Review

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Review

The Effect of Dietary Components of the Mediterranean Diet on Food Allergies: A Systematic Review

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Abstract: Allergies are a common and increasing health problem affecting millions of people worldwide. In addition to genetic predisposition, this increase in allergic cases is attributed to air pollution, climate change, more time spent indoors, lack of physical activity, and alterations in eating habits. The Mediterranean diet (MD), which includes a lot of fruits and vegetables, whole grains, legumes, nuts, olive oil and fish has been linked to a variety of health benefits, including a lower risk of chronic and allergic diseases. The purpose of this paper is to explore the effects of the dietary components of the MD on food allergies. Electronic databases PubMed, Scopus, Science Direct, and EBSCO were used to conduct this systematic review up to March 2023. 696 studies were initially identified and nine were included (five human and four animal studies). The findings of this review showed an overall beneficial effect between the food components of the MD and food allergies. Although the results are promising, the limited number of studies highlights the need for more research.

Keywords: food allergies; Mediterranean diet; MD; olive oil; polyphenols; long-chain omega-3 fatty acids

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1. Introduction

Allergies are a growing global public health problem, and it is estimated that food allergies affect up to 10% of the global population [1,2]. Asthma, allergic rhinitis, seasonal eczema, dermatitis, atopy, and food allergies are, in general, the most common allergies that people develop [3]. Allergies are characterized by abnormal adaptive immune responses that may or may not involve allergen specific IgE. During an allergic inflammatory response, sensory nerves become sensitized and activated, causing a variety of symptoms [4]. Severity of allergic reactions varies from person to person and can range from a minor irritant reaction to anaphylaxis, a potentially life-threatening emergency. Some of the allergy symptoms that may occur include itching, swelling, shortness of breath, vertigo, and loss of consciousness [2,3].

Food allergy diagnostic procedures include skin prick testing, food-specific IgE measurement, elimination diets, whilst the golden standard is a double-blind, placebo-controlled food challenge [5]. Assuming that certain foods are suspected to be the cause of an allergic disorder, they can be eliminated from the patient's diet to alleviate symptoms and confirm the diagnosis. The Food Standard Agency identifies 14 different foods as the most common causes of allergic reactions. These include celery, gluten-containing cereals (wheat, rye, barley, oats), crustaceans, eggs, fish, lupin, milk, mollusks, mustard, peanuts, sesame, soybeans, sulphur dioxide and sulfites, as well as tree nuts (cashew nuts, almonds, hazelnuts) [6].

In addition to genetic predisposition, this increase in allergic cases is likely to be attributed to air pollution, climate change, more time spent indoors, lack of physical activity, and alterations in people's eating habits, among others [7,8]. In today's modern world, people eat more foods that have been processed, altered, and modified; they consume fewer fruits and vegetables; and they consume excessive amounts of sugar, saturated fat, and junk food [9, 10].

In the last few years people have turned to healthier diets such as the Mediterranean diet (MD). The MD consists of whole grains, vegetables, beans, fruits, nuts, and seeds. Olive oil, as the primary source of fat, is the most vital component of the MD. Consumption of moderate amounts of fish, seafood, dairy products, and poultry are also components of this dietary pattern. In contrast, red meat, sweets, sugary drinks, and butter are consumed rarely [8,10, 11,12]. The MD provides various health benefits, including a lower risk of cardiovascular disease and metabolic syndrome, as well as promoting a healthy balance of gut microbiota in the digestive tract. It assists individuals in maintaining normal levels of glucose, blood pressure, and cholesterol. Recent evidence also suggests that people with allergies may benefit from the MD. This may occur because the high levels of antioxidants (such as vitamins, minerals, and fatty acids) and anti-inflammatory substances found in the MD boost immune function [9]. Kontogianni's (2008) study investigates the rates of MD adherence in a sample of Greek children and adolescents. Even though, MD consumption by children appears to have a protective effect against asthma/wheezing the findings demonstrate low adherence rates [9,13]. The role of the MD in allergic disease has been previously discussed in two comprehensive systematic reviews by Castro-Rondriguez et al (2017) and more recently by Koumpagioti et al (2022) [9,10]. The data have been mixed while both studies highlight the need for further investigation.

