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INVITED REVIEW

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Updates on Mediterranean diet and health status: active ingredients and pharmacological mechanisms

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The Mediterranean diet (MedDiet) is among the most extensively studied dietary patterns and has been consistently associated with reduced risk of all-cause mortality, cardiovascular disease, metabolic disorders, cognitive decline and several types of cancers. It is defined by a high intake of vegetables, fruits, legumes, nuts, (whole) grains, fish, seafood and extra virgin olive oil, along with moderate consumption of red wine. Several physiological pathways may contribute to its beneficial effects, including favourable modulation of lipid profiles, enhanced insulin sensitivity, reduction of inflammatory and oxidative stress markers, improved endothelial function and antithrombotic activity. These effects are largely attributed to bioactive compounds such as polyphenols, monounsaturated and polyunsaturated fatty acids and dietary fibre. This updated review summarizes the most recent evidence and discusses both established and emerging mechanisms of action related to individual dietary components within the MedDiet. It aims to provide a refined understanding of how this dietary pattern contributes to chronic disease prevention and overall health.

KEYWORDS
health status, ingredients, Mediterranean diet, pharmacological mechanisms

1 | INTRODUCTION

This article provides an updated summary of current evidence on the Mediterranean diet (MedDiet), one of the most extensively studied dietary patterns (Schwingshackl et al., 2020). High adherence to MedDiet has been consistently linked to lower risk of all-cause mortality, cardiovascular disease, type 2 diabetes, various cancers and cognitive decline (Guasch-Ferré & Willett, 2021). These benefits are largely attributed to the anti-inflammatory, antioxidant, antithrombotic, lipid-lowering and antineoplastic effects of its bioactive components.

1.1 | Defining the MedDiet

The MedDiet is characterized by a high intake of vegetables, fruits, legumes, nuts, cereals, including whole grains and extra-virgin olive oil (EVOO); moderate consumption of fish, seafood and alcohol, preferably red wine with meals and a low intake of red and processed meats and dairy products (Table 1). Adherence is commonly assessed using a-priori diet quality indices. Over 30 different scoring systems have been identified in the literature, with the Trichopoulou score being the most widely applied (Galbete et al., 2018; Trichopoulou et al., 1995; Trichopoulou et al., 2003). Although methodological differences exist, all indices

Abbreviations: apoB, apolipoprotein B; apoB-P, apolipoprotein B-containing lipoprotein particles; EVOO, extra-virgin olive oil; HbA1c, glycosylated haemoglobin; LDL, low-density lipoprotein; MedDiet, Mediterranean diet; TNF-α, tumour necrosis factor alpha.

TABLE 1 Overview of components of the two most widely used Mediterranean diet quality indices.

	Vegetables	Legumes	Fruits	Nuts	Cereals	Fish	Meat and meat products	Dairy products	Alcohol (red wine)	MUFA:SFA ratio (EVOO)
Traditional MedDiet (Trichopoulou et al., 2003)	+	+	+	+	+	+	−	−	o Women 5–25 g·day^{-1}, Men 10–50 g·day^{-1}	+
Alternate MedDiet (Fung et al., 2006)	+	+	+	+	Whole grains	+	Red and processed meat	/	o Women 5–15 g·day^{-1}, Men 10–25 g·day^{-1}	+

Note: + = higher intake suggested; − = lower intake suggested; o = moderate intake suggested; / = not included in score.
Abbreviations: EVOO, extra virgin olive oil; MedDiet, Mediterranean diet; MUFA, monounsaturated fatty acids; SFA, saturated fatty acids.

consistently reflect these core food groups and serve as a valuable tool for linking dietary patterns to health outcomes and mechanistic pathways.

1.2 | MedDiet, risk of chronic diseases and intermediate disease markers

This updated review does not aim to provide a comprehensive summary of all existing evidence on the MedDiet in the prevention of non-communicable diseases. Instead, we provide a concise synthesis of the most recent systematic reviews and meta-analyses from randomized controlled trials (RCTs) and observational studies (Tables 2 and 3). Recent meta-analyses reinforce previous evidence indicating that high adherence to the MedDiet is associated with a lower risk of all-cause mortality, cardiovascular outcomes, cancer-related mortality (e.g. breast, gastric, liver and colorectal cancer), type 2 diabetes, obesity and hypertension. Additional inverse associations have been reported for asthma, rheumatoid arthritis, hip fractures, depression, dementia and Parkinson's disease. Furthermore, recent RCT data confirm significant improvements in metabolic risk factors, including reductions in low-density lipoprotein (LDL) cholesterol, triacylglycerols, fasting glucose, insulin, glycosylated haemoglobin (HbA1c), systolic blood pressure and C-reactive protein.

1.3 | What is new?

Recent meta-analyses strengthen the evidence for an inverse association between adherence to MedDiet and non-communicable disease risk. Based on a recent network meta-analysis of randomized-controlled trials, moderate certainty of evidence shows that following a MedDiet reduces the risk of all-cause mortality by 28%, coronary heart disease by 52% and stroke by 35% (Karam et al., 2023). Meta-analyses of prospective observational studies showed concordant findings for cardiovascular disease (Taylor et al., 2024; Ungvari et al., 2025), and an inverse association between high adherence to MedDiet and risk of type 2 diabetes and several cancer types (Morze et al., 2021; Wallerer et al., 2025).

Moreover, recent meta-analyses of randomized-controlled trials have reported consistent improvements for several cardiometabolic markers, including LDL-cholesterol, triacyglycerols, HbA1c, fasting glucose, blood pressure and C-reactive protein, supporting a potential beneficial effect on cardiovascular health (Dinu et al., 2020).

Despite these findings, important limitations persist due to methodological heterogeneity in the definition of the MedDiet interventions, variability in comparator diets and the limited number of large-scale, long-term RCT randomized-controlled trials. In line with the previous version of this review, we emphasize a comprehensive, pathway-based perspective rather than a component- or disease-specific approach.

2 | KEY BENEFICIAL COMPONENTS/INGREDIENTS

As shown in Table 1, the MedDiet consists of 10 major components (eight of which are considered beneficial and are therefore described below).

2.1 | Vegetables

The MedDiet emphasizes the intake of seasonal, field-grown vegetables, such as leafy greens, tomatoes, eggplants, cucumbers, cabbages, radishes, garlic and onions, which are rich in flavonoids and other polyphenolic compounds. These vegetables substantially enhance the diet's micronutrient profile, supplying dietary fibre, potassium and a broad spectrum of essential vitamins and minerals (Delgado et al., 2017; Hoffman & Gerber, 2013).

Dose–response meta-analyses of prospective cohort studies provide consistent evidence that higher vegetable consumption is associated with a reduced risk of all-cause mortality, cardiovascular disease, cancer, type 2 diabetes, hypertension and adiposity

TABLE 2 Overview of recent meta-analytical findings investigating the effect/association (RR, HR, OR and 95% CI) between high adherence to a Mediterranean dietary pattern and risk of non-communicable diseases.

