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FROM PLATE TO CELL: THE INFLUENCE OF THE MEDITERRANEAN DIET ON INFLAMMATORY AND OXIDATIVE ACTIVITY

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Rosana Solon Tajra
Vale do Acaraú State University - Health Sciences Center
Sobral - Ceará
MED - Mediterranean Institute for Agriculture, Environment and Development
CHANGE - Global Change and Sustainability Institute
Institute for Advanced Studies and Research, University of Évora | Mitra Campus
http://lattes.cnpq.br/7618067660616738
https://orcid.org/0000-0002-5604-5828

Marízia Menezes Dias Pereira
Department of Landscape, Environment and Planning
ICAAM - Institute of Mediterranean Agricultural and Environmental Sciences, University of Évora
Évora - Alentejo - Portugal
http://lattes.cnpq.br/1332897802053890
https://orcid.org/0000-0003-2551-3825

Ana Sancha Malveira Batista
Vale do Acaraú State University
Sobral - Ceará
http://lattes.cnpq.br/8936665173123509
https://orcid.org/0000-0001-5585-8758

Francisco Douglas Canafistula de Souza
Vale do Acaraú State University
Sobral - Ceará
http://lattes.cnpq.br/9202402473099045
https://orcid.org/0000-0001-5585-8758

Abstract: The Mediterranean diet has been highlighted as a dietary model capable of modulating pathophysiological mechanisms associated with oxidative stress and systemic inflammation, especially through bioactive compounds such as flavonoids. This study aimed to analyze, in the light of recent literature, the antioxidant and anti-inflammatory effects of these compounds in the context of the Mediterranean diet, with an emphasis on biomarkers applicable to clinical and nutritional assessment. This is an integrative literature review, conducted according to the PRISMA guidelines, through a search of the MEDLINE database, totaling ten selected studies. The inclusion criteria covered publications between 2020 and June 2025, available in English and in full text. Flavonoids, such as quercetin, luteolin and catechins, have shown potential to neutralize reactive oxygen species, inhibit inflammatory pathways and modulate antioxidant genes, being associated with a reduction in biomarkers such as MDA, 8OHdG, IL-6, TNF-α and CRP. In addition to the cardiovascular effects, these substances have also indicated neuroprotective effects, suggesting a role in the prevention of diseases such as Alzheimer's and Parkinson's. The Mediterranean diet, rich in fruit, vegetables, olive oil and oilseeds, shows superiority compared to other dietary patterns in reducing oxidative stress and early inflammation. However, the clinical translation of the beneficial effects of flavonoids is still limited, especially due to the low bioavailability of these compounds. Future research exploring dietary strategies combined with emerging technologies, such as nanotechnology, is therefore recommended in order to enhance the therapeutic effects of flavonoids in the prevention and management of chronic diseases.
Keywords: Flavonoids. Mediterranean diet. Antioxidant. Oxidative stress.

INTRODUCTION

Diet, strongly influenced by sociocultural and demographic factors, plays a central role in promoting health and well-being. Although the importance of specific nutrients is widely recognized, studies indicate that dietary patterns, considered in an integrated manner, offer a more consistent correlation with positive health outcomes (Kant, 2004). In this context, nutrition stands out as a relevant modulator of oxidative stress and systemic inflammation, especially through the consumption of foods rich in bioactive compounds with antioxidant and anti-inflammatory properties, such as those present in the Mediterranean and plant-based diets.

The modulation of oxidative stress is widely recognized as one of the main mechanisms by which balanced diets, such as the Mediterranean one, exert beneficial metabolic and physiological effects. This is largely due to the deleterious role played by reactive oxygen species (ROS) and reactive nitrogen species (RNS) in the pathophysiology of several chronic non-communicable diseases, including neurodegenerative, cardiovascular and autoimmune diseases (Gambini, Stromsnes, 2022). The accumulation of ROS can induce significant structural damage to DNA, proteins and lipids, often associated with an increase in biomarkers such as malondialdehyde (MDA) and 8-hydroxydeoxyguanosine (8OHdG), which are widely used to assess oxidative stress in clinical and nutritional studies (Weber, Grune, 2021). In addition, there is evidence that oxidative stress acts as a trigger for the activation of inflammatory pathways, promoting the release of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), which contributes to the establishment and perpetuation of chronic inflammatory states (Gambini, Stromsnes, 2022).

