

Bárbara Fernanda Teixeira de Sousa

Anti-inflammatory diet and rheumatoid arthritis: overview on the current
evidence

Ciências da Nutrição
Faculdade Ciências da Saúde
Universidade Fernando Pessoa
Porto, 2022

Bárbara Fernanda Teixeira de Sousa

Anti-inflammatory diet and rheumatoid arthritis: overview on the current
evidence

Ciências da Nutrição
Faculdade Ciências da Saúde
Universidade Fernando Pessoa
Porto, 2022

Bárbara Fernanda Teixeira de Sousa

Anti-inflammatory diet and rheumatoid arthritis: overview on the current
evidence

Declaro para os devidos efeitos ter atuado com integridade na elaboração deste Trabalho de Projeto, atesto a originalidade do trabalho, confirmo que não incorri em plágio e que todas as frases que retirei de textos de outros autores foram devidamente citadas ou redigidas com outras palavras e devidamente referenciadas na bibliografia.

(Bárbara Fernanda Teixeira de Sousa)

Trabalho apresentado à Universidade Fernando Pessoa como parte dos requisitos para obtenção do grau de licenciado em Ciências da Nutrição.

Orientador:

Professora Doutora Ana Sofia Sousa

Agradecimentos

Agradeço à minha família por todo o apoio que sempre me deram.

Aos meus amigos, por terem estado sempre presentes em todos os momentos, ao longo destes anos de vida académica.

Aos professores pela partilha de conhecimento e experiências.

E ainda um agradecimento em particular à Professora Doutora Ana Sofia Sousa, por todo o apoio, empenho e dedicação na elaboração deste trabalho.

I.Index

II. Figures index.....	III
III. Abbreviations List	IV
IV. Title/authors/academic affiliation	V
V.Abstract.....	VI
VI.Resumo.....	VII
1. Introduction	12
2. Methodology.....	5
3. Anti-inflammatory Diet	5
3.1 Composition of the anti-inflammatory diet	8
3.1.1 Antioxidants	8
3.1.2 Polyunsaturated Fatty Acids.....	8
3.2. Applicability	9
3.3. Limitations	10
4. Discussion.....	12
5. Conclusion.....	15
6. Critical Reflection.....	15
7. References	16
8. Figures/Tables	21

II. Figures index

Figure 1. Flow diagram of the studies included in this review.....	21
Table 1. Summary of the studies included in the review	22

III. Abbreviations List

BMI – Body mass index

CRP – C-reactive protein

CVDs – Cardiovascular diseases

DAS28 – Disease Activity Score Calculator for Rheumatoid Arthritis

EPA n-3 – Eicosapentaenoic acid

ESR – Erythrocyte sedimentation rate

HrQoL – Health-related quality of life

IL-10 – Interleukin-10

MD – Mediterranean diet

MUFA – Monounsaturated fatty acids

PUFAs – Omega-3 polyunsaturated fatty acids

RA – Rheumatoid arthritis

RBP – Retinol-binding protein

SCFA – Short-chain fatty acid

SF-36 v2 – MOS Short Form Health Survey 36 Item v2

Th1 – T-helper type 1

Anti-inflammatory diet and rheumatoid arthritis: overview on the current evidence

Dieta anti-inflamatória e artrite reumatoide: visão geral sobre as evidências atuais

Bárbara Sousa¹; Ana Sofia Sousa²

1. Estudante finalista do 1º ciclo de Ciências da Nutrição da Universidade Fernando Pessoa.

2. Professora auxiliar da Faculdade de Ciências da Saúde da Universidade Fernando Pessoa.

Bárbara Fernanda Teixeira de Sousa

E-mail: 36688@ufp.edu.pt

Faculdade Ciências da Saúde da Universidade Fernando Pessoa

Contagem de Palavras: 6103

Número de Figuras/Tabelas: 2

Número de Referências Bibliográficas: 39

Conflito de Interesses: nada a declarar

V. Abstract

Rheumatoid arthritis (RA) being a chronic autoimmune disease, with symptoms that are characterized by inflammation of the joints, requires pharmacological treatment, however this is not enough to improve the symptoms related to RA, so nutritional intervention is necessary, as a complementary treatment, in order to achieve a significant improvement in symptoms.

In order to understand which diet would bring more benefits to patients with RA, several approaches have been studied, one of them being the anti-inflammatory diet, being it is mainly made up of foods rich in antioxidants, may contribute in a significantly positive in controlling RA symptoms.

Thus, the present study aimed to review the literature existent on the anti-inflammatory diet, in order to understand its applicability, benefits, as well as its limitations.

The literature review was elaborated through a bibliographic search, in the PubMed database, based on the inclusion and exclusion criteria defined according to what was intended for the realization of this review.

Current scientific evidence has shown positive effects of the anti-inflammatory diet in RA patients, especially the reduction of joint pain, disease activity, tender and swollen joints and improved physical functioning.

In conclusion, the anti-inflammatory diet presents beneficial effects on symptoms and disease activity in RA patients. Notwithstanding this, further studies are needed to determine whether the benefits are clinically relevant.

Keywords: Anti-inflammatory diet, Inflammation, Nutrition therapy, Rheumatoid Arthritis

VI. Resumo

A artrite reumatoide (AR) sendo uma doença autoimune crônica, com sintomas que se caracterizam pela inflamação das articulações, necessita de tratamento farmacológico. No entanto o tratamento farmacológico não é suficiente para a melhoria dos sintomas referentes à AR. Deste modo, é necessária a intervenção nutricional, como um tratamento complementar, para assim alcançar uma melhora significativa dos sintomas.

De modo a perceber qual a dieta mais indicada para os doentes com AR, diversas abordagens têm sido estudadas, entre uma das quais a dieta anti-inflamatória, que sendo constituída por alimentos ricos em antioxidantes, poderá contribuir de forma positiva no controlo dos sintomas da AR.