	Meta-analyses of RCTs		References	Meta-analyses of observational studies		References
All-cause mortality	↓	OR: 0.72 (0.56, 0.92)	(Karam et al., 2023)	↓	HR: 0.90 (0.89, 0.91)	(Soltani et al., 2019)
Cardiovascular disease	↓	RR: 0.55 (0.39, 0.78)	(Karam et al., 2023)	↓	RR: 0.85 (0.83, 0.87)	(Taylor et al., 2024)
Coronary heart disease	↓	OR: 0.48 (0.36, 0.65)	(Karam et al., 2023)	↓	RR: 0.70 (0.62, 0.80)	(Martínez-González et al., 2019)
Stroke	↓	OR: 0.65 (0.46, 0.93)	(Karam et al., 2023)	↓	HR: 0.88 (0.84, 0.91)	(Ungvari et al., 2025)
Heart failure	↓	RR: 0.45 (0.26, 0.79)	(Khan et al., 2021)	↓	OR: 0.77 (0.63, 0.93)	(Arayici et al., 2025)
Cancer	↔	RR: 0.75 (0.17, 3.33)	(Morze et al., 2021)	↓	RR: 0.87 (0.82, 0.92)	(Morze et al., 2021)
Colorectal cancer	NA	NA	NA	↓	RR: 0.83 (0.76, 0.90)	(Morze et al., 2021)
Breast cancer	↓	RR: 0.41 (0.19, 0.87)	(Morze et al., 2021)	↓	RR: 0.94 (0.90, 0.97)	(Morze et al., 2021)
Prostate cancer	NA	NA	NA	↔	RR: 0.98 (0.93, 1.04)	(Morze et al., 2021)
Gastric cancer	NA	NA	NA	↓	RR: 0.70 (0.61, 0.80)	(Morze et al., 2021)
Liver cancer	NA	NA	NA	↓	RR: 0.64 (0.54, 0.75)	(Morze et al., 2021)
Type 2 diabetes	NA	NA	NA	↓	HR: 0.92 (0.90, 0.94)	(Wallerer et al., 2025)
Obesity	NA	NA	NA	↓	RR: 0.91 (0.88, 0.94)	(Lotfi et al., 2022)
Hypertension	NA	NA	NA	↓	RR: 0.87 (0.77, 0.97)	(Taylor et al., 2024)
Rheumatoid arthritis	NA	NA	NA	↓	OR: 0.84 (0.76, 0.93)	(Hu et al., 2025)
Hip fracture	NA	NA	NA	↓	RR: 0.71 (0.55, 0.91)	(Fa-Binefa et al., 2025)
Age-related macular degeneration	NA	NA	NA	↔	OR: 0.96 (0.83, 1.11)	(Marques-Couto et al., 2025)
Depression	NA	NA	NA	↓	OR: 0.91 (0.88, 0.96)	(Molero et al., 2025)
Dementia and Alzheimer disease	NA	NA	NA	↓	OR: 0.89 (0.84, 0.94)	(Nucci et al., 2024)
Parkinson disease	NA	NA	NA	↓	OR: 0.75 (0.66, 0.84)	(Zhao et al., 2025)

Note: ↓ = lower risk; ↔ = no effect/association.
Abbreviations: HR, hazard ratio; MD, mean difference; NA, not applicable; OR, odds ratio; RCTs, randomized controlled trials; RR, risk ratio.

(Bechthold et al., 2017; Halvorsen et al., 2021; Schlesinger et al., 2019; Schwingshackl et al., 2018; Schwingshackl, Hoffmann, Lampousi, Knuppel, et al., 2017; Schwingshackl, Schwedhelm, Hoffmann, Knuppel, et al., 2017; Schwingshackl, Schwedhelm, Hoffmann, Lampousi, et al., 2017; Wang, Li, et al., 2021; Yao et al., 2023). Moreover, the substitution of animal-based with plant-based foods was inversely associated with cardiometabolic health (Neuenschwander et al., 2023).

2.2 | Legumes

Legumes such as chickpeas, lentils and various beans are commonly consumed foods of the MedDiet. Legumes are rich in plant-based protein, dietary fibre, phytosterols, B-vitamins (including **folate** and B6), flavones and a variety of essential minerals (Delgado et al., 2017). Evidence from dose–response meta-analyses of prospective cohort studies indicates that higher legume intake is linked to a lower incidence

TABLE 3 Overview of recent meta-analytical findings of randomized controlled trials investigating the effects of Mediterranean dietary pattern on intermediate disease markers.

		Meta-analyses of RCTs	Reference
Body weight (kg)	↓	MD: −1.75 (−2.86, −0.64)	(Dinu et al., 2020)
Waist circumference (cm)	↔	MD: −0.54 (0.77, −0.31)	(Kahleova et al., 2019)
Total cholesterol (mmol·L^{-1})	↔	MD: −0.13 (−0.30, 0.04)	(Dinu et al., 2020)
LDL-cholesterol (mmol·L^{-1})	↓	MD: −0.15 (−0.27, −0.02)	(Dinu et al., 2020)
HDL-cholesterol (mmol·L^{-1})	↔	MD: 0.02 (−0.01, 0.04)	(Dinu et al., 2020)
Triglycerides (mmol·L^{-1})	↓	MD: −0.09 (−0.16, −0.01)	(Dinu et al., 2020)
Fasting glucose (mmol·L^{-1})	↓	MD: −0.37 (−0.41, −0.33)	(Dinu et al., 2020)
Insulin (μU·ml^{-1})	↓	MD: −0.55 (−0.81, −0.29)	(Dinu et al., 2020)
HbA1c (%)	↓	MD: −0.47 (−0.56, −0.38)	(Dinu et al., 2020)
Systolic blood pressure (mmHg)	↓	MD: −3.10 (−4.80, −1.30)	(Taylor et al., 2024)
Diastolic blood pressure (mmHg)	↓	MD: −1.60 (−2.60, −0.60)	(Taylor et al., 2024)
CRP (mg·L^{-1})	↓	MD: −0.61 (−0.95, −0.26)	(Tran et al., 2024)

Note: ↓ = decreasing effect; ↔ = no effect.
Abbreviations: CRP, C-reactive protein; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MD, mean difference; RCT, randomized controlled trials.

of cardiovascular disease and all-cause mortality (Bechthold et al., 2017; Mendes et al., 2023; Pearce et al., 2021; Schwingshackl, Schwedhelm, Hoffmann, Lampousi, et al., 2017; Zargarzadeh et al., 2023). In meta-analyses of randomized-controlled trials, higher intake of legumes showed beneficial effects on total cholesterol, LDL-cholesterol and C-reactive protein (Hossain et al., 2024).

2.3 | Fruits

The MedDiet typically includes a broad spectrum of fruits, such as citrus (e.g. oranges and pomegranates), berries, figs, grapes and carotenoid-rich species, including apricots, peaches, nectarines and cantaloupes. These fruits provide key nutrients such as dietary fibre, potassium and **vitamin C** and are an important source of bioactive phytochemicals, particularly flavonoids and terpenes (Delgado et al., 2017). In dose–response meta-analyses of prospective observational studies, a higher intake of fruit has been associated with lower risk of all-cause mortality, coronary heart disease, stroke, type 2 diabetes, cancer, hypertension and adiposity (Bechthold et al., 2017; Halvorsen et al., 2021; Schlesinger et al., 2019; Schwingshackl et al., 2018; Schwingshackl, Hoffmann, Lampousi, Knuppel, et al., 2017; Schwingshackl, Schwedhelm, Hoffmann, Knuppel, et al., 2017; Schwingshackl, Schwedhelm, Hoffmann, Lampousi, et al., 2017; Wang, Li, et al., 2021; Yao et al., 2023).

2.4 | Nuts

Nuts such as pistachios, almonds, hazelnuts, walnuts and peanuts are characteristic components of the MedDiet. Nuts are rich in unsaturated fatty acids, polyphenols, phytosterols and key micronutrients, including vitamin E, B2, folate, fibre and minerals such as magnesium, potassium and selenium (Delgado et al., 2017). In dose–response meta-analyses of prospective observational studies, nut consumption has been associated with lower risk of all-cause mortality, coronary heart disease, hypertension and adiposity (Arnesen et al., 2023; Balakrishna et al., 2022; Bechthold et al., 2017; Schlesinger et al., 2019; Schwingshackl, Schwedhelm, Hoffmann, Knuppel, et al., 2017; Schwingshackl, Schwedhelm, Hoffmann, Lampousi, et al., 2017). In meta-analyses of randomized-controlled trials, higher nuts intake showed beneficial effects on total cholesterol, LDL-cholesterol, triacyglycerols and apolipoprotein B (apoB) (Nishi et al., 2025).

