of which around 3.5 diagnosed. The insurgence of T2DM is mainly caused by a combination of factors including diet, lifestyle, endocrine

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anomalies, female sex and genetic predisposition^{2,3}. Other potential diabetogenic factors include insufficient sleep and the mother's nutritional status during pregnancy that can induce fetal abnormalities through epigenetic mechanisms⁴. As far as lifestyle is concerned, the risk of developing T2DM is influenced by several factors, including obesity (a body mass index > 30)⁵, reduced physical activity⁶ and inaccurate diet (excessive consumption of sugar, excess of saturated and trans fatty acids, reduced intake of unsaturated fatty acids)⁷. In most cases, the predisposition to T2DM is genetically based and involves numerous genes (over 36 recognized to 2011), each one contributing partially to the disease. Most of the diabetes-related genes are involved in physiological aspects relative to insulin secreting pancreatic beta cells⁸. Many genes, alleles and allelic combinations favor the onset of T2DM, the TC-F7L2 allele being apparently the most important; these include genes belonging to the lipases family, different adrenaline receptors and several alleles of the insulin receptor⁹.

T2DM results from either insufficient insulin production by the pancreatic beta cells and a condition of insulin resistance. The latter consists of a reduced response by the body cells, particularly in the liver and the adipose tissue, to the insulin action^{8,10}. Other potentially important abnormalities associated with T2DM and insulin resistance (Fig. 1) consist of (i.) increased lipid deposits in fat cells, (ii.) a condition of dyslipidemia and liver disease/nonalcoholic steatohepatitis, (iii.) the lack, or low levels, of hormones and cytokines such as testosterone, estrogen, insulin-like growth factors, etc., that increase insulin sensitivity⁹, (iv.) the presence of elevated levels of other hormones that inhibit the action of insulin (adrenocortical hormones, glucagon, adrenalin), and (v.) an improper regulation of metabolism in the central nervous system. T2DM is a chronic condition associated with a ten years shorter life expectancy as compared to the average¹¹. This reduction is, in part, due to various T2DM-related complications including the increased risk of cardiovascular diseases, cognitive dysfunction and dementia (Alzheimer's disease, vascular dementia) and blood circulation problems.

A number of pharmacological therapies are presently available to treat T2DM with various success. In addition to these, in recent years the validity of the use of polyphenols-enriched plant extracts has increasingly gained attention in the medical and scientific communities. This review focuses recent data highlighting the potential use of olive oil and olive polyphenols as natural tools useful to prevent and to combat the metabolic syndrome and T2DM, its main related condition, in addition to the pharmacological therapy.

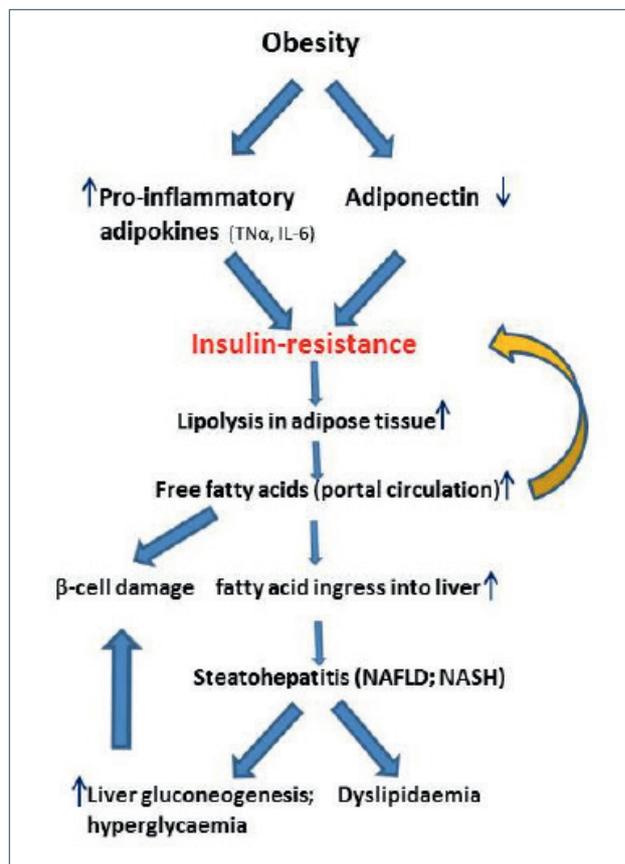


Figure 1. Schematic view of the main metabolic effects of insulin resistance in T2DM (Modified from <http://medmedicine.it/articoli/73-endocrinologia-e-metabolismo/diabete-mellito-di-tipo-2>).

T2DM AND THE METABOLIC SYNDROME

In recent years an unifying theory was established on T2DM, central obesity and cardiovascular disease (CVD). All these conditions appear to be linked into the concept of *metabolic syndrome*, but the underlying causes are not fully described¹². Figure 2 schematically describes a current hypothesis on metabolic syndrome pathogenesis.

PREVENTION AND TREATMENT OF T2DM

T2DM is a pathological condition closely related to the metabolic syndrome and its onset may be delayed or prevented by precautions such as a proper nutrition and a regular exercise that can reduce by over one half the risk of disease in healthy people.