To our knowledge there is no systematic review addressing the association of the MD or its nutritional components with the development of food allergies. The MD is rich in polyphenols, naturally occurring compounds present in a wide range of plant-based foods such as fruits, vegetables, nuts, and seeds. Evidence suggests that these compounds may play a role in lowering the risk of developing food allergies. Also, according to literature, polyunsaturated fatty acids (PUFAs), particularly omega-3 fatty acids, may reduce the risk of food allergies [14]. As such, the purpose of the current systematic review is to determine any association between the food components of the MD and food allergies.

2. Materials and Methods

2.1. Study design

The current review followed the PRISMA 2020 statement for systematic reviews [15]. The review protocol has been registered in PROSPERO—International prospective register of systematic reviews (ID: CRD42023408827). The systematic literature review was performed using the electronic databases PubMed, Scopus, ScienceDirect, and EBSCO. The following keywords and their combinations were used with Boolean logic: ("food allergies") AND (("olive oil") OR (polyphenols) OR (long-chain omega-3 fatty acids)). Only published peer-reviewed studies up to March 1st 2023 were included. There were no restrictions on language. Search and study selection were performed by three independent reviewers (E.P, S.A.N. and E.A.).

2.2. Inclusion and exclusion criteria

The PICOS (Population, Intervention, Comparison/Comparator, Outcomes, Study Type) methodology was utilized to select all eligible studies. The inclusion criteria for this review included: (i) participants of any age (e.g., infants and pregnant women and their infants) or food allergy animals models, (ii) cohort, cross-sectional, randomized controlled trials, observational studies and experimental studies, (iii) studies that state the effect of a food component of the MD (e.g., polyphenols, olive oil, long-chain omega-3 fatty acids on food allergies) and, (iv) studies published from 2000 until March 2023. Studies were excluded if: (i) they did not follow the inclusion criteria, (ii) if they investigated other diets or (iii) if they investigated other allergies/diseases.

2.3. Study Selection

Following the database search, duplicates were identified and removed. Next, the titles and abstracts of all publications were screened for relevance according to the inclusion and exclusion

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criteria. All irrelevant studies were removed. If the result was not obviously irrelevant, the entire document was downloaded and reviewed.

2.4. Data extraction

For human studies, data extracted included information on the author, year, sample size, country, study design, food component, methodology and results (effect of the food components of the MD on allergy symptoms).

For animal studies, data extracted included information on author/year, # of animals, age, strain/species, sex, component/dose, route, sensitization day, challenge day and results.

2.5. Risk of bias for included studies

To assess the risk of bias the Office of Health Assessment and Translation (OHAT) tool was used [16]. For the animal studies 9 domains were included (risk in randomization, allocation, experimental conditions, blinding during the study, incomplete data, exposure characterization, outcome assessment and reporting). For the human studies the same bias domains were included except for the risk in experimental conditions. Each domain was marked as follows: (++) Definitely Low; (+) Probably Low; (-) Probably High; (--) Definitely High; and (NA) Not Applicable.

3. Results

3.1. Selection of Studies

From the 727 identified articles by the literature search, 31 were duplicates and 670 did not meet the criteria for inclusion, so they were excluded. Of the 23 articles evaluated for eligibility during the full-text screening, 12 failed to meet inclusion criteria. In the end, 9 articles met the inclusion criteria for this systematic review, as shown in Figure 1.