2.5 | Grains

The grain food group encompasses both whole cereal grains and grain-based products, including rice, oats, popcorn, bread, breakfast cereals, pasta and crackers. Whole grains are an important source of dietary fibre, B-vitamins (**thiamine**, **riboflavin**, **niacin**, B6 and folate) and minerals, including iron, magnesium, zinc, copper, manganese, phosphorus and selenium (Delgado et al., 2017). In dose–response meta-analyses of prospective observational studies, a high consumption of whole grains has been associated with lower risk of all-cause mortality, coronary heart disease, heart failure, type 2 diabetes, cancer, hypertension and adiposity (Bechthold et al., 2017; Gaesser, 2020; Ghanbari-Gohari et al., 2022; Hu et al., 2023; Schlesinger et al., 2019; Schwingshackl et al., 2018; Schwingshackl, Hoffmann, Lampousi, Knuppel, et al., 2017; Schwingshackl, Schwedhelm, Hoffmann, Knuppel, et al., 2017; Schwingshackl, Schwedhelm, Hoffmann, Lampousi, et al., 2017). Meta-analyses of randomized-controlled trials have shown a beneficial effect of whole grain intake on total cholesterol, LDL-cholesterol, triacyglycerols, fasting glucose, HbA1c and C-reactive protein (Marshall et al., 2020; Ying et al., 2024).

2.6 | Fish/seafood

Commonly consumed fish in the MedDiet include sardines, mackerel, salmon, tuna and sea bass. The most relevant bioactive compounds in fish are the long-chain omega-3 polyunsaturated fatty acids (PUFAs), **eicosapentaenoic acid (EPA)** and **docosahexaenoic acid (DHA)**, which contribute to anti-inflammatory and cardioprotective effects (Delgado et al., 2017). In dose–response meta-analyses of prospective observational studies, fish/seafood intake has been associated with lower risk of all-cause mortality, coronary heart disease, heart failure, certain cancer types, dementia and Alzheimer disease (Bechthold et al., 2017; Godos et al., 2024; Schwingshackl et al., 2018; Schwingshackl, Schwedhelm, Hoffmann, Lampousi, et al., 2017; Zhao et al., 2023). In meta-analyses of randomized-controlled trials, higher intakes of fish showed beneficial effects on high-density lipoprotein-cholesterol and triacyglycerols (Zhao et al., 2023).

2.7 | Extra virgin olive oil (EVOO)

EVOO is considered a cornerstone of the MedDiet. It provides substantial amounts of monounsaturated fatty acids (MUFA, primarily oleic acid [OA]) and contains various polyphenolic compounds, including **oleuropein**, tyrosol, hydroxytyrosol, secoiridoids and lignans (Gaforio et al., 2019). An umbrella review of 31 meta-analyses reported that higher olive oil consumption was associated with a 15%–27% lower risk of cardiovascular disease and a 9%–22% lower risk of type 2 diabetes. Evidence from intervention studies further suggests beneficial effects on glycaemic control, blood pressure and inflammatory markers, depending on the olive oil type and phenolic content (Chiavarini et al., 2024; Schwingshackl et al., 2019). An overview of mechanistic properties of EVOO is presented in Figure 1.

2.8 | Alcohol

Within the MedDiet, alcohol intake primarily refers to moderate consumption of red wine (5–25 g·day^{-1} for women, 10–50 g·day^{-1} for men in the traditional MedDiet Score; and 5–15 g·day^{-1} for women, 10–25 g·day^{-1} for men in the alternate MedDiet Score) (Hoffman & Gerber, 2013). Red wine contains various polyphenolic compounds, among which **resveratrol** has been identified as a potentially bioactive constituent (Delgado et al., 2017). Within the MedDiet, alcohol consumption is defined not only by quantity but also by specific drinking patterns, including consumption with meals and avoidance of binge drinking. Collectively, this pattern has been associated with reduced all-cause mortality and cardiovascular disease risk. However, recommendations suggesting benefits of low-to-moderate alcohol consumption compared with complete abstinence are based primarily on observational evidence, which carries inherent limitations for causal inference (Barbería-Latasa & Martínez-González, 2025). According to the World Health

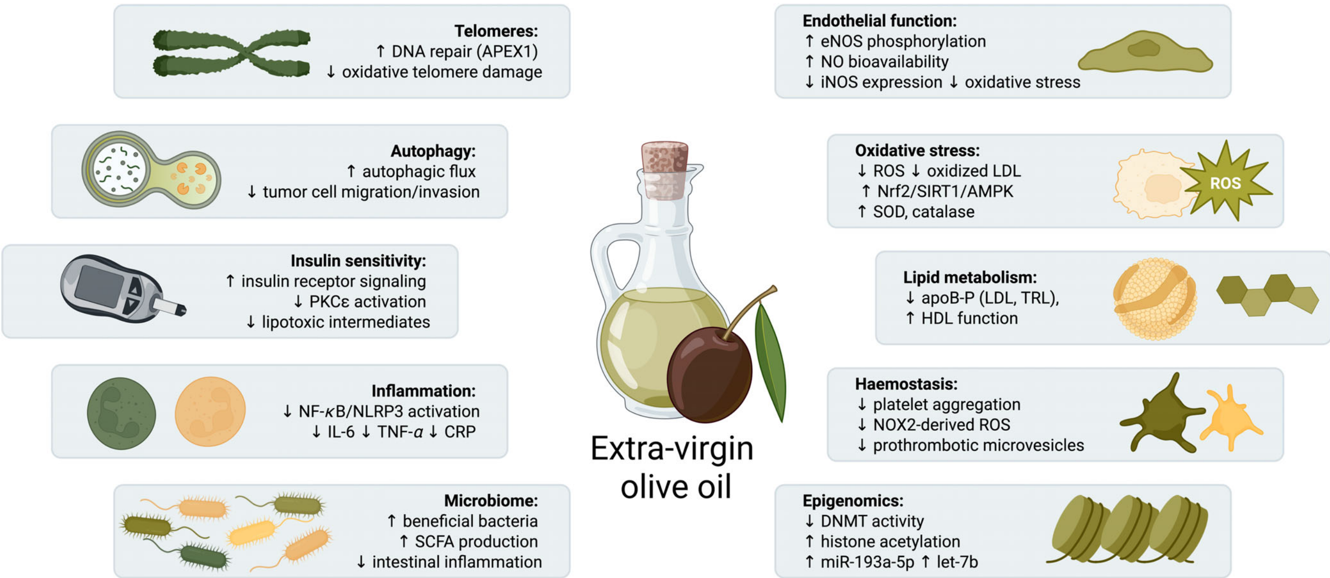

FIGURE 1 Overview of mechanistic properties of extra-virgin oil (EVOO). EVOO may provide a beneficial effect for non-communicable disease risk by modifying lipid metabolism, decreasing oxidative stress and inflammation, increasing insulin sensitivity and improving endothelial function and coagulation. Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; APEX1, AP endonuclease 1, enzyme involved in the base excision repair; apoB-P, apolipoprotein B-containing lipoprotein particles; CRP, C-reactive protein; DNMT, DNA-methyltransferases; eNOS, endothelial nitric oxide synthase; HDL, high-density lipoprotein; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; LDL, low-density lipoprotein; miR, microRNA (e.g., miR-193a-5p and let-7b); NF-κB, nuclear factor kappa B; NLRP3, NOD-like receptor family pyrin domain-containing 3; NO, nitric oxide; NOX2, NADPH oxidase 2; NRF2, nuclear factor, erythroid 2 like 2; PKCε, protein kinase Cε; ROS, reactive oxygen species; SCFA, short-chain fatty acids; SIRT1, sirtuin 1; SOD, superoxide dismutase; TNF-α, tumour necrosis factor alpha; TRL, triglyceride-rich lipoproteins;.