Diet and exercise, either alone or in combination with drug therapy may also decrease the risk of developing T2DM in patients with impaired glucose tolerance. At these initial stages, the interventions on lifestyle appear more effective than the pharmacological treatment of first choice with metformin¹³.

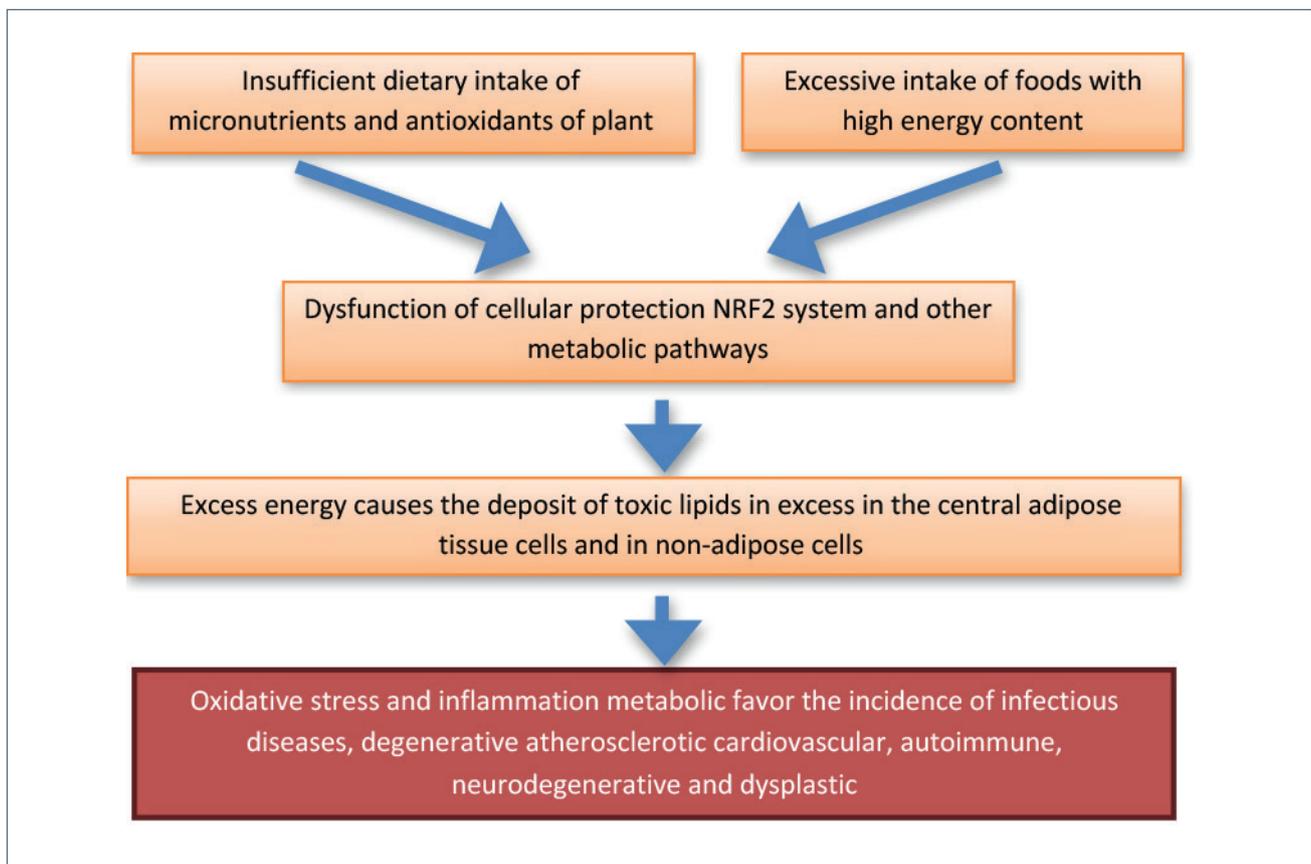


Figure 2. Scheme of the pathogenic process underlying the metabolic syndrome.

When considering the metabolic syndrome, T2DM management focuses to lifestyle interventions, to the reduction of other risk factors for CVD such as hypertension, hypercholesterolemia, microalbuminuria and to the maintenance of correct blood sugar values; in this respect, a proper diet combined with physical activity is considered essential¹⁴. It is also important that the weight-reducing diet is characterized by a low glycemic index. In patients with mild diabetes, in which food and lifestyle changes have not improved the glycemic control, the pharmacological treatment is also taken into account. Various classes of hypoglycemic agents are available as anti-diabetics (biguanide, glinides, thiazolidinediones, acarbose, sulfonyleureas, insulin) that should always be used in combination with a proper lifestyle (Fig. 3). In this regard, plant polyphenols-based nutraceutical supplements including epigallocatechin gallate, curcumin, resveratrol and oleuropein can be used for their general power to prevent pathological states associated with the metabolic syndrome, including T2DM and neurodegeneration, and to complement the pharmacological therapy. In this respect, oleuropein and other olive polyphenols appear of significant interest (see below).