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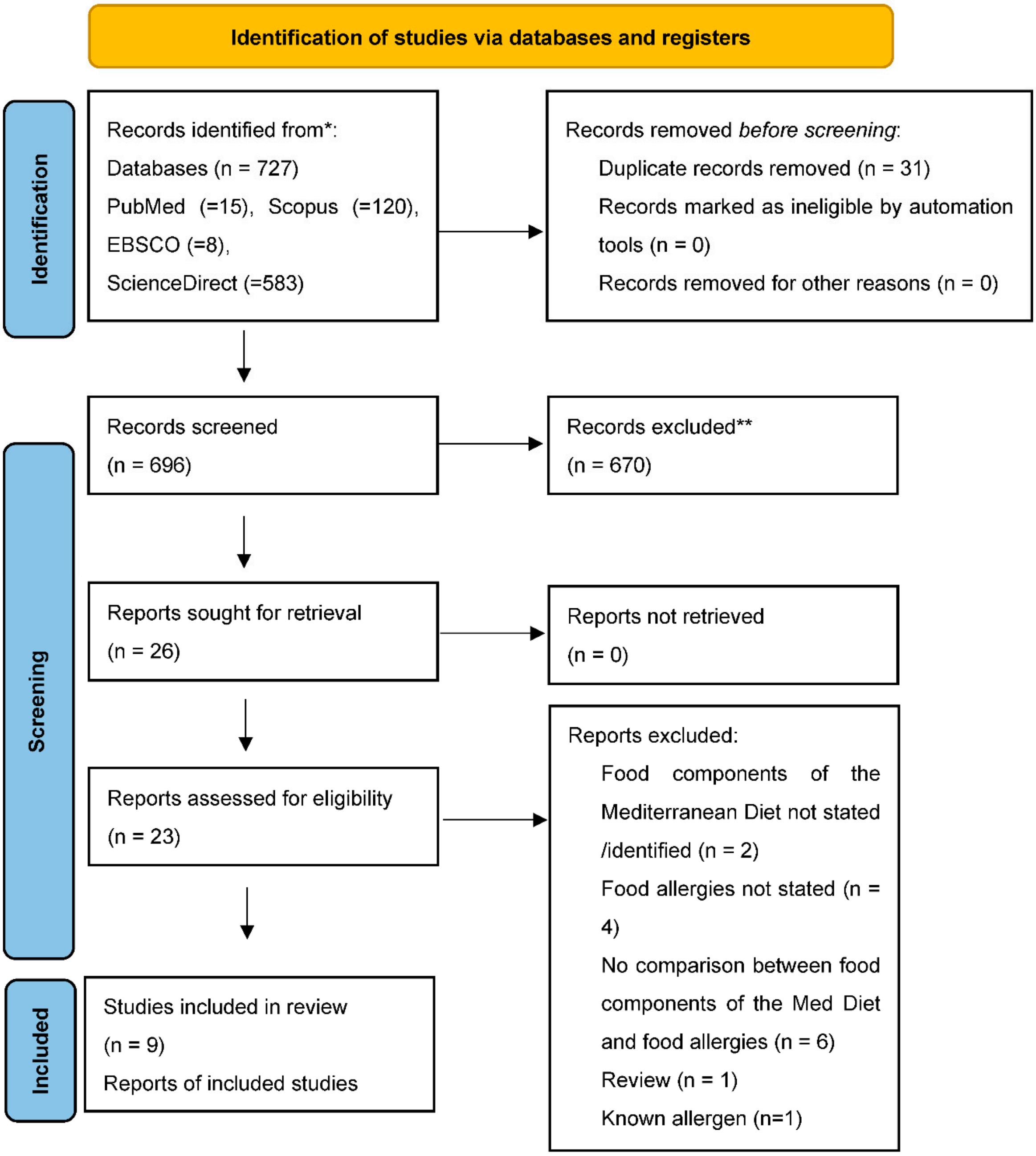

Figure 1. Schematic of selection of studies, PRISMA 2020 [15].

3.2. Quality assessment

The OHAT tool was used to evaluate the risk of bias in this systematic review (Table 1) [16]. The tool enable us to check both human and animal studies via excluding/including specific domains. All studies included in the current review were of high quality.

Table 1. Risk of Bias Assessment of included studies using the OHAT Risk of Bias Rating Tool.