Organization and the Canadian Centre on Substance Use and Addiction, the healthiest level of alcohol intake is zero (Paradis et al., 2023; WHO, 2018). Alcohol consumption has been associated with seven cancer types, including cancers of the oesophagus, pharynx, larynx, oral cavity, liver, female breast and colorectum. In contrast, data supporting a cardiovascular benefit of low-to-moderate alcohol consumption remain inconclusive. Among younger individuals (<50 years), the adverse effects of alcohol consumption are more pronounced, particularly due to higher rates of binge drinking. Moreover, any cardioprotective benefit of moderate alcohol intake is negligible in this age group because of their low baseline cardiovascular risk; accordingly, Barbería-Latasa and colleagues propose complete abstinence. In older adults (>50 years), who generally have a higher cardiovascular risk and may experience risk reduction with low-to-moderate alcohol intake, the balance of risks and benefits is less clear (Barbería-Latasa & Martínez-González, 2025). Therefore, there is an ongoing debate on whether wine should be eliminated from the MedDiet Score (Martínez-González, 2024) despite its potentially beneficial constituents such as resveratrol.

3 | PHARMACOLOGICAL MECHANISMS – INGREDIENTS

The exact pathways through which the traditional MedDiet may contribute to the prevention of cardiovascular disease, certain cancers and metabolic disorders are not yet fully understood. Multiple hypotheses have been proposed regarding the roles of specific bioactive compounds and dietary factors, many of which likely interact through overlapping or synergistic mechanisms (see Figure 2).

3.1 | More established pharmacological mechanisms

3.1.1 | Lipid metabolism

In line with current concepts of cardiovascular disease prevention, the primary benefit of healthy dietary patterns such as the MedDiet lies in lowering apolipoprotein B-containing lipoprotein particles (apoB-P), whose arterial retention drives atherogenesis and progression to ischemic clinical events. As summarized in the original review (Schwingshackl et al., 2020), the MedDiet effect on LDL concentrations is attributable to monounsaturated fatty acid and polyunsaturated fatty acids (olive oil, nuts and fish), dietary fibre (whole grains, legumes, fruits and vegetables) and phytosterols (nuts and seeds). In addition, long-chain n-3 polyunsaturated fatty acids (fish) were highlighted for their role in reducing triacyglycerols-rich lipoproteins.

Accumulating evidence suggests that the effects of the MedDiet on lipid metabolism extend beyond alterations in circulating lipoprotein levels. A broad remodelling of circulating lipid metabolites with distinct biological functions including inflammatory signalling, oxidative stress responses, apoptosis, insulin signalling or mitochondrial function are further effects of the MedDiet. Studies employing high-throughput metabolic and lipidomic techniques, showed that both, greater adherence to the MedDiet and the replacement of dietary saturated fats (SFA) with unsaturated fats, shift circulating lipid composition towards reduced saturated triacyglycerolss, diacylglycerols and lysophospholipids and increased long-chain polyunsaturated fatty acids and ether-linked phospholipids, plasmalogens, sphingomyelins and omega-3-enriched cholesteryl esters (Eichelmann et al., 2024; Li et al., 2020). These lipidomic shifts persisted after adjustment for changes in conventional lipoprotein measures and were independently associated with risk of cardiovascular disease and type 2 diabetes, underscoring the importance of lipoprotein particle composition and functionality. Supporting this concept, a recent trial demonstrated that ethyl eicosapentaenoate supplementation through its incorporation into apoB-P surface phospholipids reduced particle atherogenicity independently of concentration. This was achieved by altering surface charge, fluidity and ApoB conformation, thereby electrostatic and hydrophobic interactions with arterial proteoglycans were diminished. Arterial proteoglycans are key determinants of subendothelial retention and early atherogenesis (Äikäs et al., 2025).

3.1.2 | Oxidative stress

Oxidative stress, through excessive generation of reactive oxygen species, perturbs redox-sensitive signalling pathways and induces cellular damage and ageing. As reported in the original review the antioxidant potential of the MedDiet can be linked to vitamins A, C and E (vegetables, citrus fruits, olive oil and nuts), polyphenols (EVOO, red wine and berries) and essential minerals such as magnesium (whole grains and legumes) and selenium (fish and nuts) (Schwingshackl et al., 2020).

Antioxidant vitamins and polyphenols can directly scavenge reactive species, thus increasing total antioxidant capacity and decreasing biomarkers of oxidative stress. In a long-term intervention with a MedDiet in patients with obesity, total serum antioxidant capacity significantly increased after 12 months (Ortner Hadžiabdić et al., 2016). Adherence to MedDiet has consistently been associated with reductions in multiple biomarkers of oxidative stress including F2-isoprostanes, oxidized LDL, malondialdehyde, 8-hydroxy-2′-deoxyguanosine, carboxymethyl-lysine, myeloperoxidase activity and enhanced antioxidant defences reflected by higher superoxide dismutase (SOD), elevated SOD protein levels and catalase (Aleksandrova et al., 2021).

Additionally, active components of the MedDiet can modulate redox-sensitive signalling pathways, including **nuclear factor, erythroid 2 like 2 (NRF2)**, **sirtuin 1 (SIRT1)** and **adenosine monophosphate-activated protein kinase (AMPK)**, thereby enhancing the expression and activity of key antioxidant enzymes. These effects have been consistently observed for EVOO polyphenols such as hydroxytyrosol and **oleuropein** (Schwingshackl et al., 2020). Oleic acid the principal monounsaturated fatty acid in olive oil can directly bind and allosterically activate SIRT1, leading to enhanced mitochondrial fatty acid oxidation, upregulation of antioxidant genes and a significant reduction in cellular reactive oxygen species levels. Although resveratrol is also a known