Among the most widely used inflammatory biomarkers, both in clinical practice and in scientific research, is C-reactive protein (CRP), whose hepatic synthesis is stimulated by inflammatory cytokines, such as interleukin-6 (IL-6), in response to acute inflammatory processes. CRP not only reflects the presence of inflammation, but also has prognostic value in various clinical conditions, especially in cardiovascular and chronic inflammatory diseases (Dupuy *et al.,* 2003).

In this context, bioactive compounds of dietary origin, especially polyphenols such as flavonoids, have been widely investigated for their ability to modulate the inflammatory response. These compounds act by inhibiting pro-inflammatory signaling pathways, such as the activation of nuclear factor kappa B (NF-κB), and by suppressing enzymes involved in the inflammatory process, such as cyclooxygenase-2 (COX-2). In addition, they exert antioxidant effects by neutralizing reactive oxygen species, thus contributing to the attenuation of both oxidative stress and systemic inflammation (Rudrapal *et al.,* 2024).

The Mediterranean diet, characterized by a high intake of fruits, vegetables, legumes, whole grains, olive oil, fish and white meat, stands out for its richness in flavonoids and other bioactive polyphenols, which justifies its recurrent association with beneficial effects on human health (Papadaki *et al.,* 2020; Quetglas-Llabrés *et al.*, 2024). Several experimental studies have explored the molecular mechanisms through which flavonoids exert their protective actions (Zhang; Tsao, 2016; Gualtieri *et al.*, 2023; Castellanos-Tapia *et al.*, 2020; Gambini; Stromsnes, 2022). These compounds have a high antioxidant potential, acting to neutralize reactive oxygen species and inhibit lipid peroxidation, which contributes to maintaining cell integrity and reducing oxidative stress. In addition, flavonoids have demonstrated the ability to modulate intracellular signaling pathways, such as PI3K/Akt and ERK, involved in fundamental processes such as apoptosis regulation, neuroprotection and tissue repair, suggesting a promising role in the prevention and management of chronic diseases related to oxidative stress (Rudrapal *et al.*, 2024).

Specific flavonoids, such as quercetin, luteolin and catechins, have been widely investigated for their role in reducing the expression of pro-inflammatory cytokines and positively regulating antioxidant genes. Recent studies indicate that these bioactive compounds can attenuate the accumulation of β-amyloid plaques and promote improved neuronal function, contributing to the prevention of neurodegenerative diseases such as Alzheimer's and Parkinson's (Quetglas-Llabrés *et al.,* 2024). These neuroprotective effects are in line with the benefits observed in flavonoid-rich dietary patterns, such as the Mediterranean diet, recognized for its positive impact on cardiovascular health and reducing the risk of chronic diseases. The combination of foods that are sources of bioactive compounds, such as fruits, vegetables, olive oil and nuts, not only modulates oxidative stress and inflammation, but also influences metabolic and epigenetic pathways associated with neuronal protection and the maintenance of vascular integrity (Martínez-González, Gea, Ruiz-Canela, 2019).

In physically active individuals, the phenolic compounds present in extra virgin olive oil, such as oleocanthal and hydroxytyrosol, have been shown to be effective in attenuating exercise-induced inflammation, favoring tissue recovery and sports performance (Lillis *et al.*, 2025; Griffiths *et al.*, 2022). There is also evidence that the Mediterranean diet exerts protective effects in conditions of lipid overload, as demonstrated in studies with hepatocytes exposed to Western dietary patterns (Castellanos-Tapia *et al.*, 2020).

Comparative analyses between different dietary patterns indicate greater efficacy of the Mediterranean diet in reducing oxidative stress and early inflammation, compared to vegan and vegetarian diets, although all show beneficial health profiles (Ilari *et al*., 2025). These results are corroborated by population studies that associate greater adherence to the Mediterranean diet with lower concentrations of biomarkers of oxidative stress and systemic inflammation, which highlights its role in promoting global health (Crawford *et al*., 2024).

Despite the growing interest in the use of bioactive compounds with antioxidant properties, such as dietary polyphenols, the clinical translation of their benefits is still controversial. Although experimental and observational studies point to a significant reduction in oxidative stress biomarkers and inflammation after consuming foods rich in these compounds, the clinical effects are not always evident, which may be related to the etiological complexity of chronic diseases or the secondary role of oxidative stress in certain pathological contexts (Zhang, Tsao, 2016). In this scenario, the adoption of dietary patterns rich in antioxidant and anti-inflammatory compounds, such as those found in the Mediterranean diet, represent a promising preventive approach, although it still requires further investigation to elucidate its effects in specific clinical conditions (Gambini, Stromsnes, 2022).