Assim, o presente estudo teve como objetivo realizar uma revisão da literatura acerca da dieta anti-inflamatória, tendo em conta a aplicabilidade, benefícios, além das suas limitações.

A revisão da literatura realizou-se através de uma pesquisa bibliográfica, na base de dados PubMed, tendo por base os critérios de inclusão e exclusão definidos de acordo com o pretendido para a realização desta revisão.

A evidencia científica atual, tem demonstrado efeitos positivos da dieta anti-inflamatória em pacientes com AR, sobretudo a diminuição da dor nas articulações, da atividade da doença, das articulações sensíveis e inchadas e melhor funcionamento físico.

Em conclusão, a dieta anti-inflamatória apresenta efeitos positivos nos sintomas e na atividade da doença, em pacientes com AR. Apesar disso, são necessários mais estudos para determinar se os benefícios são clinicamente relevantes.

Palavras Chave: Artrite Reumatoide, Dieta anti-inflamatória, Inflamação, Terapia Nutricional

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial inflammation, production of autoantibodies, cartilage and bone destruction, malformation and destruction of several joints (1,2). Pain, swelling, stiffness and reduced function in peripheral joints are the most common symptoms, and the main responsible for compromising the quality of life of these patients (2,3).

RA is one of the most common autoimmune diseases, its prevalence varies by geographic region (3,4). The prevalence of RA is higher in Western countries, particularly in North America and Europe where RA affects about 0.5% to 1% of the population, with variation among different populations (2–4). In Portugal the prevalence 0.8% to 1.5%, being more common in women, especially post menopausal women (5).

Genetic and environmental factors are considered the main causes for the development of RA (4). Environmental factors such as smoking, air pollution, diet and viral infections contribute to the development of systemic autoimmunity and the appearance of autoantibodies (4). The association of these factors with genetical predisposition increases the risk of RA (4).

RA pathophysiology involves a pathway of T-cell activation, in the initial phase and progression phases of the disease (1). However, the progression of RA involves a more complex autoimmune response, *i.e.*, RA is associated with CD4+T effector cells (both Th-1, 2, 17), which can be detected in synovial joints, *i.e.*, the expression of CD41 regulatory T cells, produce high levels of interleukin-10 (IL-10), which can induce downregulation of T-cell tolerance and T-helper type 1 (Th1), cell-mediated immune responses, causing the progression of inflammation in RA (1,6).

Eating habits can represent both a risk factor and a protective factor for RA (4). The Western diet is associated with an increased risk of RA, since this dietary pattern is characterized by high intake of red meat, trans and saturated fats, refined carbohydrates and a low proportion of omega-3:omega-6 fatty acids, which may lead to increased inflammation (4). The influence of diet on the development of RA has been widely studied, because specific foods can exert pro-inflammatory effects while other foods may have anti-inflammatory effects (4). In addition, diet also impacts the composition of gut microbiota, *i.e.*, a diet rich in animal protein and saturated fat, contributes to the increase in the concentration of the bacterium *Prevotella copri spp* in the gut microbiota, which in

turn is related to the development of RA, as this bacterium induces Th17-related cytokines, such as IL-6 and IL-23, and increased intestinal permeability (7). Furthermore, high levels of this bacterium in the early stages of RA may be an important mechanism linking dysbiosis to the pathogenesis of RA, hence the importance of diet in the prevention and treatment of this disease, hence the importance of diet in the prevention and treatment of this disease (4,7,8).

The most commonly used strategies in the management of RA are based on pharmacological therapy, with the use of immunosuppressants that aim to prevent or reduce symptoms (2). However, in several cases there is no improvement, with some disabling symptoms prevailing, such as pain and fatigue (2). Besides, although pharmacological treatment has improved substantially in recent decades, there is no cure for RA and most patients need pharmacological treatment throughout their lives (3,5). Furthermore, the drugs used are frequently associated with significant side effects, such as insulin resistance and weight gain, which in turn increases the risk of cardiovascular diseases (CVDs) and general morbidity (6).

RA has been shown to be associated with an impairment of nutritional status of multifactorial etiology (11). Thus, in addition to the classical symptoms that characterize RA, this disease, has also been associated with gastrointestinal disorders, including dyspepsia, *i.e.*, upper abdominal pain, burning, bloating, nausea, belching, postprandial fullness and early satiety, mucosal ulcers and intestinal disorders, namely diarrhea or constipation. In the most severe cases of RA, there also na increased risk of nutritional deficiencies, especially of folic acid, vitamin D, zinc, retinol-binding protein (RBP) and thyroxine-binding prealbumin, frequently caused by disease activity and glucocorticoid therapy (12). Glucocorticoid therapy affects the ingestion, digestion and absorption of food and can also lead to intestinal problems such as irritation, ulcers, acid reflux and even kidney failure (12,13).

The clinical condition of RA patients, particularly at an advanced stage, may lead to the development of malnutrition and in most severe cases, to rheumatoid cachexia (13). Due to the presence of chronic inflammation, patients with RA present metabolic abnormalities, namely hypermetabolism induced by the increase of pro-inflammatory cytokines (13,14). Hypermetabolism combined with decreased physical activity causes an increase in nutritional needs, as well as a diminished fat-free mass and increased body

fat mass (13,14). Nevertheless, RA patients do not necessarily present weight loss or loss of fat mass, which is why BMI changes are not always observed (13,14). Therefore, it may not fit into the diagnostic criteria of cachexia, hence a unique abnormal metabolic state called rheumatoid cachexia (14).

Rheumatoid cachexia usually runs in parallel with an increase in body fat mass, which in many cases results in a normal or even above-normal BMI, because the increase in body fat mass often masks a reduction in fat-free mass (11,13,14).