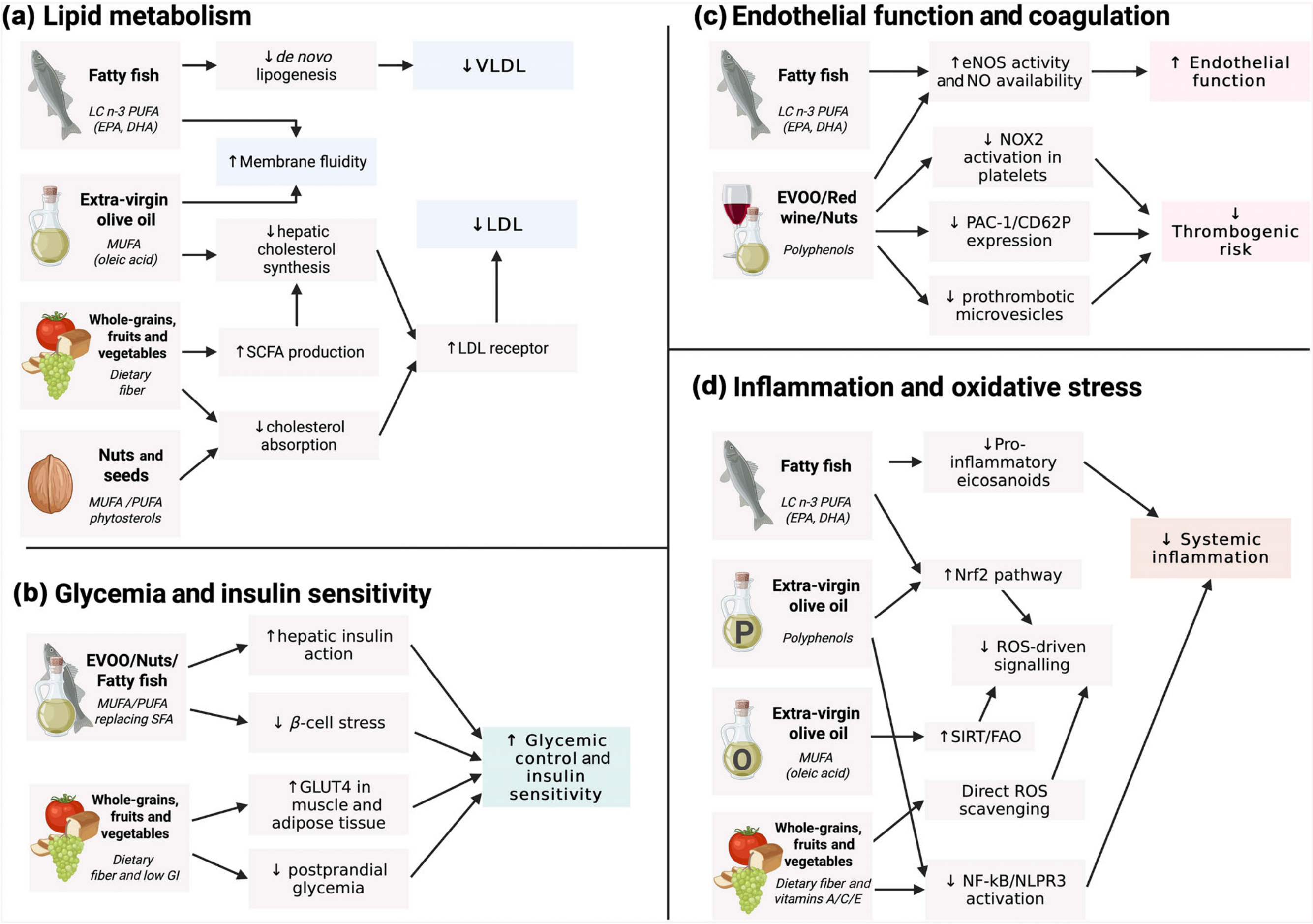

FIGURE 2 Schematic overview of potential mechanisms involved in the effects of bioactive compounds of ingredients of the Mediterranean diet. Long-chain n-3 PUFAs may contribute to lower VLDL concentration, improved membrane fluidity and endothelial function and reduce systemic inflammation by inhibiting synthesis of pro-inflammatory eicosanoids; oleic acid from EVOO has been shown to improve membrane fluidity and to reduce LDL concentration as well as systemic inflammation. Moreover, polyphenols from EVOO contribute to a reduced thrombogenic risk via various mechanism, for example, reduced NOX2 activation. Dietary fibre may contribute to lower LDL and cholesterol synthesis, as well as to improve insulin sensitivity, to reduce fasting glucose and systemic inflammation. Phytosterols from nuts and seeds may lower cholesterol absorption and therefore LDL concentration. Vitamins A, C and E reduce systemic inflammation by directly scavenging ROS and reduced NF-κB activation. Additional effects are attributed to the synergistic action of other agents such as omega-3 fatty acids, phytosterols, resveratrol, spermidine, anti-oxidative vitamins and nitrates. Abbreviations: CD62P, P-selectin CD62; DHA, docosahexaenoic acid; eNOS, endothelial nitric oxide synthase; EPA, eicosapentaenoic acid; EVOO, extra-virgin olive oil; FAO, fatty-acid oxidation; GLUT4, glucose transporter type 4; LC n-3 PUFA, long-chain n-3 PUFA; LDL, low-density lipoprotein; MUFA, monounsaturated fatty acids; NF-κB, nuclear factor kappa B; NLRP3, NOD-like receptor family pyrin domain-containing 3; NO, nitric oxide; NOX2, NADPH oxidase 2; NRF2, nuclear factor, erythroid 2 like 2; PAC-1, first procaspase activating compound; PUFA, polyunsaturated fatty acids; ROS, reactive oxygen species; SCFA, short-chain fatty acids; SFA, saturated fatty acids; SIRT, sirtuins; VLDL, very lsow-density lipoprotein.

activator of SIRT1, the doses achievable through dietary intake are too low to elicit pharmacological effects (Najt et al., 2020). In both *in vitro* and human settings, supplementation with omega-3 fatty acids lead to upregulation of NRF2 signalling leading to improved antioxidant defence (Golpour et al., 2020; Tatsumi et al., 2019).

3.1.3 | Inflammation

Acting as a silent but pivotal driver of chronic diseases, subclinical inflammation contributes to cardiovascular, metabolic and oncogenic risk, with several of its molecular mediators being modulated by the MedDiet. Similarly to oxidative stress defence, which is an associated process, the primary anti-inflammatory benefits of the MedDiet are mainly attributed to omega-3 fatty acids (fish) and polyphenols (olive oil, red wine and nuts) acting on different pathways of innate and adaptive immunity.

Nuclear factor kappa B (NF-κB) activates the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome. This is a central process of underlying chronic low-grade inflammation. It drives the release of IL (interleukin)-1β and IL-18 and promotes systemic inflammatory responses reflected by elevated IL-6 and hs-CRP (high sensitive C-reactive protein). Several classes of dietary polyphenols have been demonstrated to suppress NLRP3 inflammasome activation in *in vitro* models (Villalva et al., 2023). Both EVOO and omega-3 fatty acid supplementation in humans led to a decrease in pro-inflammatory cytokines related to reduced NLPR3 activation (Lamantia et al., 2024; Ruiz-García et al., 2023). Similar decreases in tumour necrosis factor-alpha (TNF-α), IL-6 and C-reactive protein have been reported in long-term interventional trials of the MedDiet, corroborating these findings.

Omega-3 fatty acids, particularly EPA and DHA, exert anti-inflammatory effects by incorporating into cell membranes, displacing arachidonic acid and competitively inhibiting **cyclooxygenase (COX)** and **lipoxygenase/lysyl oxidase (LOX)** enzymes, thereby reducing synthesis of pro-inflammatory eicosanoids. In patients post–myocardial infarction, omega-3 supplementation increased DHA- and EPA-derived epoxides: - 11-HDoHE (11-Hydroxydocosahexaenoic acid), 20-HDoHE (20-Hydroxydocosahexaenoic acid), 16,17-EDP (16,17-epoxydocosapentaenoic acid) and EEQ (epoxyeicosatetraenoic acid) and decreased **arachidonic acid** derived **PGJ_2 (prostaglandin J2)** and **LTB_4 (leukotriene B4)**, showing a shift towards an anti-inflammatory and vasoprotective eicosanoid profile (Yuan et al., 2021).

3.1.4 | Insulin sensitivity

In the previous version of the review, improvements in insulin sensitivity and glycaemic control were attributed to unsaturated fatty acids (olive oil, nuts and fish), dietary fibre (whole grains, legumes, fruits and vegetables) and polyphenolic compounds (EVOO and red wine) (Schwingshackl et al., 2020).

Increased intake of monounsaturated fatty acid and polyunsaturated fatty acids at the expense of saturated fatty acids is associated with better glycaemic control and lower risk of type 2 diabetes. In β-cells saturated fatty acids drives endoplasmatic reticulum-stress and blocks autophagic flux, leading to cell death, whereas unsaturated fats antagonize these effects, restoring autophagy and preserving viability (Dhayal et al., 2019). Additionally, a diet rich in saturated fatty acids leads to accumulation of lipotoxic metabolites such as diacylglycerols and ceramides which activate **protein kinase Cε (PKCε)**. These metabolites translocate to the membrane and phosphorylate the insulin-receptor kinase. Thereby its autophosphorylation is prevented and hepatic insulin resistance is enhanced (Lyu et al., 2020). Therefore, much of the metabolic benefit attributed to unsaturated fat intake in the MedDiet arises from counteracting the deleterious effects of high saturated fatty acids consumption.

An additional benefit of the MedDiet on glycemia may be attributed to a lower glycaemic index, as shown in a recent study where further reducing the glycaemic index within a MedDiet improved postprandial glucose control and reduced 24-h glycaemic variability compared with a higher-glycaemic index version of the diet (Bergia et al., 2022). Dietary intake of cereal fibre improves insulin sensitivity by reducing dietary protein absorption, lowering circulating amino acids and downregulating **mechanistic target of rapamycin (mTOR)**/**ribosomal protein S6 kinase 1 (S6K1/p70S6K)** signalling. This prevents lipotoxicity and enhances pancreatic and hepatic insulin function (Weickert & Pfeiffer, 2018). Moreover, intake of dietary fibre stimulates the gut microbiota to produce short-chain fatty acids, which enhance glucose homeostasis by upregulating **GLUT4 (glucose transporter type 4)** expression in skeletal muscle and adipose tissue, suppressing hepatic gluconeogenesis and promoting the secretion of **glucagon-like peptide-1 (GLP-1)** and **peptide YY (PYY)**, thereby increasing satiety via the gut–brain axis (Salamone et al., 2021).