Considering the relevance of flavonoid-mediated antioxidant mechanisms in the context of the Mediterranean diet, this study aims to **analyze, based on recent evidence from the literature, the antioxidant and anti-inflammatory effects of flavonoids present in the Mediterranean diet, highlighting their mechanisms of action and implications for the prevention of chronic diseases associated with oxidative stress.**

METHODOLOGY

This is an integrative literature review, which used the PRISMA *(Preferred Reporting Items for Systematic Reviews and Meta-Analyses)* guidelines as a guide for data collection and selection, developed with the aim of helping authors to ensure the transparency and completeness of systematic reviews and meta-analyses (Galvão, Pansani, Harrad, 2015).

This investigation was guided by the following question: *"What are the effects of the Mediterranean diet, especially its flavonoid compounds, on the modulation of oxidative stress and inflammation, based on the analysis of biomarkers in physiological and pathological contexts?"* This question arises from the growing evidence of the therapeutic potential of the Mediterranean diet in the prevention and control of chronic diseases, although uncertainties persist as to the clinical efficacy and applicability of the antioxidant mechanisms described.

The Virtual Health Library (VHL) was used to search for sources. Ten articles were obtained as a result of the search, available in the *Medical Literature Analysis and Retrieval System Online* (MEDLINE) database. The search strategy was based on the following descriptors: "flavonoids" OR "Mediterranean diet" AND "antioxidant" AND "oxidative stress".

INCLUSION AND EXCLUSION CRITERIA

Articles available in full in the databases, published between 2020 and June 2025, in English, were included. Articles such as "clinical practice guidelines", "prevalence studies" and "prognostic studies" were excluded, as were studies that were not directly related to the central theme of the project. Studies using experimental animal models and those not accessible on the selected databases were also excluded.

QUALITY ASSESSMENT AND DATA EXTRACTION

At this stage, Rayyan - *Intelligent Systematic Review* (Rayyan) software was used to systematically screen studies by analyzing titles, authors and abstracts. Rayyan offers tools for selecting and excluding studies, detecting duplicates, descriptive evaluation and peer review (Ouzzani, Hammady, Fedorowicz, Elmagarmid, 2016).

Two independent researchers assessed the methodological quality of each included study. The analysis considered the comparability of the topics covered and the relevance of the evidence. In cases of disagreement, a third researcher was consulted for the final decision.

ELIGIBILITY OF STUDIES

After screening in Rayyan, the eligible articles were organized according to the PRISMA flowchart. The initial search resulted in 39 articles, 38 from MEDLINE and 1 from LILACS. In the analysis of titles and abstracts, 20 articles were excluded. After evaluating the full text, 9 articles were excluded because they did not meet the study's objective. Thus, 10 articles were considered eligible for the final analysis, as illustrated in the PRISMA Flowchart (Figure 1).

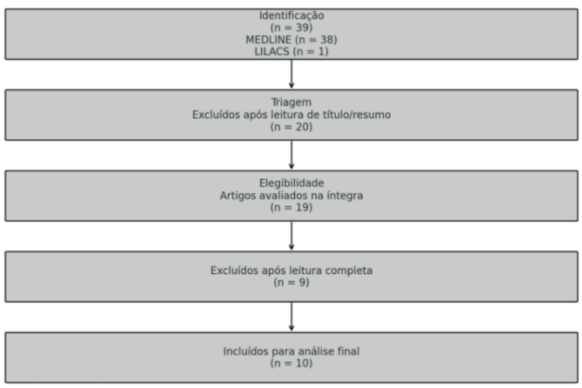

Figure 1 - PRISMA Flowchart

Representation of the process of identification, screening, eligibility and inclusion of the studies selected to make up the integrative review, according to the established criteria.

RESULTS

The search conducted in the Virtual Health Library (VHL) resulted in the selection of ten studies that met the inclusion criteria, all of which focused on the Mediterranean diet and its effects on oxidative stress and inflammation, with special emphasis on flavonoids. The sample included experimental studies, observational studies and systematic reviews (Chart 1), reflecting the methodological diversity of scientific production on the subject and allowing for a comprehensive analysis of the available evidence.