NUTRITIONAL AND HEALTHY PROPERTIES OF OLIVE (*OLEA EUROPAEA*) POLYPHENOLS

FOOD POLYPHENOLS

The phenolic compounds contained in plant foods, whose progenitor is considered hydroxybenzene (C_6H_5OH), also known as phenol or carboic acid, are a heterogeneous mixture of substances chemically derived from aromatic hydrocarbons by substitution of one (phenols) or more (polyphenols) hydrogen atoms with hydroxyl groups. Polyphenols are found mainly in foods of plant origin, while their presence in food of animal origin is occasional, resulting from the assumption of plant foods by animals; tyrosine and its metabolites (catecholamines, thyroid hormones and several intermediates of melanin synthesis) are the only important exceptions.

Over 10,000 different compounds of phenolic nature are known in plants, where they play important functions, such as defense as repellants for herbivores and insects, protection against the ionizing effects of the ultraviolet radiation, attraction of pollinators, elimination of microbes and insects (phytoalexins) and inhibition of the

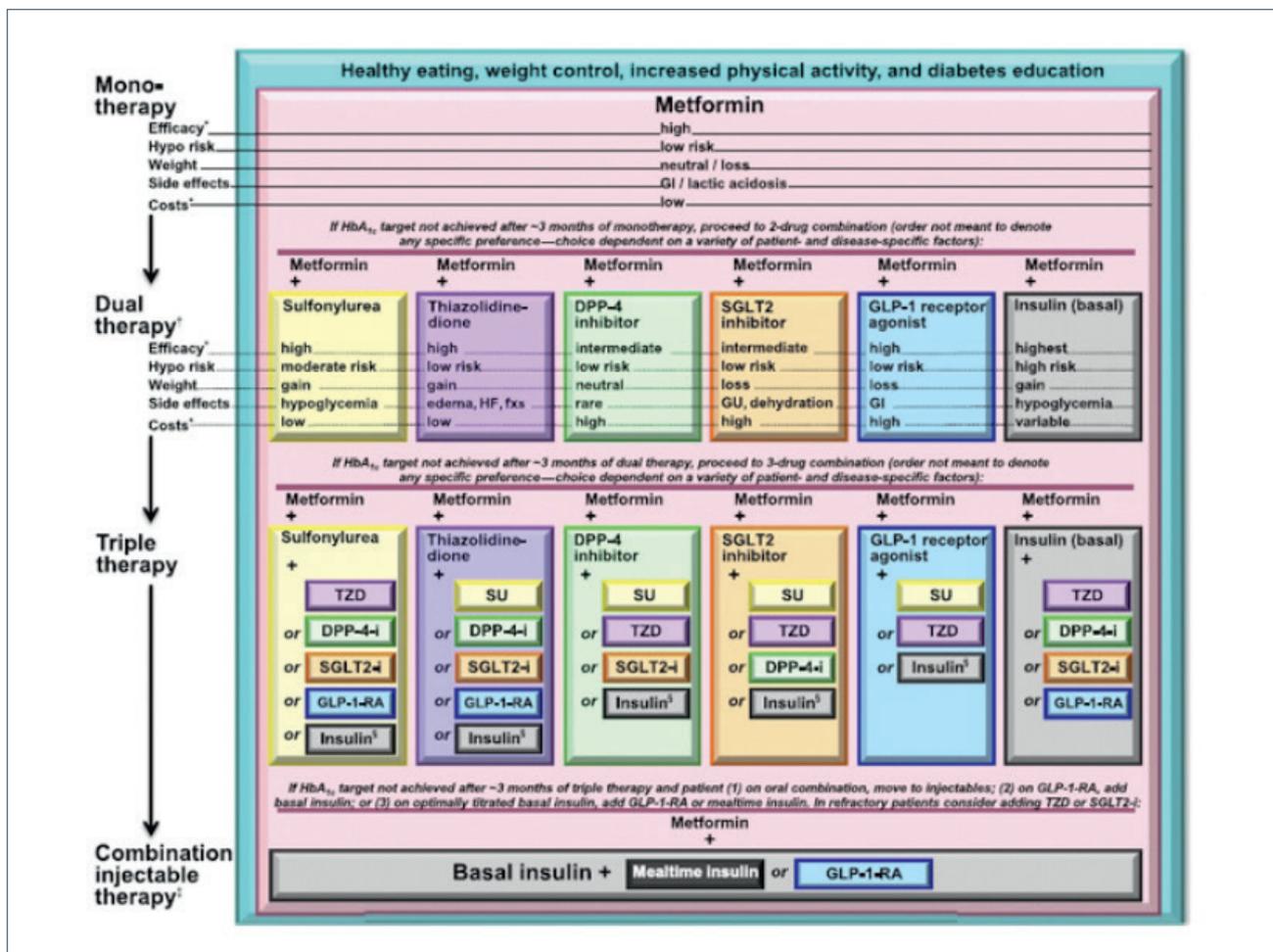


Figure 3. Algorithm for the T2DM therapy (Taken from <http://care.diabetesjournals.org/content/38/1/140>).

growth of competing plant species. Figure 4 shows the molecular structures of different polyphenols of plant origin with claimed beneficial properties against aging and many aging-related diseases, including cancer, neurodegenerative, immunological, metabolic, cardiovascular and inflammatory, diseases. These properties, are known since long time and presently are supported by many experimental data, both in animal models and in humans (reviewed in 15). The polyphenols found in foods characteristic of the Mediterranean diet (MD), such as olive oil and red wine, have been particularly studied in relation to the beneficial properties of this alimentary regimen and to their claimed efficacy against several chronic degenerative diseases (see below).