3.1.5 | Endothelial function

As described in the original review (Schwingshackl et al., 2020), the MedDiet can support endothelial function through hydroxytyrosol and oleuropein (EVOO), resveratrol (red wine), omega-3 fatty acids (fatty fish) and antioxidant vitamins and other polyphenols (fruits and vegetables).

Improved endothelial function is partially secondary to reduced inflammation and oxidative stress as described above. Beyond these indirect effects, a key direct mechanism involves **nitric oxide (NO)** signalling, particularly through enhanced **endothelial nitric oxide synthase (eNOS)** expression and activity. For example, hydroxytyrosol, tyrosol and their metabolites modulate NO metabolism by increasing eNOS phosphorylation and NO production, while suppressing **inducible NOS (iNOS)** expression through inhibition of NF-κB and **MAPK (mitogen-activated protein kinase)** signalling (Serreli et al., 2019). Similarly, omega-3 fatty acids, especially EPA, enhance endothelial function by increasing NO bioavailability through upregulation and phosphorylation of eNOS, activation of **Akt (protein kinase B)** and AMPK signalling and reduction of oxidative stress that limits NO degradation (Sherratt et al., 2024).

The potential mechanisms through which the MedDiet confers endothelial benefits are not limited to NO metabolism. In the CORDIOPREV randomized-controlled trial of 805 patients with coronary heart disease, the diet led to lower concentrations of endothelial microparticles, indicating reduced endothelial injury and higher levels of endothelial progenitor cells, reflecting enhanced endothelial repair and angiogenic capacity (Yubero-Serrano et al., 2020). It also reduced oxidative and carbonyl stress, with lower reactive species and methylglyoxal concentrations, thereby limiting redox imbalance and protein glycation. Moreover, the authors identified epigenetic and proteomic changes indicating suppression of pro-apoptotic, pro-inflammatory and senescence pathways pointing towards inhibited NF-κB and **cyclin-dependent kinase 5 (CDK5)**/SIRT1 signalling.

3.1.6 | Haemostasis, platelet aggregation and coagulation

Activation of platelets and the coagulation cascade jointly promotes thrombus formation in both atherothrombosis and venous thromboembolism, bridging endothelial dysfunction, inflammation and clotting. In the original review, specific phenolic compounds (EVOO) were identified as contributors to improved platelet function (Schwingshackl et al., 2020). The effects of acute consumption of phenolic-matched, **oleocanthal**-rich versus oleocanthal-poor EVOO were investigated in an randomized-controlled trial of healthy men. The EVOO rich in oleocanthal reduced collagen-induced platelet aggregation independently of its total phenolic content, highlighting that the specific composition of phenolic compounds, rather than their overall concentration, plays a crucial role (Agrawal et al., 2017). In another trial, platelets from healthy volunteers were incubated with different EVOO, revealing that EVOO supplementation markedly inhibited hydrogen peroxide–induced **NADPH oxidase 2 (NOX2)** activation and ROS generation. The magnitude of inhibition correlated with the oils' vitamin E and polyphenol content (Carnevale et al., 2018). In a 1-year observational analysis of PREDIMED (Prevención con dieta Mediterránea), MedDiet diet enriched with EVOO or nuts was associated with reduced circulating prothrombotic microvesicles bearing platelet activation markers (**PAC-1**$^{+}$, **CD62**P^{+} and CD61^{+}), leukocyte adhesion molecules (**CD11a**$^{+}$) and the coagulation initiator tissue factor (**CD142**$^{+}$). This indicates long-term attenuated platelet activation and diminished thrombotic potential (Chiva-Blanch et al., 2020).

3.2 | Less established pharmacological mechanisms

A high proportion of the mechanistic data supporting the following mechanisms is based on preclinical (*in vitro* or animal) studies. For detailed information, see Table 4.

3.2.1 | Microbiome

The various preventive effects of the MedDiet cannot likely be explained solely by the content of specific micronutrients. The fact that positive effects can be observed after just a few weeks (Meslier et al., 2020) points to additional mechanisms of action, for example, affecting the microbiome. Polyphenols act as prebiotics, promoting the growth of beneficial bacteria and inhibiting pathogenic strains. In a study by Martin-Pelaez et al. (2016), phenolic-rich EVOO content showed immunomodulatory effects, likely mediated by the microbiome. Furthermore, the high intake of long-chain omega-3 fatty acids in the MedDiet can reduce intestinal inflammation and modulate microbial diversity, further contributing to a healthier intestinal environment (Back & Hansson, 2019; Gundogdu & Nalbantoglu, 2023; Merra et al., 2020). A healthy intestinal flora, in turn, can utilize fibre as a substrate for bacterial fermentation and produce short-chain fatty acids and other compounds that have anti-inflammatory effects and strengthen the intestinal barrier (Cani & Van Hul, 2020).

3.2.2 | Autophagy

The protective effect of polyphenols via modulation of autophagic processes was already mentioned in the original article (Schwingshackl et al., 2020). This effect has also been discussed in the context of cancer progression, particularly in relation to migration and invasion. Hydroxytyrosol and oleuropein exerted inhibitory effects on these events in tumour cells, possibly mediated by autophagy (Lu et al., 2021).

3.2.3 | Telomeres

In the reference article (Schwingshackl et al., 2020), we mentioned the stabilizing effects of oleuropein on telomerase activity. Another beneficial mode of action of ingredients of the MedDiet might be the protection of telomeres themselves. Telomere damage can be promoted by oxidative stress. Components of olive oil were able to induce Heme oxygenase-1 and activate the transcription factor NRF-2, thereby strengthening the antioxidative mechanisms (Levonen et al., 2007). Furthermore, polyphenols from olive oil protected the DNA repair gene AP endonuclease 1 (Erol et al., 2012). Thus, polyphenols in general might contribute to a reduction in oxidative stress, which protects telomeres from premature wear and tear (Meccariello & D'Angelo, 2021; Pereira et al., 2023).

In addition, polyunsaturated fatty acids especially as omega-3 fatty acids, are considered to provide anti-oxidative effects. Some studies have found a positive association between polyunsaturated fatty acid consumption and telomere stability (Farzaneh-Far et al., 2010; Seo et al., 2022).

Numerous micronutrients can influence telomere length and stability as well. They can act either as antioxidants (vitamin C and vitamin E) (Fenech et al., 2023) or through involvement in DNA repair processes (Welendorf et al., 2019). Moreover, increased intake of certain micronutrients has been associated with improved genome stability (Ames, 2018).

3.2.4 | Epigenomics

With respect to fatty acid quality, a MedDiet is mostly represented by monounsaturated fatty acid in the form of oleic acid present in EVOO. In human THP-1 monocytes, oleic acid induced DNA-hypomethylation, while treatment with arachidonic acid was associated with DNA-hypermethylation. This was interpreted as a beneficial effect of oleic acid on inflammatory processes (Silva-Martinez et al., 2016).

In a study by Schuldt et al., oleic acid mediated anti-inflammatory mechanisms on fibroblasts via acetylation of histone-3-lysin moieties which was accompanied by increased expression of anti-inflammatory cytokines (Schuldt et al., 2022).

Moreover, numerous studies have demonstrated an effect of polyphenols on the epigenome. Phenolic acids (Milosevic et al., 2021),

TABLE 4 Overview of mechanistic pathways linking the Mediterranean diet to health outcomes, classified by source of evidence.