	Reference	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
Human	(Furuhjelm et al., 2011)	++	++	NA	NA	NA	++	++	+	++	++
	(Palmer et al., 2012)	++	++	NA	NA	NA	++	++	+	++	++

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	(D'Vaz et al., 2012)	++	++	NA	NA	NA	++	+	+	++	++
	(Furuhjelm et al., 2009)	++	++	NA	NA	NA	++	+	+	++	++
	(Wu et al., 2018)	NA	NA	++	--	NA	NA	++	+	+	+
Mice	(Ma et al., 2022)	++	+	NA	NA	++	+	++	+	+	++
	(Ma et al., 2023)	++	+	NA	NA	++	+	++	+	+	++
	(Zuercher et al., 2010)	++	+	NA	NA	++	+	++	+	+	++
	(Singh et al., 2014)	++	+	NA	NA	++	+	++	+	+	++

Scoring: (++) - Definitely Low; (+) - Probably Low; (-) - Probably High; (NR) – Not reported; (--) – Definitely High; NA – Not Applicable. Domains Judgement, D1: Risk in randomization; D2: Risk in allocation concealment; D3: Risk in comparison groups; D4: Risk Risk in confounding factors; D5: Risk in experimental conditions; D6: Risk in blinding during study; D7: Risk due to incomplete data; D8: Risk in exposure characterization; D9: Risk in outcome assessment; D10: Risk in reporting.

3.3. Study Characteristics

This study included a total of nine studies, of which five were conducted on humans (randomized controlled trial, n=4; cross-sectional, n=1), and four were were conducted on animals (experimental, n=4). The human studies were conducted in Sweden (n=2), Australia (n=2) and China (n=1) while the animal studies were conducted in China (n=2) and Switzerland (n=2).

In two of the human studies by Furuhjem et al (2011, 2014) researchers followed pregnant mothers at risk of having an allergic infant (n=290) from the 25th week of pregnancy and their infants for either 12 or 24 months. In these two studies mothers received LCPUFA supplementation from the 25th week of gestation and for 3-4 months of lactation. Palmer et al (2012) followed pregnant mothers at risk of having an allergic infant (n=706) from the 21th week of pregnancy and their infants for 12 months. In this study mothers received LCPUFA until birth. In the study by D'Vaz and colleagues (2015) infants (birth to six months of age) received fish oil supplementation and the effect on allergic disease was investigated. The fifth human study conjugated the knowm cow milk allergen bovine β-lactoglobulin (βLG) to the polyphenols epigallo-catechin 3-gallate (EGCG) and chlorogenic acid (CA) to reduce the allergenity of cow's milk.

All four animal studies used the Ovalbumine (OVA)-Sensitised BALB/c mouse model as their food allergy model. The two studies by Ma and colleagues (2022, 2023) fed their animals olive oil prior to sensitization. In the studies by Singh et al and Zuercher et al [23,24] they fed their mice with enriched polyphenols (either epicatechin or flavonol). Tables 2 and 3 summarise the characteristics of the human and animal studies respectively.

Table 2. Summary of studies conducted with humans reporting any association between food allergies and food components of the MD.