Although the use of more effective therapies to control inflammation has reduced the incidence of rheumatoid cachexia, there is still a high risk of impairment of nutritional status in RA patients (11).

Malnutrition has been shown to reduce the quality of life of these patients and their resistance to infections, as well as increase the risk of morbidity, hospitalization and even mortality (13). In the case of hospitalized patients, 1 out of 3 RA patients can be at nutritional risk (13).

Thus, adequate control of disease activity in combination with physical exercise and nutritional intervention, can be an important strategy to manage rheumatoid cachexia and related metabolic problems (12,14).

As a form of additional treatment to pharmacological therapy, nutritional intervention has been studied, in order to understand what type of diet can bring benefits to these patients, such as symptom relief with minimal side effects (5).

Diet can alleviate RA symptoms by interfering with patients metabolic profile and increasing antioxidant levels, but it can also alter gut microbiota, which in turn has the potential to modify pro-inflammatory or anti-inflammatory mediators (2). Among the nutrients that have demonstrated benefits, *i.e.*, that decrease the degree of inflammation and relieve symptoms, are omega-3 polyunsaturated fatty acids (PUFAs), monounsaturated fatty acids (MUFAs), flavonoids, antioxidants and vitamin D (2,5).

RA patients frequently associate the consumption of some foods with the worsening of symptoms (15). Therefore, they tend to eliminate these foods from their diet (15). Elimination diets are often implemented by these patients (15). Foods such as meat, fish, eggs, cottage cheese, beans, rice, peas, chickpeas, as well the “nightshades”, *i.e.*, foods that contain solanine, such as tomato, potato, eggplant and peppers are often eliminated from daily diet (15,16). It is worth noticing that most of these dietary

restrictions are empirical and not based on scientific evidence (15,16). Moreover, these strategies may even lead to unbalanced dietary patterns (15).

A number of dietary interventions have been studied as potentially beneficial in the treatment of RA include the elimination or fasting diet, the vegetarian diet, the gluten-free diet, the Mediterranean diet (MD) and the anti-inflammatory diet (6).

A consistent body of evidence demonstrated that MD, together with other genetic and other environmental factors, may contribute to a lower incidence of RA in Southern Europe compared to Northern Europe and North America (4). Due to the similarity of the anti-inflammatory diet with MD, and because it has potential benefits in RA, the possible beneficial association of this diet with RA began to be studied (17,18).

Fasting or caloric restriction can improve some of the symptoms of RA and even disease activity, especially through total fasting for specific periods, however this dietary strategy is unsustainable or even impossible in some cases, and therefore its implementation is not recommended (10).

Vegetarian and vegan diets, consisting mainly of fruits, grains and vegetables, have shown very individualized responses, and improvements can be seen especially in morning stiffness and reduction in concentrations of C-reactive protein (CRP), in addition to this, the benefits can still be seen be related to the reduction of immune responses to food allergens in the gut microbiota or the reduction of meat-induced intestinal inflammation (10). These benefits may be due to the presence of antioxidants, lactobacillus, fiber and possible changes in the microbiota (19).

The Mediterranean diet is a balanced and nutritionally adequate diet, characterized by the consumption of plant foods such as unrefined cereals, fruit, vegetables, legumes, and extra-virgin olive oil, moderate consumption of poultry, dairy products, eggs, low consumption of sweets and red meat (1,3,20). Evidence has shown a positive association in the reduction of disease activity, pain, morning stiffness and even improvements in physical function and vitality, there are still beneficial effects in decreasing the risk of CVDs, and it also provides a secondary benefit of decreasing the future complications of the disease (10,21–23).

The anti-inflammatory diet is based on the principles of MD, consisting of foods rich in antioxidants, polyphenols, carotenoids, PUFAs, low glycemic index foods, and the use of extra virgin olive oil as the main source of fat (18). In addition, this diet promotes low consumption of refined carbohydrates, foods rich in trans fat and saturated fat, sugary drinks, alcoholic beverages, red and processed meat (18).

The aim of this literature review is to analyze the implementation, applicability, benefits, as well as limitations of the anti-inflammatory diet in RA.

2. Methodology

To collect the information necessary for this literature review, a literature search was carried out using the PubMed database. The search term used was: “((inflammation AND diet*) OR anti-inflammatory diet) AND (Arthritis, Rheumatoid OR rheumatoid arthritis)”. In order to obtain specific publications for this review, inclusion criteria publications from the last 10 years, studies in adults, anti-inflammatory diet and RA, as exclusion criteria were established, studies in animals, supplements other than diet, other diets and other pathologies other than RA.

A total of 234 articles was found, of which 216 articles were excluded, because of not complying with the inclusion criteria.

Finally, 18 articles were selected. Through the bibliographic references of the selected articles, it was possible to obtain 9 more articles as a result of snowball research.

The flowchart displayed in figure 1 represents the process of selection of the articles included in the present literature review.

3. Anti-inflammatory Diet

The anti-inflammatory diet, has been recently studied and has been associated with positive effects in improving the symptoms of RA, namely of sensitive and swollen joints, physical function, pain, weight loss and in the reduction of disease activity (2,3,9,18,24–27). These positive effects are associated with the abundance of nutrients such as antioxidants, fiber, vitamins and minerals, with anti-inflammatory properties, which can have an impact on inflammatory processes and thereby improve symptoms (27). Therefore, there is a reduction of oxidative stress, inflammatory cytokines levels and the fiber exerts effects on gut microbiota, *i.e.*, increases Short-chain fatty acid (SCFA) producing bacteria, which in turn has benefits in the structure of the intestinal barrier (27).

The results of the studies included in this review are summarized in Table 1.

Vadell et al. (2020) in a single-blinded controlled crossover trial, participants aged 18-75 years, with disease duration ≥ 2 years, were randomly assigned to the intervention

group (anti-inflammatory diet) and control group (control diet). After a 4 month washout period, the diet was switched (2).