More established pathways			
Lipid metabolism	↑ adherence to MedDiet, EVOO	↑ Favourable shifts in circulating lipid concentrations	+ +
		↓ apoB-P (LDL, TRL)	+ +
		↑ HDL	+ +
	Whole grains, fruits, vegetables	↑ SCFA production	+ +
	Nuts and seeds	↓ cholesterol absorption	+ +
Oxidative stress	↑ adherence to MedDiet, EVOO	↓ ROS; ↓ oxidized LDL	+ +
		↑ NRF2/SIRT1/AMPK	+
		↑ SOD, catalase	+ +
	Fatty fish (EPA, DHA)	↓ pro-inflammatory eicosanoids	+ +
	Whole grains, fruits, vegetables,	Direct ROS scavenging	+ +
Inflammation	EVOO, whole grains, fruits, vegetables	↓ NF-κB/NLRP3 activation	+
	↑ adherence to MedDiet, EVOO	↓ IL-6, ↓ TNF-α, ↓ CRP	+ +
Insulin sensitivity	↑ adherence to MedDiet, unsaturated fatty acids, dietary fibre	↑ insulin receptor signalling	+
		↑ PKCε activation, ↑ hepatic insulin resistance (SFA-driven)	+
		↑ Lipotoxic metabolites	+
		↓ β-cell stress	+
	↑ adherence to MedDiet, whole grains, fruits, vegetables	↑ GLUT4 in muscle and adipose tissue	+
		↓ postprandial glycemia	+ +
Endothelial function	EVOO, red wine, nuts, fatty fish	↑ eNOS activity, ↑ NO availability	+
		↑ NO bioavailability; ↓ iNOS expression	+
		↓ Prothrombotic microvesicles	+ +
Haemostasis, platelet aggregation and coagulation	↑ adherence to MedDiet, EVOO	↓ platelet aggregation	+ +
	EVOO	↓ NOX2-derived ROS	+
	EVOO	↓ Prothrombotic microvesicles	+ +
Less established pathways			
Microbiome	↑ adherence to MedDiet, EVOO, whole grains	↑ beneficial bacterial growth, ↑ microbial diversity	+ +
	EVOO	Immunomodulatory effects	+ +
	↑ adherence to MedDiet, EVOO, fatty fish (EPA, DHA)	Anti-inflammatory effects	+ +
	↑ adherence to MedDiet, whole grains, EVOO	↑ SCFA production	+ +
Autophagy	EVOO	Modulation of autophagic processes (autophagic flux and tumour cell migration)	+
Telomeres	Polyphenols	Telomere protection (via NRF2, APEX1)	+

(Continues)

TABLE 4 (Continued)

More established pathways			
	Long-chain PUFAs	Telomere protection	
	Micronutrients (whole grains, fruits, vegetables)	Influence on telomere stability and length	++
Epigenomics	OA, MUFA	↑ DNA hypermethylation of pro-inflammatory genes	+
	Polyphenols, isoflavones, anthocyanins	↑ methyltransferase activity	+
	Flavanone, flavone, tyrosol	↑ (in)activation of histone protein-modifying enzymes	+
microRNA	Quercetin	↑ miR-34a-5p	+
	Apigenin	↑ miR-34-5p, ↑ miR10, ↑ miR-520	+
	Resveratrol	↑ miR-622, miR-520 h	+
	Naringenin	↑ microRNA let-7a	+
	Kaempferol	↑ miR-26a-5p	+
	EVOO components (OA, hydroxytyrosol)	↑ let-7b, ↑ miR-193a-5p	+
Ageing			
Genomic stability	↑ adherence to MedDiet	↓ DNA damage	++
Epigenetic effects	↑ adherence to MedDiet	↓ miR-155-3p; ↑let-7b	++
	Resveratrol	Activation SIRT1, inactivation of NF-κB	+
Proteostasis	Polyphenols	↓ activation of autophagy, aggregation of amyloids	+
Nutrient sensing pathways	MedDiet	↑ AMPK, ↓mTORC	+
Mitochondrial dysfunction	EVOO components (OA, hydroxytyrosol)	↑ mitochondrial function, toxin resistance	+
Stem cell exhaustion	EVOO components (oleuropein)	↑ survival rate of hematopoetic stem cells	+

Note: ↑ = increased; ↓ = decreased; + = evidence derived predominantly from preclinical (in vitro or animal) studies; ++ = evidence supported by human data (randomized-controlled trials and/or observational studies).

Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; APEX1, AP endonuclease 1; apoB-P, apolipoprotein B-containing lipoprotein particles; CRP, C-reactive protein; DHA, docosahexaenoic acid; DNMT, DNA-Methyltransferases; eNOS, endothelial nitric oxide synthase; EPA, eicosapentaenoic acid; EVOO, extra-virgin olive oil; GLUT4, glucose transporter type 4; HDL, high-density lipoprotein; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; LDL, low-density lipoprotein; miR, microRNA (e.g., miR-193a-5p and let-7b); MedDiet, Mediterranean diet; mTORC, mechanistic target of rapamycin complex; MUFA, monounsaturated fatty acid; NF-κB, nuclear factor kappa B; NLRP3, NOD-like receptor family pyrin domain-containing 3; NO, nitric oxide; NOX2, NADPH oxidase 2; NRF2, nuclear factor, erythroid 2 like 2; OA, oleic acid; PKCε, protein kinase Cε; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; SCFA, short-chain fatty acids; SFA, saturated fatty acids; SIRT1, sirtuin 1; SOD, superoxide dismutase; TNF-α, tumour necrosis factor alpha; TRL, triglyceride-rich lipoproteins.

isoflavones (Kocabas & Sanlier, 2023) and anthocyanins (Persico et al., 2021) influenced the activity of DNA methyltransferases. Furthermore, activation or inactivation of histone protein-modifying enzymes could be triggered by tyrosols (Farras et al., 2021), flavanones (Wang, Sheng, et al., 2021) or flavones (Kocabas & Sanlier, 2023).

3.2.5 | MicroRNA

Regarding studies on the effects of MedDiet components on microRNAs, particular attention has been given to polyphenols. Thus, quercetin demonstrated beneficial effects on the proliferation profile of lung carcinoma cells by upregulating miR-34a-5p (Chai et al., 2021). In congruence with these observations, apigenin also showed stimulatory effects on miR-34-5p (Aida et al., 2021). Resveratrol demonstrated comparable anti-tumorigenic properties by upregulating miR-622 (Han et al., 2012) or miR-520 h (Yu et al., 2013). Apigenin inhibited the growth of a hepatocellular carcinoma cell line by upregulating miR101 and miR-520 (Gao et al., 2018). However, the influence of polyphenols on microRNAs is not limited to tumour growth; apigenin reduces the expression of the liver-specific miR122, which has been linked to inhibition of hepatitis C virus replication (Shibata et al., 2014). Furthermore, in an animal model of rats with diabetes, naringenin showed protective effects that were attributed to upregulation of the microRNA let-7a (Yan et al., 2016). **Kaempferol** exerted cardioprotective effects through microRNA modulation, for example, through the upregulation of miR-26a-5p in human endothelial cells (Zhong et al., 2018). In addition, kaempferol may inhibit vascular muscle cell migration via miR-21 activation (Kim et al., 2015), which is considered an indicator of intimal hyperplasia and stenosis.

With respect to components of olive oil, oleic acid was shown to increase let-7b in macrophages and human colorectal adenocarcinoma CACO cells, both considered to be involved in the regulation of inflammatory processes (Gil-Zamorano et al., 2014; Marques-Rocha et al., 2018). Further, EVOO-derived hydroxytyrosol affected the expression of microRNAs involved in the regulation of lipid metabolism in a mouse model. In an intervention study, hydroxytyrosol induced a significant increase in miR-193a-5p when compared to placebo (Tomé-Carneiro et al., 2016). This miRNA is involved in lipid metabolism, but also in the immune response (Feng et al., 2024).