OLIVE TREE POLYPHENOLS

Olive oil, obtained by pressing the drupes produced by *Olea europaea*, can be considered a basic ingredient of the MD and, more generally, of the Mediterranean lifestyle (Fig. 5). An important aspect, often not adequately

considered by consumers, is that oil freshness influences considerably the organoleptic, nutritional and healthy profile of an olive oil. The spicy flavor of a fresh olive oil decreases with aging because the polyphenols responsible for it are increasingly lost due to oxidation and to slow sedimentation of the minute water droplets in suspension in the oil phase where they are largely contained. In addition to the components found in major amounts, olive oil and olive leaf extracts contain many other substances at low concentrations. These include phenols (*tyrosol* and *hydroxytyrosol*) together with two main polyphenols, *oleuropein* and *oleocanthal* (Figs. 5 and 6) both in the glycosylated form or as aglycones. Olive oil also contains carotenoids, tocopherols (mainly α -tocopherol) and tocotrienols, catechins, terpene alcohols, phytosterols, etc. The presence of tocopherols and polyphenols gives the oil significant antioxidant and “anti-aging” properties in part due to their ability to detoxify free radicals, while the presence of some phenols (hydroxytyrosol) confers antiplatelet and

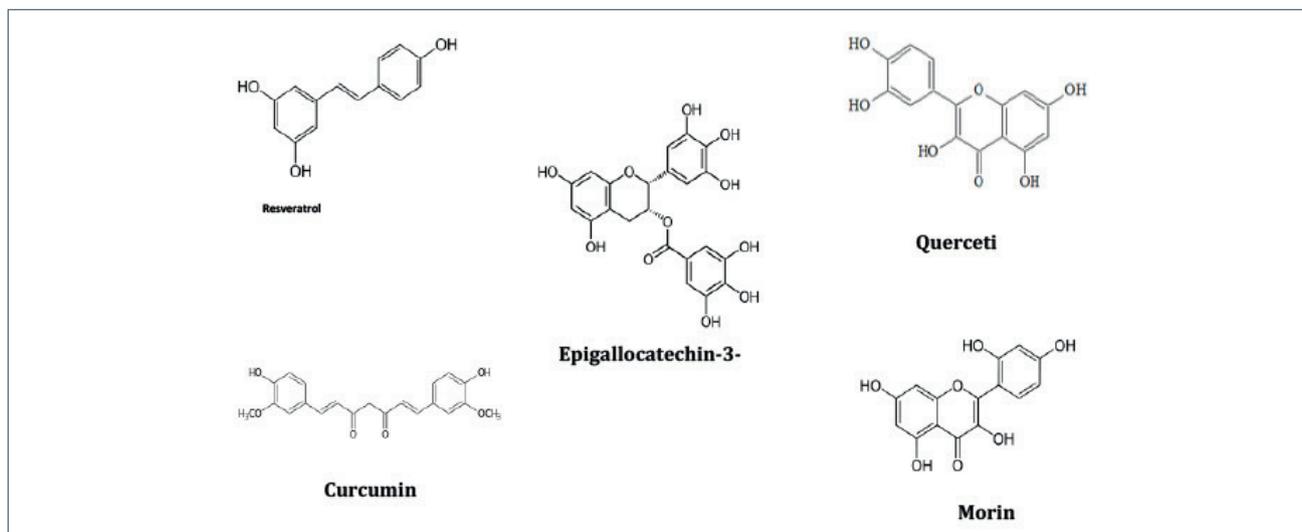


Figure 4 Molecular structures of some common plant polyphenols.

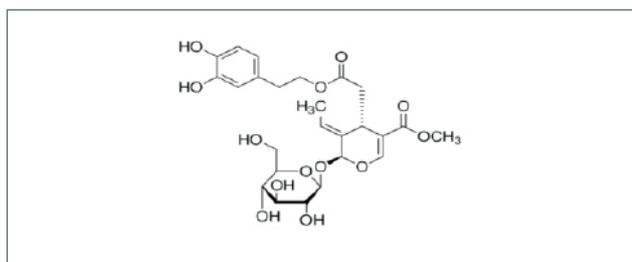


Figure 5 Molecular structure of oleuropein glycoside. It is plentiful in leaves and green olive drupes. In olive oil and in ripe olives the aglycone form prevails.