Author / Year	Country	Duration	Sample Characteristics	Study Design	Food component of Med Diet	Methodology	Results – Effect on food allergies symptoms
Furuhjelm et al. 2011 [17]	Sweden	24 month infant follow-up	145 pregnant women (25th week) at risk of having an allergic infant and their infants	Randomized Control Trial	Long-Chain unsaturated Fatty acids (LCPUFA): Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) or placebo	Intervention group daily dose of: 1.6g EPA and 1.1g DHA or placebo from the 25th week of pregnancy to the first 3.5 months of breastfeeding Control group: placebo	(a) Dose-dependent beneficial effect in allergic sensitization and IgE associated disease in the infant ($p = 0.01$-0.05). (b) No obvious preventive effect on symptoms of allergic disease.
Palmer et al. 2012 [14]	Australia	12 month infant follow-up	706 infants (Follow-up study of DHA to Optimize Mother Infant Outcome [DOMInO] trial)	Randomized controlled trial	Fish oil capsules (n-3 – LCPUFA; DHA and EPA)	Intervention group (n=368): daily dose of fish oil capsules (900mg of n-3 LCPUFA; 800mg DHA and 100mg EPA) from 21 weeks' gestation until birth. Control group (n=338): capsules of vegetable oil without n-3 LCPUFA	No effect in IgE associated food allergy. Unadjusted relative risk 0.68, 95% confidence interval 0.43 to 1.05, p=0.08; adjusted relative risk 0.7, 0.45 to 1.09, p=0.12
D'Vaz et al. 2012 [18]	Australia	6 months	420 infants	Randomized Controlled Trial	Fish oil (DHA and EPA) or a control olive oil.	Intervention group (n=218): From birth to 6 months, received a daily supplement of fish oil comprising 280mg DHA and 110mg EHA Control group (n=202): olive oil.	No effect on allergic outcomes including food allergy.
Furuhjelm et al. 2009 [19]	Sweden	12-month infant follow-up	145 pregnant women (25th week) at risk of having an allergic infant and their infants	Randomized Controlled Trial	EHA and DHA or placebo	Intervention group (n=52): Daily dose 1.6 g EHA and 1.1 g DHA from the 25th gestational week – 3-4 months of breastfeeding. Control group (n=65): soy oil capsules	Beneficial effect. Compared to the placebo group (10/65, 15%), the omega-3 group had a reduced rate of food allergy (1/52, 2%; $p<0.05$).
Wu et al. 2018 [20]	China		Sera from 10 children with cow milk allergy.	Cross-sectional study	Bovine β-lactoglobulin (βLG) (cow milk allergen) conjugated with	A pool of sera from children with cow milk allergy (n = 10) and a pool of sera from individuals without the allergy (n = 5)	Beneficial effect. βLG conjugated with polyphenols was effective in lowering IgE-binding capability ($p < 0.05$).

					epigallo-catechin 3-gallate (EGCG) and chlorogenic acid (CA)	Were exposed βLG conjugated with EGCG and CA			

EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; LCPUFA: Long-chain polyunsaturated fatty acids; βLG: bovine β-lactoglobulin, EGCG: epigallo-catechin 3-gallate; CA: chlorogenic acid.

Table 3. Summary of studies conducted with animals reporting any association between food allergies and the food components of the MD.

Author / year	# of animals	Age	Strain / Species	Sex	Food component of Med Diet	Sensitization Day	Challenge day	Methodology	Results – Effect of food components of Med Diet on food allergies symptoms
Ma et al. 2022 [21]	48	4 weeks of age	BALB/c mice. Ovalbumine (OVA)-sensitized mice (FA model)	Female	Olive oil	14^{th} day	33^{rd} day	Experimental groups: 2 weeks of olive oil prior to sensitization. 1.0 or 2.0 or 3.0 g/kg·day olive oil with and without sensitization, Phosphate-buffered saline (PBS) group and OVA group.	Beneficial effect. Dose-dependent inhibition of IgG, IgE and histamine. Dose-dependent increase of TGF-β expression in the ilea of allergic mice.
Ma et al. 2023 [22]	15	3-5 weeks of age	BALB/c mice. OVA-sensitized mice	Male	Olive oil	14^{th} day	28-40^{th} day	Experimental groups: 2 weeks of olive oil prior to sensitization to olive oil group, allergy model group and PBS group.	Beneficial effect. Decrease in clinical symptoms of allergy. Decrease in IgE, mouse mast cell protease (mMCP)-1, and TNF-α levels in the olive oil group ($p < 0.01$). Positive effect on intestinal epithelial mucosal immunity.
Zuercher et al. 2010 [23]	10-15 / group	6 weeks old	BALB-c mice per group. OVA-sensitized mice	Female	Polyphenol enriched apple extract (flavonols)	1-42^{nd} day	49^{th} day	Experimental groups: OVA-sensitized mice fed with the apple extract at Day 0 (primary prevention) or Day 42 (secondary prevention, positive and negative control.	Beneficial effect. Decrease of the severity of allergic symptoms and mediator release (mMMCP-1) comparable in Day 0 and Day 42 groups. IgE level remained the same. Variable cytokine data.