Among the most methodologically relevant studies, we highlight the systematic reviews and meta-analyses by Ilari *et al.* (2025) and Papadaki *et al.* (2020), which synthesize data from randomized clinical trials and observational studies, confirming the protective role of the Mediterranean diet on markers of inflammation and oxidative stress. Lillis *et al.* (2025) complement this approach by exploring specifically olive-derived polyphenols in the context of exercise-induced inflammation. The clinical trials by Gualtieri *et al.* (2023) and Quetglas-Llabrés *et al.* (2024) provide direct evidence of the efficacy of polyphenol-enriched diets in modulating gene expression related to oxidative stress and inflammation in populations at metabolic risk. The methodological validity of these studies is high, given the use of control groups, randomization and molecular biomarkers.

Observational studies also add value to the discussion, such as the case-control study by Bekar *et al.* (2025), which showed correlations between adherence to the Mediterranean diet, nutritional status and antioxidant status in women with rheumatoid arthritis. Similarly, Crawford *et al.* (2024) demonstrated significant associations between healthy eating patterns and oxidative stress levels in a large cohort of women. Ruiz-Saavedra *et al.* (2020) extend the analysis by correlating different

Author (Year)	Type of Study	Population / Model	Main Objective	Main Variables	Main Results
Ilari *et al.* (2025)	Systematic review and meta-analysis	Human studies (n=30 studies)	Comparing dietary patterns (Mediterranean, vegan, vegetarian) and inflammatory biomarkers	Diet, inflammatory and oxidative markers	Mediterranean diet showed better anti-inflammatory and antioxidant profile
Lillis *et al.* (2025)	Scoping review	Clinical trials with athletes and active individuals	Evaluating olive polyphenols on exercise-induced inflammation	Phenolic compounds, inflammatory cytokines	Olive compounds, rich in flavonoids, reduce post-exercise inflammation
Bekar *et al.* (2025)	Case-control study	Women with rheumatoid arthritis (n=110)	To assess adherence to the Mediterranean diet and antioxidant profile	Diet, nutritional status, antioxidant levels	Greater adherence to the diet was associated with better antioxidant status
Quetglas-Llabrés *et al.* (2024)	Randomized clinical trial	Patients with metabolic syndrome (n=80)	Evaluate intervention with polyphenols and physical activity	Oxidative stress, inflammation, dietary polyphenols	Significant improvement in inflammatory and oxidative profiles after 12 weeks
Crawford *et al.* (2024)	Observational cohort	Women from the Sister Study (n>30,000)	Linking dietary patterns and oxidative markers	Dietary indices, urinary isoprostanes	Healthy diets, including Mediterranean, were associated with lower oxidative stress
Gualtieri *et al.* (2023)	Randomized clinical trial	Healthy adults (n=100)	To evaluate the effects of a diet enriched with antioxidants	Gene expression, oxidative stress	Flavonoid-rich diet regulated pro-inflammatory and antioxidant genes
Griffiths *et al.* (2022)	Narrative review	Elite and recreational athletes	Review evidence of the Mediterranean pattern in sport	Diet, inflammation, performance	Mediterranean diet improves recovery and reduces inflammation in athletes
Ruiz-Saavedra *et al.* (2020)	Observational study	Adults and elderly (n=88)	Comparing dietary indices and their relationship with biomarkers	Diet, inflammation, microbiota	Adherence to the Mediterranean diet correlated with lower inflammation and better microbiota
Papadaki *et al.* (2020)	Systematic review and meta-analysis	Clinical trials (n=37)	To evaluate the effects of the Mediterranean diet on metabolic health	Blood glucose, lipids, blood pressure	Results indicated significant improvement in metabolic markers
Castellanos-Tapia *et al.* (2020)	Experimental study (*in vivo* and *in vitro*)	Western diet mice + hepatocytes	To evaluate the protective effect of a Mediterranean lipid mixture	Cellular oxidative stress, apoptosis	Mixture induced cell protection mediated by phenolic compounds

Table 1. Summary of selected studies on the Mediterranean diet, flavonoids and oxidative stress/ inflammation biomarkers

dietary indices with inflammatory markers and gut microbiota composition. Finally, mechanistic studies such as Castellanos-Tapia *et al.* (2020) investigated the cytoprotective effects of Mediterranean lipid mixtures in experimental models, while Griffiths *et al.* (2022) highlighted the functional role of this dietary pattern in sports performance, reinforcing its potential for application in different physiological contexts.