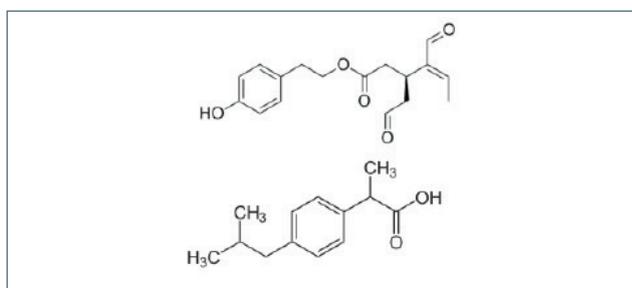


Figure 6. Molecular structure of oleocanthal (top) and ibuprofen (bottom).

anti-inflammatory power. In this regard, recent research has associated the mild anti-inflammatory activity of olive oil to the content of oleocanthal, the main responsible of the spicy flavor of fresh olive oil, whose structure is similar to that of ibuprofen, a widely used anti-inflammatory drug (Fig. 6). Accordingly, oleocanthal has been proposed to act similarly to ibuprofen inhibiting

the activity of cyclooxygenases, enzymes involved in the inflammatory response ¹⁶.

The phenolic content in the olive oil may vary considerably as an effect of many factors. These include olive variety and degree of ripeness, climate, cultivation, oil production techniques, together with time and mode of storage. The polyphenols content in olive oil decreases remarkably with oil aging, mainly due to oxidation; oil separation from the polyphenol-rich minute water droplets by filtration or precipitation also reduce considerably polyphenol content. At the best conditions, the highest concentration of total polyphenols in olive oil reaches values of 600-800 mg/kg. Fig. 7 reports the different content of polyphenols in some Italian olive cultivars.

Oleuropein, hydroxytyrosol and oleocanthal are among the main components of the olive leaves extracts and are considered responsible for the beneficial properties of the latter. The benefits of a diet rich in olive oil and of the assumption of olive leaf extract-based nutraceuticals have been highlighted in recent years by many clinical studies and population surveys carried out on Mediterranean or non-Mediterranean populations. However, the clinical trials with polyphenol-enriched olive extracts are scarce and have mainly been carried out on small cohorts of patients, which reduces the statistical significance of the reported results (see later).

THE HEALTHY PROPERTIES OF OLIVE POLYPHENOLS

The MD and the intake of olive leaf extract-based nutraceuticals have been associated with reduced risk of CVD, as shown by the *Seven Countries Study*, performed since early 1960s, an important contribution to our knowledge on the relationship between consumption of monounsaturated fatty acids in a Mediterranean