3.2.6 | MedDiet-derived miRNAs

Although mainly seen as an epigenomic phenomenon, the effects of a MedDiet on human microRNAs may represent only one aspect of the preventive measures mediated by this diet. Also discussed is the ingestion of microRNAs from food, which exert effects in the human organism after passing through the digestive tract, for example, by influencing gene expression. These interactions are referred to as 'cross-kingdom communication' or 'inter-kingdom communication', since primarily the effects of plant microRNAs have been studied (Wagner et al., 2015). Plant microRNAs are methylated at the 3′ OH-end. This keeps them stable in the gastrointestinal tract and could mediate their mechanism of action in the human organism. Given the large number of naturally occurring microRNAs, a comprehensive overview is not possible. Pt-miR-159 from broccoli shows growth-inhibiting effects in breast cancer cells (Chin et al., 2016), pt-miR-156a from spinach or lettuce exerted an immunomodulatory effect *in vitro* (Hou et al., 2018), and the same was observed for cpa-mir1403 from papaya (Jha et al., 2022). Of note, there are a number of studies questioning these findings. Snow et al. (2013) could not reproduce the transfer of plant-derived microRNA to mammalian organisms and its corresponding effects. Methodological limitations in the separation of microRNAs (Chan & Snow, 2017), including unspecific amplification or cross-contamination, are held responsible for these discrepancies. The different preparation of the initial samples as described by Xu et al. (2024) might provide another explanation for these inconsistencies. A detailed review by Tambaro et al. (2025) gives an overview of this controversial field.

4 | AGEING

In order to describe the possible influences of MedDiet on ageing in more detail, the following is based on the hallmarks of ageing as proposed by Lopez-Otin et al. in 2013 (López-Otín et al., 2013). Interconnections to the effects of the ingredients of the MedDiet already described are unavoidable.

4.1 | Genomic stability

An enhancement of genomic stability by a MedDiet can be explained by changes in gene expression, epigenetic mechanisms, telomere stabilization, or favoured repair mechanisms. Thus, in a branch of the EPIC (European prospective investigation into cancer and nutrition) study from Florence, increased adherence to a MedDiet was associated with a lower incidence of DNA damage (lower concentrations of deoxyguanosine adducts) (Saieva et al., 2016). Regarding telomere stability, see Section 3.2.3.

4.2 | Epigenetic effects

In a human study, adherence to a MedDiet was associated with a decrease in the microRNA miR-155-3p in white blood cells and a concomitant increase in let-7b. Both changes are thought to have a protective effect in relation to age-related tumours (Marques-Rocha et al., 2016). Studies on resveratrol show an improved energy metabolism in mitochondria (Ungurianu et al., 2023). This polyphenol has also been described as an inhibitor of several pro-inflammatory mechanisms. Resveratrol exerts beneficial effects through activation of the sirtuin protein family, primarily SIRT1. Among other things, it promotes the deacetylation and inactivation of NF-κB, which contributes to the inhibition of inflammatory reactions (Iside et al., 2020). The anti-inflammatory effects of resveratrol could have positive effects on a number of age-related diseases with an inflammatory component, including cognitive impairment (Meng et al., 2020).

4.3 | Proteostasis

Proteostasis was defined as a hallmark of ageing, since its deregulation is associated with an accumulation of misfolded proteins. Polyphenols, like oleuropein, oleocanthal and resveratrol in the MedDiet are supposed to counteract this deregulation via activation of autophagy. This reduces the aggregation of amyloids, a typical symptom of neurodegenerative diseases such as Alzheimer disease (Roman et al., 2019).

4.4 | Nutrient sensing pathways

With respect to nutrient sensing pathways, the MedDiet was reported to stimulate AMPK (Menendez et al., 2013) as well as to inhibit mechanistic target of rapamycin complex which may protect against excessive anabolic metabolism (Jung et al., 2010). In addition, interactions between AMPK and sirtuins were shown to affect autophagy and to inhibit the pro-inflammatory transcription factor NF-κB (Lee et al., 2008; Russo et al., 2014).

4.5 | Mitochondrial dysfunction

There is considerable evidence of a mitochondrial protective function through ingredients of MedDiet. However, it should be noted that the underlying study design (in vitro, animal experiment) is representative of many of the findings in this review. Olive oil, for example, showed a positive effect on the structure, function and toxin resistance of mitochondria in rats (Amel et al., 2016; Varela-Lopez et al., 2018).

Hydroxytyrosol and oleuropein, in particular, improved mitochondrial function by reducing oxidative stress (Schaffer et al., 2007; Sun et al., 2017). Comparable protective effects were observed with omega-3 fatty acids in the brain and skeletal muscle (Afshordel et al., 2015), with a study by Lalia et al. (2017) conducted in humans.

4.6 | Stem cell exhaustion

In vitro studies demonstrated that oleuropein and other EVOO-derived polyphenols increased the survival rate of hematopoetic stem cells (Fernández del Río et al., 2016).

5 | LIMITATIONS AND FUTURE PERSPECTIVES

The main limitations of this review arise from the origin of mechanistic insights. Most mechanistic insights are based on cell culture and animal experiments, limiting their transferability to humans. Moreover, these studies typically examined isolated nutrients, which may exert different effects than when consumed as part of a complex food matrix. Synergistic or additive effects between various dietary components, as well as lower real-life intake levels, further complicate interpretation. For instance, most populations fail to meet recommended intakes of long-chain omega-3 fatty acids (Calder et al., 2026) and the bioavailability of these compounds is influenced by multiple host-related factors, including sex, genetic background, age and body mass index (de Groot et al., 2019). Bioavailability is also a key determinant of the proposed health effects of polyphenols, for which interindividual variability in absorption, distribution, metabolism and excretion is dependent on gut microbiota composition and genetic variation (Tosi et al., 2025). Therefore, long-term human intervention studies are needed to verify these findings and clarify biotransformatory changes and pharmacodynamics of the active ingredients of a MedDiet. In addition, included studies are very heterogeneous in design which explains the chosen narrative review design, a systematic review would have been subject to considerable restrictions in terms of the number of studies suitable for inclusion.

6 | CONCLUSIONS

Recent meta-analyses confirm an inverse association between adherence to the MedDiet and non-communicable disease risk, supported by intervention trials showing improvements in lipid metabolism and reductions in inflammation and oxidative stress. This is largely attributable due to higher intakes of unsaturated fatty acids (particularly oleic acid) accompanied by a reduced intake of saturated fatty acids, as well as polyphenols from EVOO, fruits and vegetables. Phenolic compounds, which are characteristic components of the MedDiet, were shown to reduce LDL-cholesterol, pro-inflammatory cytokines, oxidative stress and endothelial damage. Beyond these more established effects, mechanistic studies,, mostly conducted in cell and animal models, suggest additional roles in insulin sensitivity, thrombosis prevention, gut microbiota modulation and epigenetic regulation, thereby complementing epidemiological findings. Despite its inherent limitations, accumulated research supports MedDiet as a dietary recommended strategy for preventing various chronic diseases. Nevertheless, further research is warranted to elucidate how bioactive compounds influence gut microbiota, autophagy, telomerase activity and gene expression, thereby clarifying the molecular pathways linking the MedDiet to disease prevention.

6.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2025/2026 (Alexander, Davenport, et al., 2025; Alexander, Fabbro, et al., 2025).

AUTHOR CONTRIBUTIONS

Lukas Schwingshackl: Conceptualization; investigation; methodology; project administration; supervision; supervision; visualization; writing—original draft; writing—review and editing. **Jakub Morze:** Conceptualization; investigation; methodology; project administration; visualization; writing—original draft; writing—review and editing. **Sabina Wallerer:** Conceptualization; investigation; methodology; project administration; visualization; writing—original draft; writing—review and editing. **Georg Hoffmann:** Conceptualization; investigation; methodology; project administration; visualization; writing—original draft; writing—review and editing.

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None.

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