Taken together, the studies analyzed present coherence between their findings, despite methodological heterogeneity, and support the hypothesis that the Mediterranean diet, especially due to its high content of flavonoids and other polyphenols, contributes to reducing oxidative stress and inflammation, making it a relevant dietary strategy for promoting health and preventing chronic diseases.

THEORETICAL BASIS

MEDITERRANEAN DIET AND INFLAMMATORY AND OXIDATIVE BIOMARKERS

Recent studies reinforce the role of the Mediterranean diet in modulating inflammatory and oxidative biomarkers, highlighting its therapeutic potential in different pathophysiological contexts (Crawford *et al*., 2024; Bekar *et al*., 2025; Papadaki *et al*., 2020).

Ilari *et al*. (2025), in a systematic review with meta-analysis, compared the effects of Mediterranean, vegetarian and vegan diets on inflammatory biomarkers, such as C-reactive protein (CRP), and oxidative biomarkers, such as malondialdehyde (MDA), in the early stages of various clinical conditions. Although all the diets had beneficial effects, the Mediterranean diet showed the most consistent results, especially in reducing CRP levels. These findings suggest a more significant impact of the Mediterranean diet on low-grade systemic inflammation, which is often associated with chronic diseases. Similar results regarding the beneficial effects of vegetarian and vegan diets had already been observed by Key, Appleby and Rosell (2006), who highlighted their association with a lower risk of cardiovascular and metabolic diseases. However, as pointed out by Gibbs and Cappuccio (2024), vegetarian and vegan diets can present specific nutritional deficiencies - such as vitamin B12, iron, zinc and omega-3 fatty acids - which should be carefully monitored, especially in vulnerable populations.

The analysis also highlights that flavonoids, abundant in the foods that make up this dietary pattern, exert important physiological effects by modulating cellular pathways. The actions of these compounds include inhibiting the NF-κB transcription factor, suppressing the expression of pro-inflammatory cytokines such as IL-6, TNF-α, IL-1β and inducing endogenous antioxidant enzymes. According to Ilari *et al.* (2025), these effects should not be attributed exclusively to isolated flavonoids, but to the dietary synergism promoted by balanced dietary patterns, such as the Mediterranean diet, which act in an integrated manner in the prevention and management of chronic diseases.

IMPACT ON PERFORMANCE AND RECOVERY IN ATHLETES

The relationship between the Mediterranean diet and sports performance has been the subject of growing interest. Griffiths *et al.* (2022), in a narrative review, critically evaluated the effects of adherence to the Mediterranean diet on high-performance athletes. The Mediterranean dietary pattern, rich in phenolic compounds such as flavonoids, has shown potential to improve inflammatory parameters, promote post-exercise muscle recovery and reduce oxidative stress induced by intense physical activity. These effects are associated with the presence of natural antioxidants, especially polyphenols from olive oil, red fruits, nuts and green leafy vegetables.

Despite the promising evidence, the authors warn of the scarcity of randomized controlled clinical trials in specific athletic populations. Griffiths *et al.* (2022) also stress the need for standardized doses of bioactive compounds, strict control of the type of exercise practiced and longitudinal evaluation of clinical outcomes, in order to more robustly validate the beneficial effects attributed to the Mediterranean diet on sports performance.

OLIVE OIL AND EXERCISE-INDUCED INFLAMMATION

Among the components of the Mediterranean diet, extra virgin olive oil stands out for its high concentration of polyphenols, especially hydroxytyrosol. Lillis *et al.* (2025), in a *scoping review*, mapped studies that investigated the effects of these compounds on exercise--induced inflammation. They included clinical trials and pre-clinical studies that evaluated the modulation of interleukins (IL-6), TNF-α and CRP in different exercise protocols. The findings suggest that olive oil polyphenols have a significant anti-inflammatory effect, promoting a reduction in the acute inflammatory response and favoring cellular integrity.

Lillis *et al.* (2025) highlight the importance of the dose and time of intervention as determining variables in the effectiveness of the results. In addition, greater benefit was observed in studies with high adherence to the Mediterranean diet, reinforcing the importance of the synergistic dietary context. These data are in line with the findings of Ilari *et al.* (2025), who indicated that the Mediterranean diet, as an overall dietary pattern, is more effective than the supplementation of bioactive compounds alone.