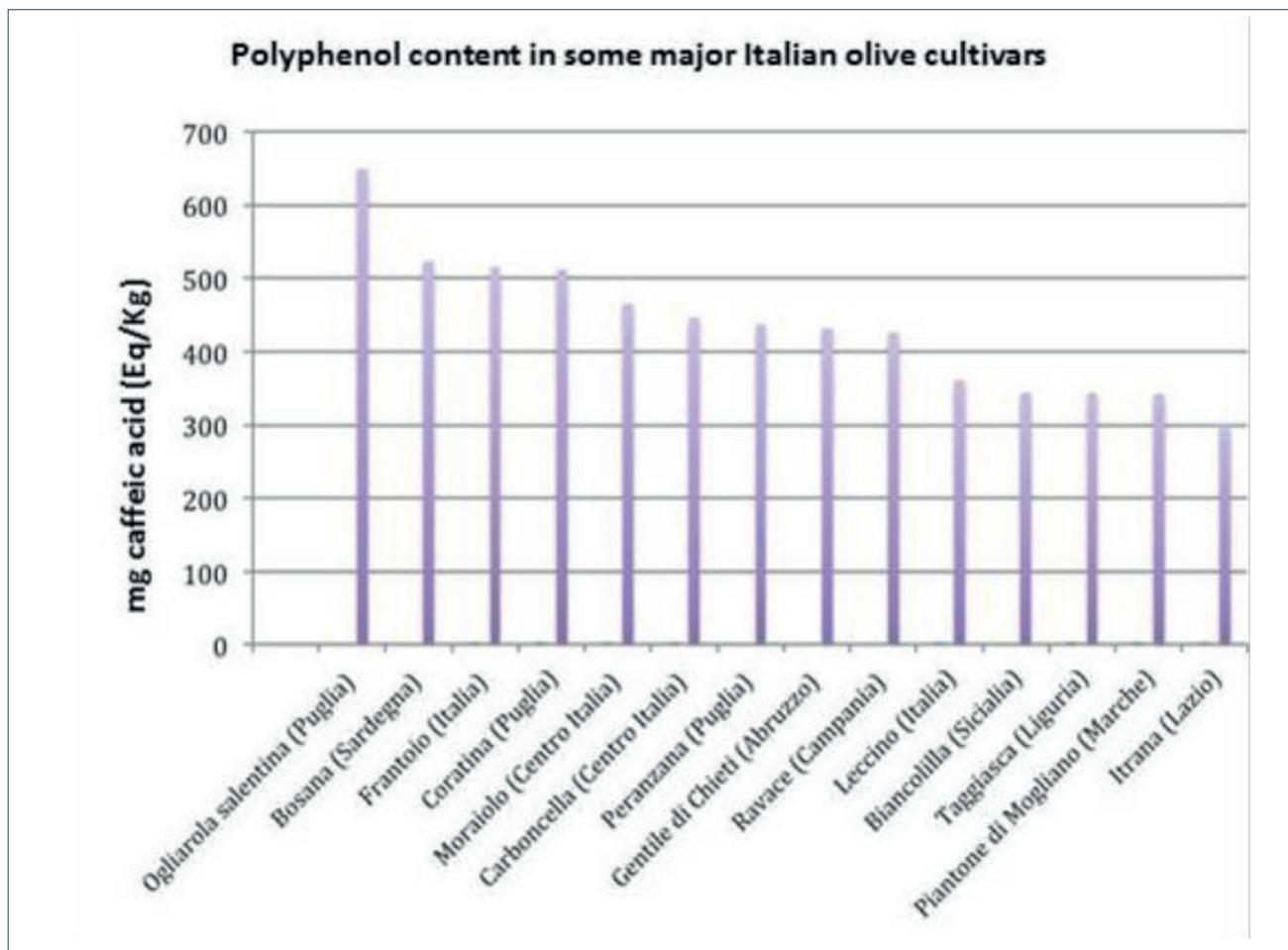


Figure 7. Polyphenol content in some major Italian olive cultivars.

diet and risk of cardiovascular disease¹⁷. Subsequently, the *Three-City Study*, carried out on 7,000 subjects and published in 2009, suggested the existence of a significant correlation between olive oil consumption and reduced risk of age-associated cognitive impairment¹⁸. A recent analysis of the scientific literature related to clinical trials and population studies has confirmed these ideas, leading to conclude that the MD, particularly when supplemented with olive leaf extract-based nutraceuticals, provide consistent and significant protection against the risk of major chronic degenerative diseases including cardiovascular disease, cancer, T2DM and neurodegenerative diseases^{15 19 20}. Table I shows the main beneficial effects associated with the consumption of olive oil.

Olive oil and olive leaf extracts exert their beneficial effects against CVD by different molecular mechanisms. The reduction of the risk factors of CVD is due not only to the high levels of monounsaturated fatty acids but also to other compounds found both in the olive oil and in

Table I. Beneficial properties of olive oil (evidence from nutritional intervention studies in different populations).

Reduction of LDL-cholesterol and increase of the ratio total cholesterol /HDL-cholesterol
Reduction of non-alcoholic fatty liver disease
Reduction of the oxidation of LDL-cholesterol
Improvement of glucose metabolism, reducing blood glucose and insulin, and insulin resistance
Improvement of endothelial function
Antithrombotic effect with reduction of some thrombogenic factors

olive leaf-extracts. Monounsaturated fatty acids modify the lipid profile by reducing both total and LDL-cholesterol, while leaving unmodified or increasing HDL-cholesterol; they also decrease LDL oxidation, a key modification in atherosclerotic plaque formation and growth. The high consumption of monounsaturated fatty acids and the reduced consumption of saturated fatty acids, typical of the MD together with other features, including

the intake of polyphenol-enriched olive leaf extracts, also result in increased protection against the onset of obesity, a major risk factor for T2DM and the metabolic syndrome. It has been shown that a typical MD, in which 50% of the energy is provided by carbohydrates and 35% by lipids (mainly monounsaturated), results in a significant reduction of glycated hemoglobin and improved glycemic control respect to a standard diet ²¹. These effects also appear associated with the amount of olive oil polyphenols taken up (see below).

In general, the beneficial effects of olive oil have been consistently attributed to the content in polyphenols, due to the antioxidant, anti-inflammatory, anti-cancer, anti-microbial, anti-viral, anti-atherogenic, hypoglycemic, liver- heart- and neuro-protective power of the latter ²²⁻²⁶. In addition to the effects on lipid and glyce-mic parameters, several studies confirm a reduction in blood pressure in people who follow a Mediterranean-style diet rich in monounsaturated fatty acids and olive oil ²⁷. Finally, in recent years, in addition to the beneficial effects against the risk factors for CVD and T2DM reported above, several studies deal with a protection by olive oil and olive leaf extracts also against thrombosis-related factors (hemostasis primary, secondary, platelet aggregation, fibrinolysis) that contribute to the onset of CVD ²⁸. Beneficial effects of olive oil and polyphenols-enriched olive leaf extracts against neoplastic diseases have also been reported in various studies carried out mainly in animal and cell models ^{19 29}.

METABOLIC EFFECTS OF OLEUROPEIN

Oleuropein aglycone (OLE), together with its main metabolite, hydroxytyrosol, is considered the main responsible for many nutraceutical properties of olive oil and olive leaf extracts. Recent studies on OLE have provided a more detailed scientific basis for the reported anti-aging effects of the MD and the beneficial properties of olive oil, particularly against T2DM and other conditions associated with the metabolic syndrome. The beneficial effect of OLE against T2DM is suggested by a number of experiments on animal models and by clinical trials on human subjects, even though the latter are still limited also for what their number and the number of enrolled people are concerned. The scientific literature supports the beneficial properties of OLE and OLE-enriched olive leaf extracts in animal and cell models of T2DM. In particular, it has been reported that olive polyphenols (i.) prevent amylin tendency to aggregate into amyloid fibrils whose pancreatic deposits are considered among the main causes of the sufferance and functional impairment of insulin-secreting cells in T2DM (30); (ii.) decrease blood glucose and cholesterol levels by repairing the oxidative damage in diabetic murine ^{31 32} and rabbit ³³ models; (iii.) reduce starch digestion and

intestinal absorption of dietary carbohydrates in murine models of diabetes ³⁴; (iv.) improve oral glucose tolerance in rats at carbohydrate- and lipid-rich diet ³⁵; (v.) modify the expression, among others, of genes involved in lipogenesis and insulin resistance, in mice fed with high-fat diet ³⁶. Olive polyphenols also appear to prevent the onset of T2DM by increasing the tolerance to oral glucose and by mitigating high-fat diet-induced fatty liver and obesity in murine models ^{34 37-39}.