The intervention consisted of an anti-inflammatory diet, constituted by foods with potential anti-inflammatory effects (2). The main foods composing this diet were fish, vegetables, potatoes, whole grains, fruit such as pomegranate and blueberries and low-fat dairy products (2). Participants during the study received weekly food to prepare breakfast, 1 snack, and 1 main dish, for the meals not provided, participants in the intervention group were instructed to limit meat intake to a maximum of 3 times a week, and eat ≥ 5 servings of fruit and vegetables, particularly berries, low-fat dairy products, and whole grains (2). Both diets provided the same amount of energy and carbohydrates, relative to fat, the intervention diet provided mainly unsaturated fat, while the control diet provided mainly saturated fat, in addition this diet provided lower amounts of protein in contrast to the control diet (2).

Disease Activity Score Calculator for Rheumatoid Arthritis (DAS28) was applied at the screening visit, blood samples were collected for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), during the intervention, fasting blood samples were collected, before and after each period of the diet, so after the intervention period, there was a significant reduction in disease activity (median: 3.05; IQR: 2.41; $P = 0.04$) (2). There were no significant differences for tender and swollen joints, yet in this study 56% of participants showed improvement in joint pain after the intervention period (2).

The authors concluded, through their main analyses, that the reduction in disease activity after intervention was neither significant nor clinically relevant. However, the improvements that occurred during the intervention period, as well as in the final results of the two diet periods, were significant (2). Thus, the study indicates positive effects of the anti-inflammatory diet as a complementary therapy to pharmacological therapy in patients with RA (2).

Hulander et al. (2021) in the randomized controlled crossover trial, patients with RA also showed a significant decrease in TNFSF14. This is important because this protein induces osteoclasts that promote bone destruction in RA (3). Another aspect to consider is weight loss, which is seen in overweight or obese patients who implement this diet, because weight loss in these patients can reduce inflammation associated with excess adipose tissue (18,25).

Another aspect that significantly improved was physical functioning, Wadell, A et al. (2021) in the controlled crossover study, 50 RA patients were randomized to start

an anti-inflammatory diet and a control diet, with the aim of evaluating whether an anti-inflammatory diet improves the health-related quality of life (HrQoL) of these patients (24). Through evaluation with the standard form MOS Short Form Health Survey 36 Item v2 (SF-36 v2), they found a significant improvement in physical functioning after intervention with an anti-inflammatory diet (24).

Bustamante, M et al. (2020) in an observational study, with the objective of developing an adequate diet for RA patients, which included foods with anti-inflammatory properties, consisted of 4 phases, in phase I they evaluated the dietary habits of patients, in phase II gathered information on patient knowledge, accessibility and food preferences, of the proposed ingredients, in phase III they developed a diet proposal and evaluated the acceptability and ability to understand the implementation of the diet, finally in phase IV the diet was implemented during 7 days, after patient feedback, adjustments were made (9). They found that the applicability of this diet consisting of foods with anti-inflammatory properties had a high adherence by RA patients (9).

Tedeschi, S et al. (2017) in the prospective longitudinal study, in a sample of 300 RA patients, evaluated how foods affect RA symptoms, through a list of 20 foods, patients reported which of these foods worsened, improved, or did not change your symptoms (26). Through this study, the authors found that 24.0% of individuals reported that at least one food affected their symptoms, with foods only worsening RA in 9.2% of subjects and foods only improving RA in 4.6 % (26).

In these mentioned studies, they found that, some foods may be pro-inflammatory and others may have anti-inflammatory properties, which in turn can have a positive or negative impact on RA symptoms (9,26,27). Patients with RA report that some specific foods cause their symptoms to worsen, while when they eat others, they experience an improvement in their symptoms, which allows us to verify an association between specific foods and RA symptoms (9,26,27).

The most mentioned foods associated with the improvement of symptoms are blueberries, strawberries, fish and spinach, this is justified because they are rich in antioxidants, vitamins and minerals, which have anti-inflammatory properties, thus having an influence on reducing inflammation (9,26). Other foods, such as red meat, soft drinks, and sweet desserts, because they are high in sugar aggravate RA symptoms (9,27). Taking into account the foods mentioned by these patients, it appears that the anti-inflammatory diet may meet their needs, because this diet includes foods referred to as beneficial and reduces/excludes foods associated with worsening symptoms (2).

3.1 Composition of the anti-inflammatory diet

The anti-inflammatory diet is based on the Mediterranean diet and as such consists in abundance of fruit, vegetables, legumes, whole grains, olive oil as the main source of fat, a moderate amount of fish, meat and dairy products and low consumption of red meat, processed foods, foods high in saturated fat, sugary drinks and alcohol (18,21). This is reflected in a diet rich in some nutrients and bioactives with anti-inflammatory properties, such as antioxidants, polyphenols, carotenoids, flavonoids, PUFA, MUFA, phytochemicals and vitamin D (9,18,21).

3.1.1 Antioxidants

In RA there is a marked increase in oxidative stress, that is, patients with RA demonstrate an increase in the formation of reactive oxygen species, lipid peroxidation and protein oxidation (28).

The effects of antioxidants on disease activity in RA have been studied. In three studies comparing the effect of antioxidants with placebo, the intervention with antioxidants consisted of providing each participant with 1200 mg/d of alpha lipolic acid, 500 mg/d of quercetin, 1 g/d of resveratrol and 100 mg/d of ubiquinone, the results of these studies showed that alpha lipolic acid had no effect on reducing disease activity, however, quercetin showed beneficial effects, and in relation to resveratrol there was an improvement in sensitive and swollen joints, the same was verified with ubiquinone, this in patients with intermediate to high disease activity (29–32).