EFFECTS ON INDIVIDUALS WITH CHRONIC INFLAMMATORY DISEASES

Ruiz-Saavedra *et al.* (2020), through a cross-sectional study with adults and the elderly, showed that adherence to the Mediterranean diet is associated with more favorable inflammatory and oxidative profiles. The authors used different dietary indices (MDS [Mediterranean Diet Score], HEI [*Healthy Eating Index]*, DII [*Dietary Inflammatory Index]*) and identified positive correlations between healthy eating patterns and the presence of anti-inflammatory markers. In addition, they observed a greater presence of beneficial gut bacteria, suggesting a gut-immunity-food axis modulated by compounds such as flavonoids.

In women with rheumatoid arthritis, Bekar *et al.* (2025) found that those with greater adherence to the Mediterranean diet had higher serum levels of total antioxidants, as well as lower inflammatory intensity. These data support the hypothesis that polyphenols, particularly flavonoids, act as modulators of the immune system, exerting a protective effect against chronic oxidative stress.

SYNERGISTIC EFFECTS BETWEEN THE MEDITERRANEAN DIET AND SUPPLEMENTARY COMPOUNDS

The potentiation of the antioxidant effects of the Mediterranean diet through supplementation with bioactive compounds has been explored by Gualtieri *et al.* (2023), in a clinical trial with 24 healthy adults. When comparing the Mediterranean diet alone with its combination with mixed apple and bergamot juice (rich in flavonoids), the authors observed greater gene expression of antioxidant markers such as SOD1, CAT and PPARγ, as well as a reduction in the total cholesterol/HDL ratio. These findings suggest that the synergy between bioactive compounds and the Mediterranean dietary pattern can potentiate the modulation of the redox system and systemic inflammatory processes.

This evidence is corroborated by Crawford *et al.* (2024), who identified an association between greater adherence to the alternative Mediterranean diet (aMED) and lower urinary levels of F2-isoprostanes among premenopausal women, demonstrating a reduction in oxidative stress even in healthy individuals. The authors emphasize the protective role of antioxidant-rich diets in preventive contexts as well.

LIPID COMPOSITION AND ANTIOXIDANT EFFECTS IN EXPERIMENTAL MODELS

Castellanos-Tapia *et al.* (2020) investigated the effects of a combination of fatty acids similar to that found in the Mediterranean diet in a murine model with hepatocytes subjected to lipid overload. The intervention promoted a reduction in lipid peroxidation, up-regulation of antioxidant genes and modulation of pathways related to endoplasmic stress. Although the focus of the study was lipid composition, the authors highlight the importance of the flavonoids present in this dietary pattern, suggesting that the beneficial effects observed result from the interaction between healthy lipids and phenolic compounds.

These data reinforce that the Mediterranean diet, by integrating foods rich in flavonoids, unsaturated fatty acids and phenolic compounds, is an effective nutritional strategy for preventing oxidative and inflammatory damage and is applicable to different clinical conditions and populations.

SYNTHESIS OF FINDINGS

In general, the studies analyzed show that the Mediterranean diet has consistent effects on reducing biomarkers of oxidative stress and systemic inflammation. Flavonoids such as quercetin, luteolin and catechins modulate intracellular signaling pathways, regulate the expression of antioxidant genes and reduce the production of pro-inflammatory mediators. Adherence to this dietary pattern has been shown to have a positive impact on healthy individuals, athletes and patients with chronic inflammatory diseases. These results support the use of the Mediterranean diet as an evidence-based dietary strategy with applicability in the prevention and management of diseases associated with oxidative and inflammatory imbalance.

CONCLUSION

By providing a rich source of flavonoids, the Mediterranean diet has beneficial effects on health, not only in modulating cardiovascular diseases, but also in controlling chronic inflammatory and neurodegenerative diseases. The role of flavonoids as modulators of oxidative stress and inflammation is emerging as a promising field for future therapeutic interventions, especially if combined with technologies such as nanotechnology, which aim to improve the bioavailability of these compounds and maximize their therapeutic effects.

It is worth noting that more studies are needed to explore the best dietary strategies and their combinations with pharmacological treatments, with the aim of potentiating antioxidant and anti-inflammatory effects, reducing the impact of chronic diseases.

Conflict of interest: the authors of the article entitled "*From the plate to* the cell: the *influence of The Mediterranean Diet on* inflammatory and oxidative activity" declare, for all intents and purposes, that there is no conflict of interest that could influence the content or evaluation of this manuscript.

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