Singh et al. 2014 [24]	10-15 / group	6 weeks old	BALB-c mice per group. OVA-sensitized mice	Female	Polyphenol-enriched apple extracts A and B, polyphenol-enriched with cocoa or polyphenol-enriched with epicatechin	3rd day	49th day	Experimental groups: OVA-sensitized mice fed with the extracts, cholera toxin-sensitized mice (negative control) and regulary fed mice (positive control).	Beneficial effect. Dose-dependent decrease in clinical symptoms of allergy and IgE in mice given the epicatechin extract (p = 0.01).

FA: Food Allergy; OVA: ovalbumin; PBS: Phosphate-buffered saline; mMCP: mouse mast cell protease; TGF-β: Transforming growth factor-beta; IgE: Immunoglobulin E;mMCP-1: TNF-α: Tumor necrosis factor-α.

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3.4. Effect of components of the MD on food allergy in infants and animal models

Four of the human studies investigated the effect of PUFAs on food allergies [14,17, 18,19]. Fujuhjem (2009 and 2011) that initiated the supplementation during pregnancy and the first month of lactation found a beneficial effect while Palmer (2012) and D'Vaz (2012) that supplemented either the mother until birth or the infant until six months found no effect [14, 17, 18, 19]. The fifth human study investigated the effect of conjugating an allergen with polyphenols and showed that IgE-binding capacity was lowered indicating a beneficial effect [20].

Two of the animal studies investigated the effect of olive oil on food allergies and demonstrated a beneficial effect [21, 22]. This was demonstarted by a does-dependent inhibition of allergen-specific antiboDies (IgG and IgE) as well as a decrease in the expression of TGF-β [21]. The second study also found a decrease in clinical symptoms of allergy (dose-dependent) as well a a decrease in IgE, mouse mast cell protease (mMCP)-1, and TNF-α levels in the olive oil group ($p < 0.01$). The other two animal studies invesigated the effect of polyphenols on food allergies [23, 24]. The study by Singh et al (2014) that used epicatechin showed a dose-dependent decrease in clinical symptoms and IgE. Similarly, Zuercher et al (2010), that used flavonol enriched polyphenols showed a decrease in the severity of allergic symptoms while IgE levels remained unchanged and cytokine data was inconclusive. To determine clinical severity allergic symptoms were graded (scratching, rubbing / swelling around snout and mouth, piloerection, wheezing, lack of activity, tremor/convulsions, death).

4. Discussion

The aim of the current systematic review was to determine whether components of the MD such as olive oil, polyphenol or PUFAs have any effect on food allergies in infants and animal models. The human studies indicated that when the intervention occurs during pregnancy and though lactation a beneficial effect is observed [17, 19]. However, when the intervention is given to pregnant mothers either until birth or to the infants for their first six months of life no effect is observed [14, 18]. All the animal studies indicated a positive relationship between the food components of the MD and food allergies. The food components used were olive oil and enriched polyphenols [21,22,23,24].

Epidemiological studies have demonstrated that the prevalence of food allergies in Western nations is correlated with the excessive consumption of n-6 PUFAs in the diet [2]. In the MD n-3 PUFAs are predominant and more beneficial. According to the findings, two of the randomised controlled studies included in this review, ω-3 supplementation during pregnancy and breastfeeding may lower the risk of food allergy during the first year of life [17, 19]. Also, a cohort study by Chatzi et al (2017) investigated the association between MD adherence during pregnancy and childhood respiratory outcomes. The findings suggest that higher adherence to the MD during pregnancy is associated with a reduced risk of childhood wheezing and asthma, however three other studies showed no effect [9, 25]. Another study that examined the link between asthma, rhinoconjunctivitis, obesity, exercise, and the MD in children in Spain showed a lower risk of asthma and rhinoconjunctivitis [26].