3.1.2 Polyunsaturated Fatty Acids

PUFAS, due to their anti-inflammatory properties, can reduce the risk of developing RA, through the synthesis of eicosanoids, *i.e.*, eicosapentaenoic acid (EPA n-3) being a homologue of arachidonic acid, acts as a competitive substrate for the same enzymes, cyclooxygenase and lipoxygenase, giving rise to anti-inflammatory eicosanoids (33). In addition, non-classical eicosanoids derived from PUFAS, such as resolvins, protectins and lipoxins, function as mediators that allow pain suppression, so eicosanoids not only reduce the risk of developing RA, but also already in their presence they allow to reduce the pain caused by it (34).

PUFAS from fatty fish can act as a competitive substrate with arachidonic acid for cyclooxygenase, lipoxygenase, and cytochrome P450 enzymes, producing less inflammatory eicosanoids (3). In certain fish, the PUFAs present influence the functions of lymphocytes and monocytes, which regulate inflammatory pathways in chronic inflammatory diseases, such as RA, thus verifying a significant reduction of inflammatory biomarkers, such as IL-6 (27).

Studies also show that PUFAS significantly reduce disease activity, with improvements in tender joint counts and a decrease in morning stiffness, this improvement in symptoms is mainly due to the reduction of inflammation through increased autophagy in macrophages (10,27,35–37).

Giuseppe, D et al. (2013) in a prospective cohort study, with a sample of 205 women with RA, showed that a daily intake of PUFAS higher than 0.21g reduces the risk of developing RA by 35%, however, if the intake is long-term, the risk decreases by 52%, the same was not true with an intake of 0.21g or less (33). If the intake of PUFAS is through the consumption of ≥ 1 serving of fish per week it is found to be associated with a 29% decrease in risk (33).

3.2. Applicability

The implementation of this diet may require a change in dietary habits, however it does not involve extreme food restrictions, which can increase compliance (2). The importance of this diet in complementary treatment to pharmacological therapy is due to the anti-inflammatory and protective properties of the main nutrients present in the foods that constitute it (2). For the anti-inflammatory diet to be as beneficial as possible, before its implementation it is important to know the eating habits of these patients, to understand which foods they are most exposed to and, therefore, make the necessary changes, that is, restricting foods that are not part of the anti-inflammatory diet, being those that have been shown to worsen RA symptoms, and including those that are part of it, which are those that have been shown to have benefits (9).

According to Bustamante M.F. et al. (2020) in a sample of thirty-four patients with RA, identified dairy products, mainly yogurts, simple carbohydrates such as cakes and cookies, vegetables such as lettuce and onions, and fruits, mainly peaches, nectarines, as the most consumed foods apricots, oranges, apples and pears, on the contrary, it was

found that they did not usually consume seeds, however, in general, the amount of consumption, as well as the type of meat, fish, eggs, grains, vegetables and fruits, does not differ much from the anti-inflammatory diet (9).

Some foods such as red meat, soft drinks, cheese, milk, sweet desserts, coffee and alcohol, that is, refined carbohydrates, foods rich in trans and saturated fats worsen the symptoms of RA, so they should be excluded or minimized, on the contrary, fruit, fish, whole grains and vegetables should be included in the diet of these patients (2,18,26,32). As the anti-inflammatory diet is based on the principles of the Mediterranean diet, it emphasizes the consumption of whole grains, fresh or dried fruits and vegetables (5 portions/day), the consumption of frequent use of olive oil as the main fat, and moderate consumption of fish, giving preference to fatty fish, meat, with a maximum consumption of 3 times a week, and low-fat dairy products (18,21,24).

The distribution of these foods in the meals can be done as follows, for breakfast and snacks include low-fat dairy products or vegetable drinks, whole grains and fruits or berries, lunch and dinner should consist of fish or meat, legumes, vegetables, whole grains and fruit, and using olive oil as the main source of fat (9,24).

In order to have a good compliance to this diet, it is also necessary to understand if the patient has access to the proposed foods, as a rule most foods are already known and even consumed by this population, which makes its implementation easier, in addition to that there is a good acceptability in substitute refined grains for whole grains, trans fatty acids and saturated fatty acids for PUFA and MUFA and soft drinks for natural juices (9).

To ensure that patients follow the recommendations, it is essential to provide all the necessary guidelines and clarifications, namely the foods to be included and excluded, what are their characteristics and, therefore, the reason why their exclusion or inclusion is important for the relief of symptoms (9).

3.3. Limitations

Despite the benefits demonstrated by current evidence, adverse effects were also observed in some patients during the intervention periods with the anti-inflammatory diet, namely stomach ache, gas, diarrhea, heartburn and nausea, these effects may be caused by increased fiber intake compared to intake previous to the intervention (2,3,24,27).

Furthermore, in some studies there were no significant improvements or improvements in RA, but this may be due to the limitations presented in these studies (2,3,24,27).

One of the limitations of the studies verified was the intervention time, having been found in one of the studies that a longer intervention period, namely more than 3 months, allows greater effects, however another study showed that in an intervention period of 2-4 months, the results demonstrated that the said anti-inflammatory contributes to the reduction of anti-inflammatory biomarkers, turn out to be of low quality, according to the same, the ideal intervention period would be between 4-6 months, in this period the results would be more significant for physical improvement, pain and health in general (18,25). Furthermore, all studies included in the meta-analysis by Katja A. et al. (2021) present a high risk of bias in the domain measurement of outcome, since it was not possible to blind the diathetic intervention, it is also verified that, having been the level of self-reported pain, makes it subjective and, therefore, can generate bias, in relation to objectively measured secondary outcomes, all studies had some concerns, since there was no information whether the results were analyzed accordingly with a pre-specific analysis plan (25).