Clinical studies have also been carried out in human subjects whose diet contained controlled amounts of olive oil. From these studies it emerged that olive oil polyphenols improve glucose homeostasis and reduce glycated hemoglobin and fasting insulin levels ⁴⁰. Very recently, a study carried out by Italian researchers has reported that the intake of polyphenol-rich olive oil during lunch by normal subjects reduces significantly the peak of postprandial glycaemia ⁴¹. The study confirms a preceding one on the effects of OLE on glucose metabolism showing a sharp reduction of both postprandial blood glucose and of glycated hemoglobin in subjects administered with OLE ⁴². Finally, as reported above, a clinical trial was recently carried out in New Zealand on a group of middle-aged overweight individuals at risk for development of the metabolic syndrome treated for 12 weeks with an olive leaf extract enriched in OLE and, in a minor amount, of oleocanthal ³⁶. At the end of the treatment, the subjects showed a significant improvement in insulin sensitivity and insulin-secreting pancreatic cell function, suggesting a significant anti-diabetic effect ³⁶. Even though carried out on small cohorts of subjects, these results suggest that olive polyphenols, particularly OLE, possess significant anti-diabetic power, particularly against T2DM, and agree with *in vitro* results on the effect of OLE against amylin aggregation ³⁰.

Another disease related to insulin resistance and the metabolic syndrome is non-alcoholic fatty liver disease (NAFLD) and the ensuing nonalcoholic steatohepatitis (NASH). Studies on cell and animal models report that OLE can counteract these states in several ways. These include (i.) an anti-lipidemic action ⁴³; (ii.) the protection of cultured cells against hepatocellular steatosis induced by free fatty acids ⁴⁴; (iii.) the protection against liver damage in CCl₄-treated mice ⁴⁵; (iv.) the prevention of the occurrence of spontaneous NASH in a mouse model ⁴⁶; (v.) the prevention of the progression of NASH toward fibrosis in high-fat diet mice ⁴⁷; (vi.) the dose-dependent suppression of the intracellular accumulation of triglycerides during adipocyte differentiation ³⁸; (vii.) the reversal of weight increase of the liver and the decrease of blood lipid levels in high-fat diet mice by interfering with signaling

pathways involved in lipogenesis and in the onset of fatty liver^{29 31 38 48}. The positive effects of OLE on NASH have been shown in a recent study carried out in mice fed with a normo-caloric diet, with high-fat diet or with high-fat diet supplemented with 3% OLE for a further eight weeks²³. These studies have not been replicated in human subjects; accordingly, the efficacy of OLE and other olive polyphenols against these disease in humans is not adequately supported and remains unproven.

OLIVE POLYPHENOLS COULD BE PROTECTIVE AGAINST ALZHEIMER'S DISEASE: THE DIABETES-AD LINK

Evidences from epidemiological, cell biology and animal models suggest that pre-diabetes and diabetes increase the risk of dementia and that the risk to develop AD is increased by 2-3-fold in patients with diabetes, notably T2DM⁴⁹; in particular, recent research has highlighted the importance of brain insulin signaling and that insulin-resistance may lead to AD⁵⁰. Accordingly, a close relation between diabetes and dementia⁵¹, particularly AD, has been proposed, possibly through protection against alterations in mitochondrial function/biogenesis and in autophagy⁵². Even though the relation between AD and diabetes has been questioned very recently⁵³, many data suggest that impairment of brain insulin signaling is at the core of the neurodegeneration cascade in late onset AD, leading some authors to define some AD symptoms as "brain-type diabetes" or "type 3 diabetes"^{54 55}. Therefore, it is not surprising that recent research has reported a significant protection by OLE not only against T2DM but also against brain neurodegeneration and the ensuing behavioral and memory impairment; the latter data have been reported in a number of studies carried out on TgCRND8, a mouse model of A β deposition⁵⁶. However, these studies have not been replicated in human subjects; accordingly, the efficacy of OLE and other olive polyphenols against neurodegeneration in humans has not been proven yet.

OLE and oleocanthal were previously shown to modify favorably the tendency of the A β peptide and tau protein to aggregate *in vitro* into cytotoxic amyloid assemblies^{57 58}; they were also shown to protect transgenic animal models against A β aggregation and aggregate toxicity^{44 59} in several ways, including a strong activation of autophagy⁴⁴, a protective response known to be deficient in brain dementia⁶⁰⁻⁶³. Hydroxytyrosol, the main product of OLE metabolism has also been shown to be protective not only due to its high anti-oxidant power but also by sharing most of the above mentioned effects of OLE both in cell and in animal models (reviewed in⁶⁴), particularly against neurodegeneration (reviewed in⁶⁵).