One way of assessing allergic outcomes is food allergen specific IgE. In the papers included herein higher maternal and newborn proportions of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) were related to a decreased prevalence of IgE-associated illness ($p = 0.01–0.05$) in a dose-dependent manner [19]. According to the findings of a systematic review conducted by Sartorio (2021), supplementation with PUFAs inhibits allergic response in preclinical studies [27]. Still, other studies investigating general atopy indicated that long chain PUFA supplementation during pregnancy did not decrease the general rate of IgE-associated allergies in the first year of life, however atopic eczema and egg sensitization were reduced [14, 17]. This was also noted in two of the human studies discussed here as PUFAs did not show any effect [14, 18]. This may due to timing and dosing effects. To illustrate, despite the relatively large dose of n-3 PUFA utilised in the D'vaz et al research study, only a small increase in n-3 PUFA levels was observed, which may indicate problems with the bioavailability and absorption of supplements [14]. The results of clinical studies regarding the optimal timing and dosages of supplementation, as well as the individuals most likely to benefit, are still contradictory; consequently, definitive conclusions cannot yet be drawn [28].

An alternative to studying human disease is with animal models and food allergy is no exception. There are a number of animal models that mimic the human clinical features of food allergy, and these are discussed elsewhere [29, 30]. These food allergy models show a tendency for Th2 responses that are expected in allergic responses [29, 30]. In the current study, the same animal model, with variations in sensitization, was used (OVA-sensitised BALB/c mice with adjuvant). The animals were fed either olive oil or polyphenols which are key nutritional components of the MD.

Olive oil consumption has been linked to several health benefits. Olive oil has direct (tocopherols, polyphenols, mono-unsaturated fatty acids) and indirect (lower saturated fats, balanced linoleic/alpha linolenic acid) effects on the immune system and inflammatory responses (lower saturated fats, balanced linoleic/alpha linolenic acid) [31]. Two of the experimental studies included in this review used a mouse model to investigate the relationship between olive oil and food allergies [21, 22]. These two studies found that administering olive oil orally to mice improved epithelial mucosal immunity [21, 22]. Further, olive oil alleviates the symptoms of OVA-induced anaphylaxis, lowers intestinal inflammation, and reduces the level of OVA-specific IgE and anaphylactic mediator in the serum [21]. Over 8000 distinct polyphenols are found in fruit, vegetable, and cereal. Recent studies have identified a protective role of polyphenols against food allergies and investigated the underlying mechanisms [32]. Also as shown in this review, polyphenols showed a beneficial effect on food allergies on mice [23,24]. Polyphenols can bind to allergens either covalently or noncovalently, forming conjugates or complexes. These changes cause secondary structural changes in the proteins (like less -helical and -sheet content), which covers the immunoglobulin E (IgE) epitope and changes the way antigens are presented, which stops the allergic reaction in vivo. Likewise, in the cellular model, the complexes inhibited the degranulation of rat basophil leukemia cells via the mitogen-activated protein kinase signaling pathway, resulting in a decrease in hexosaminidase and histamine levels [19, 27, 32].

The current study has some limitations. Initially, high-quality human studies were sought. However, the search indicated that there are a limited number of human studies that investigated the effect of the components of the MD on food allergies and the search was expanded to include animal studies as well. As a result, there is heterogeneity in terms of research design, methodology and characteristics. Still, this enables a more holistic view of the available studies. This review's strength is that inclusion and exclusion criteria were clearly established and consistently applied across all studies. The current review highlights the need for more research in the field.

5. Conclusions

The MD is well-known for its health-promoting and anti-inflammatory properties, as it contains valuable nutrients such as n-3 long chain PUFAs and other fat-soluble micronutrients. Olive oil, polyphenols, and fatty acids are just a few of the many nutritious food components that are prevalent in the MD. Understanding the basic and current information behind the function of food components in allergy may enhance the diagnosis, treatment, and prevention measures utilised for food allergy due to the increasing demand for processed foods in the global market [2]. This review has demonstrated that the food components of the MD appear to have a positive effect on food allergies, but further research studies should be conducted.

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