Other variables that may have caused bias in the results of the studies were the sample size, which in most interventions was small, in one of the studies only specific foods were evaluated, as such eating patterns and their relation with the symptoms of the disease were not evaluated and the participants in that same study were highly educated and predominantly white, leading to the fact that the results of the study cannot be generalized (2,26).

Genel F. et al. (2020) reports that as most dietary interventions were only a simulation of an anti-inflammatory diet and did not involve a nutritionist, the validity of dietary therapy may be questionable (18).

Therefore, in randomized clinical trials, in relation to the primary outcome of pain, some studies showed some concerns about potential bias in relation to the randomization process, intervention deviations and in the selection of reported results and a high risk of bias in relation to the measurement of results (25). In non-randomized studies, there was a moderate risk of bias in the selection of participants and classification of the intervention, and a very high risk of bias in the measurement of results and general bias (25). In randomized and prospective studies, there is a low-quality of evidence regarding

the association of the anti-inflammatory diet with the reduction of inflammatory biomarkers, joint pain and improvement physical function, compared to other diets (18).

4. Discussion

Currently, the main treatment for RA consists of drug therapy, namely immunosuppressants (9). Although pharmaceutical advances are contributing to the improvement of the treatment of RA, most patients need this therapy throughout their lives, in addition to the fact that it is not enough to relieve all symptoms and still have side effects, compromising even more the quality of life of these patients (2).

In this sense, most patients look for therapies that are complementary to drug therapy, because they feel the need to alleviate the symptoms that still prevail, as well as the side effects caused by the drugs (3). These patients often ask for specific dietary advice, or they start themselves begin to make changes to their diet when they notice that certain foods worsen and others improve their symptoms (3,9).

In fact, studies have shown that food can act as environmental triggers in genetically susceptible individuals, which can lead to the development of RA, that is, the resulting inflammatory process encompasses a cascade of events, as well as the production of cytokines and chemokines by the joint tissue cells, causing joint damage and inflammation with increased CRP (10).

Notwithstanding this, special attention should be paid to patients who make these changes autonomously and without scientific basis, since patients with RA have a impairment of nutritional status, particularly those in an advanced stage, in which malnutrition and namely rheumatoid cachexia, even with the use of more effective therapies, this impairment of nutritional status is verified in most cases (10,21,25). In addition, eviction diets and the elimination of nightshades from the diet, which RA patients often do, without any follow-up or recommendation from a health professional, contribute to the development of unbalanced diets, thus increasing impairment nutritional status and clinical status (10).

After verifying this need and searching for diets that contribute to the relief of symptoms and better quality of life for these patients, several studies began to be carried out with the aim of identifying foods with a possible positive association between diet and RA, in this sense the most studied dietary approaches today are the Mediterranean

diet, vegetarian/vegan diets, elimination or fasting diets, and the anti-inflammatory diet (10).

According to evidence, the different components of the diet may be related to different beneficial effects on RA, that is, a high intake of fruits, vegetables, nuts and seeds, containing phytochemicals, can attenuate oxidative stress, which in turn could reduce inflammatory activity, in addition the antioxidants present in fruits and vegetables, contribute to the reduction of oxidative stress levels and protect against the development of free radicals, preventing inflammation as well as the symptoms of RA (3,27,32).

The use of foods/dietary patterns and isolated nutrients have different effects, *i.e.*, a dietary pattern being constituted by a set of foods that in turn are constituted by several nutrients, these nutrients together have more beneficial effects, this is because these substances exert influences one over the other and can potentiate their effects, the same does not happen with the use of isolated nutrients (32).

Supplementation with n-3 fatty acids has been shown to reduce inflammatory markers such as CRP, IL-6 and TNF levels, as well as pain, however there are still contradictory results regarding the benefits of n-3 fatty acid supplementation, thus these should not be used in the treatment of RA (27,32,34). It also appears that the anti-inflammatory diet, rich in PUFAS in combination with omega-3 supplementation, may be ineffective, despite doses of n-3 fatty acids unattainable with diet alone, omega-3 supplementation will only contribute a very small portion of daily fat intake (27).

The use of antioxidant supplements has shown beneficial effects in RA, however it also shows adverse effects and the safety of long-term high dose intake is uncertain, as such the intake of antioxidants proves to be more beneficial and safer through foods rich in this nutrient inserted on a diet, such as the anti-inflammatory diet (32).

With this, the effects of an isolated food are not the same as a dietary pattern or the effects of a supplement are also not the same as a nutrient inserted in a food matrix (3,27,32,34).

It should also be considered that, as this is a nutritionally adequate diet which does not require many food restrictions, it also allows weight reduction, namely in fat mass (18,24). Fat mass reduction may contribute to decrease inflammation that results from adipose tissue (18,25).

Implementation of anti-inflammatory diet as it does not require drastic change in the dietary habits of these patients (9). Which increases compliance (9).

Nevertheless, frequent monitoring is essential to optimize the intervention (9).

Taking into account all the diets studied so far, the association between diet, microbiota and gut permeability has been shown to be related to the inflammatory response induced by intestinal dysbiosis (imbalances in the composition and function of these gut microbes), contributing to the development of rheumatic diseases (7,10,38,39). According to experimental and clinical evidence, a chronic inflammatory response induced by intestinal dysbiosis, which contributes to the development of RA (7). In addition to contributing to the development of this disease, it also contributes to its progression, RA patients with fail to maintain the correct balance between beneficial and potentially harmful bacteria, a critical role has been attributed mainly to the increase in concentration of *Prevotella copri spp* in the gut microbiota, as it seems to be related to the onset and severity of RA (8,22). Thus, reduced concentrations of this have been shown to improve disease activity (8).

In order to reduce this bacterium, it is important to consider the diet of these patients, because the diet has an influence on the increase or reduction of its concentration (7).