MOLECULAR DETERMINANTS OF THE BENEFICIAL EFFECTS OF OLIVE POLYPHENOLS

The effects of OLE and other olive polyphenols have also been studied at the molecular level in cell and animal models as well as in human subjects. The reported molecular modifications following administration of olive oil, olive extracts or pure polyphenols include (i.) the down-regulation of the expression of pro-atherogenic genes in a clinical trial with healthy volunteers upon assumption of olive polyphenols in the context of a traditional MD⁶⁶; (ii.) the prevention of cytokine-mediated inflammation and oxidative damage^{43 48}; (iii.) the increase under fasting conditions of the levels of signaling molecules such as IL-6, IGFBP-1 and IGFBP-2³⁶. The anti-obesity and anti-steatosis effects were associated with increased metabolic utilization of lipids and energy expenditure and with the modulation of glucose homeostasis (see above); they also appear to depend on the down-regulation of the expression of genes involved in the differentiation of adipocytes³⁸ and in Wnt10b inhibition as well as on the increased expression of genes involved in thermogenesis³⁹ and mitochondrial biogenesis in visceral adipose tissue⁴⁰. Finally, the molecular effects underlying the anti-neurodegeneration power of olive oil polyphenols include, in addition to autophagy activation, increased amyloid- β clearance from the brain by oleocanthal⁶⁷ and reduction of A β production by OLE through the promotion of the non-amyloidogenic pathway following increased α -secretase cleavage of the amyloid precursor protein⁶⁸.

The reported effects of OLE are similar to those produced by other natural polyphenols found in typical foods of the MD and the Asian diet²⁰. Often these effects are the result of modifications of the expression of genes involved in epigenome modulation, as recently shown in the case of OLE and other polyphenols, resulting in protection against numerous cancers⁶⁹ and neurodegenerative disorders⁶⁹⁻⁷¹. Figure 8 summarizes the most referenced healthy effects of OLE and its metabolites reported in animal models and/or in humans.

BIOAVAILABILITY OF DIETARY POLYPHENOLS

It is commonly believed that OLE and other natural polyphenols are, in general, poorly bioavailable both because of their reduced intestinal absorption and of their rapid biotransformation which helps their urinary excretion. Nevertheless, recent studies conducted in rats and in humans have shown that these compounds are indeed absorbed in reduced, yet appreciable, amounts from the intestine and rapidly distributed throughout the body, including the brain⁷²⁻⁷⁴. The administration of polyphenols-enriched nutraceuticals is hindered by the lack of in depth studies about the effective dose to be administered daily in humans to

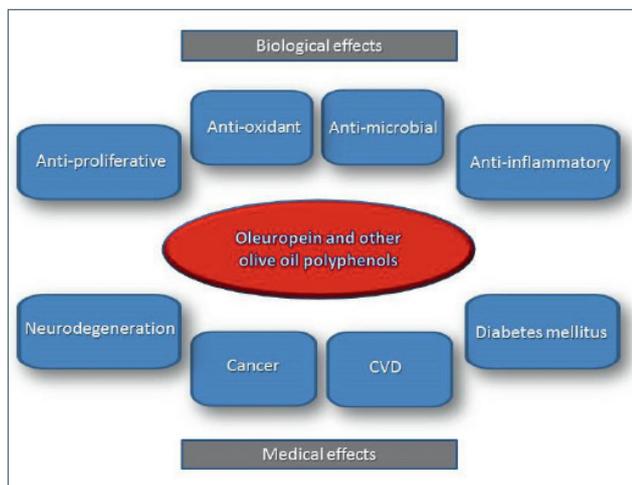


Figure 8. A schematic view of the healthy effects of oleuropein.

get acute effects. Actually, it appears that the amount of OLE and other polyphenols in food is not adequate to ensure the intake, with a common diet, of doses that can produce short-term acute effects. Yet, clinical and experimental evidence suggest that a continuous intake of foods containing low concentrations of these molecules can be effective in the long term, representing a continuous low intensity stimulus of the cellular defenses against T2DM, CVD, the metabolic syndrome and aging-associated neurodegeneration. Therefore, following a nutritional style conformed to the MD appears to provide a useful protection against the risk of the metabolic syndrome, particularly T2DM, whereas more rapid and acute effects against the latter, seem to require a significantly higher daily intake of plant, notably olive, polyphenols.

CONCLUSIONS

The results of experimental studies carried out in cultured cells and model animals as well as the efficacy evidence in humans, confirmed by recent population studies and clinical trials^{18 21 27 36 41 42 66 72}, provide consistent support to the use of OLE in dysmetabolic states of carbohydrates and lipids as well as, possibly, in neurodegeneration. However, these data must still be confirmed by larger population studies, mainly for what OLE protection against aging-associated neurodegeneration is concerned. Ongoing studies, both experimental, clinical and observational, on the metabolic effects of olive polyphenols will further confirm or resize the role of these molecules, particularly OLE, as diet supplements or even nutraceuticals useful for the

prevention of aging- and lifestyle-related degenerative conditions including T2DM, the metabolic syndrome and aging-associated neurodegeneration.

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