The increase in the concentration of this bacteria may be related to a diet rich in fat and animal protein (7). Thus, studies have shown that diet can directly affect the immune response, stimulating or inhibiting inflammatory processes, due to food-derived molecules interacting with the gastrointestinal epithelial barrier, mucosal immune system and gut microbiota, and provoke local and systemic modifications (8). Fiber has an important impact on the microbiota, that is, diets rich in this nutrient increase SCFA producing bacteria, which in turn has benefits on intestinal barrier structure (7).

Evidence also demonstrates that dietary therapy can improved well-being and decrease psychological distress (10).

In addition to the benefits described by the studies included in this review, most of them have some limitations (2,18,25,26).

There is a lack of more high-quality studies investigating the effects of an anti-inflammatory diet on RA, namely whether a diet with anti-inflammatory foods can be a complement to pharmacological therapy and whether it contributes to the reduction of symptoms (2).

5. Conclusion

In conclusion, the anti-inflammatory diet is beneficial as a complementary treatment of RA, namely in reducing disease activity, tender and swollen joints, pain, and inflammatory biomarkers, as well as improving physical function. Notwithstanding this, it should be taken into account that the results of the studies included in this review showed some inconsistencies, thus requiring high-quality studies to verify that this dietary approach is indeed important to include in the treatment of RA.

However, it should be taken into account that scientific research on the benefits of this diet is still recent, and there is a need for better quality studies in order to draw more effective conclusions and recommendations.

6. Critical Reflection

Nutritionists have a fundamental role in monitoring RA patients, whether in the implementation of beneficial strategies in the treatment of RA, but also for an adequate nutritional status, which is often compromised. Through the current evidence, it is possible to implement a nutritional intervention that guarantees a complete, balanced and varied diet, namely through the anti-inflammatory diet, thus ensuring the reduction of the severity of the symptoms of RA, as well as meeting the nutritional needs of these patients.

According to the current literature, the anti-inflammatory diet may be useful for application in clinical practice. For the implementation of this diet, it is important to take into account not only the clinical status of these patients, but also their usual dietary pattern, clinical history, nutritional status, tolerance, and the predisposition to adhere to it, since the greater the adherence, the greater the success of the nutritional intervention. In this way, the nutritional education is essential for a better intervention.

7. References

1. Rondanelli M, Perdoni F, Peroni G, Caporali R, Gasparri C, Riva A, et al. Ideal food pyramid for patients with rheumatoid arthritis: A narrative review. *Clinical Nutrition*. 2021 Mar;40(3):661–89.
2. Vadell AKE, Bärebring L, Hulander E, Gjertsson I, Lindqvist HM, Winkvist A. Anti-inflammatory Diet In Rheumatoid Arthritis (ADIRA)—a randomized, controlled crossover trial indicating effects on disease activity. *Am J Clin Nutr*. 2020 Jun 1;111(6):1203–13.
3. Hulander E, Bärebring L, Turesson Wadell A, Gjertsson I, Calder PC, Winkvist A, et al. Proposed Anti-Inflammatory Diet Reduces Inflammation in Compliant, Weight-Stable Patients with Rheumatoid Arthritis in a Randomized Controlled Crossover Trial. *J Nutr*. 2021 Dec 3;151(12):3856–64.
4. Gioia C, Lucchino B, Tarsitano MG, Iannuccelli C, di Franco M. Dietary Habits and Nutrition in Rheumatoid Arthritis: Can Diet Influence Disease Development and Clinical Manifestations? *Nutrients*. 2020 May 18;12(5):1456.
5. Artrite Reumatóide - Sociedade Portuguesa de Reumatologia [Internet]. [cited 2022 Sep 6]. Available from: <https://spreumatologia.pt/artrite-reumatoide/>
6. Yudoh K, Matsuno H, Nakazawa F, Yonezawa T, Kimura T. Reduced expression of the regulatory CD4+ T cell subset is related to Th1/Th2 balance and disease severity in rheumatoid arthritis. *Arthritis Rheum*. 2000 Mar;43(3):617.
7. Guerreiro CS, Calado Â, Sousa J, Fonseca JE. Diet, Microbiota, and Gut Permeability—The Unknown Triad in Rheumatoid Arthritis. *Front Med (Lausanne)*. 2018 Dec 14;5.
8. Paolino S, Pacini G, Patanè M, Alessandri E, Cattelan F, Goegan F, et al. Interactions between microbiota, diet/nutrients and immune/inflammatory response in rheumatic diseases: focus on rheumatoid arthritis. *Reumatologia/Rheumatology*. 2019;57(3):151–7.
9. Bustamante MF, Agustín-Perez M, Cedola F, Coras R, Narasimhan R, Golshan S, et al. Design of an anti-inflammatory diet (ITIS diet) for patients with rheumatoid arthritis. *Contemp Clin Trials Commun*. 2020 Mar;17:100524.

10. Philippou E, Petersson SD, Rodomar C, Nikiphorou E. Rheumatoid arthritis and dietary interventions: systematic review of clinical trials. *Nutr Rev.* 2021 Mar 9;79(4):410–28.
11. Reina D, Gómez-Vaquero C, Díaz-Torné C, Solé JMN. Assessment of nutritional status by dual X-Ray absorptiometry in women with rheumatoid arthritis. *Medicine.* 2019 Feb;98(6):e14361.
12. Tański W, Wójciga J, Jankowska-Polańska B. Association between Malnutrition and Quality of Life in Elderly Patients with Rheumatoid Arthritis. *Nutrients.* 2021 Apr 12;13(4):1259.
13. Olsen MN, Tangvik RJ, Halse AK. Evaluation of Nutritional Status and Methods to Identify Nutritional Risk in Rheumatoid Arthritis and Spondyloarthritis. *Nutrients.* 2020 Nov 21;12(11):3571.
14. Masuko K. Rheumatoid Cachexia Revisited: A Metabolic Co-Morbidity in Rheumatoid Arthritis. *Front Nutr.* 2014 Nov 24;1.
15. Kianifard T, Chopra A. In the absence of specific advice, what do patients eat and avoid? Results from a community based diet study in patients suffering from rheumatoid arthritis (RA) with a focus on potassium. *Clin Nutr ESPEN.* 2018 Dec;28:214–21.
16. 10 Arthritis Food Myths [Internet]. [cited 2022 Sep 6]. Available from: <https://www.arthritis.org/health-wellness/healthy-living/nutrition/anti-inflammatory/10-arthritis-food-myths>
17. Johansson K, Askling J, Alfredsson L, di Giuseppe D. Mediterranean diet and risk of rheumatoid arthritis: a population-based case-control study. *Arthritis Res Ther.* 2018 Dec 9;20(1):175.
18. Genel F, Kale M, Pavlovic N, Flood VM, Naylor JM, Adie S. Health effects of a low-inflammatory diet in adults with arthritis: a systematic review and meta-analysis. *J Nutr Sci.* 2020 Aug 27;9:e37.
19. Badsha H. Role of Diet in Influencing Rheumatoid Arthritis Disease Activity. *Open Rheumatol J.* 2018 Feb 8;12(1):19–28.
20. Vranou P, Gkoutzourelas A, Athanadou D, Zafiriou E, Grammatikopoulou MG, Bogdanos DP. Let Food Be Thy Medicine: The Case of The Mediterranean Diet in Rheumatoid Arthritis. *Mediterr J Rheumatol.* 2020;31(3):325.

21. Forsyth C, Kouvari M, D’Cunha NM, Georgousopoulou EN, Panagiotakos DB, Mellor DD, et al. The effects of the Mediterranean diet on rheumatoid arthritis prevention and treatment: a systematic review of human prospective studies. *Rheumatol Int.* 2018 May 18;38(5):737–47.
22. Picchianti Diamanti A, Panebianco C, Salerno G, di Rosa R, Salemi S, Sorgi ML, et al. Impact of Mediterranean Diet on Disease Activity and Gut Microbiota Composition of Rheumatoid Arthritis Patients. *Microorganisms.* 2020 Dec 14;8(12):1989.
23. Raad T, George E, Griffin A, Larkin L, Fraser A, Kennedy N, et al. A randomised controlled trial of a Mediterranean Dietary Intervention for Adults with Rheumatoid Arthritis (MEDRA): Study protocol. *Contemp Clin Trials Commun.* 2022 Aug;28:100919.
24. Turesson Wadell A, Bärebring L, Hulander E, Gjertsson I, Hagberg L, Lindqvist HM, et al. Effects on health-related quality of life in the randomized, controlled crossover trial ADIRA (Anti-inflammatory Diet In Rheumatoid Arthritis). *PLoS One.* 2021 Oct 14;16(10):e0258716.
25. Schönenberger KA, Schüpfer AC, Gloy VL, Hasler P, Stanga Z, Kaegi-Braun N, et al. Effect of Anti-Inflammatory Diets on Pain in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. *Nutrients.* 2021 Nov 24;13(12):4221.
26. Tedeschi SK, Frits M, Cui J, Zhang ZZ, Mahmoud T, Iannaccone C, et al. Diet and Rheumatoid Arthritis Symptoms: Survey Results From a Rheumatoid Arthritis Registry. *Arthritis Care Res (Hoboken).* 2017 Dec;69(12):1920–5.
27. Raad T, Griffin A, George ES, Larkin L, Fraser A, Kennedy N, et al. Dietary Interventions with or without Omega-3 Supplementation for the Management of Rheumatoid Arthritis: A Systematic Review. *Nutrients.* 2021 Oct 4;13(10):3506.
28. Mateen S, Moin S, Shahzad S, Khan AQ. Level of inflammatory cytokines in rheumatoid arthritis patients: Correlation with 25-hydroxy vitamin D and reactive oxygen species. *PLoS One.* 2017 Jun 8;12(6):e0178879.
29. Khojah HM, Ahmed S, Abdel-Rahman MS, Elhakeim EH. Resveratrol as an effective adjuvant therapy in the management of rheumatoid arthritis: a clinical study. *Clin Rheumatol.* 2018 Aug 3;37(8):2035–42.

30. Nachvak SM, Alipour B, Mahdavi AM, Aghdashi MA, Abdollahzad H, Pasdary Y, et al. Effects of coenzyme Q10 supplementation on matrix metalloproteinases and DAS-28 in patients with rheumatoid arthritis: a randomized, double-blind, placebo-controlled clinical trial. *Clin Rheumatol*. 2019 Dec;38(12):3367–74.
31. Javadi F, Ahmadzadeh A, Egtesadi S, Aryaeian N, Zabihyeganeh M, Rahimi Foroushani A, et al. The Effect of Quercetin on Inflammatory Factors and Clinical Symptoms in Women with Rheumatoid Arthritis: A Double-Blind, Randomized Controlled Trial. *J Am Coll Nutr*. 2017;36(1):9–15.
32. Nelson J, Sjöblom H, Gjertsson I, Ulven SM, Lindqvist HM, Bärebring L. Do Interventions with Diet or Dietary Supplements Reduce the Disease Activity Score in Rheumatoid Arthritis? A Systematic Review of Randomized Controlled Trials. *Nutrients*. 2020 Sep 29;12(10):2991.
33. di Giuseppe D, Wallin A, Bottai M, Askling J, Wolk A. Long-term intake of dietary long-chain n-3 polyunsaturated fatty acids and risk of rheumatoid arthritis: a prospective cohort study of women. *Ann Rheum Dis*. 2014 Nov;73(11):1949–53.
34. Lourdudoss C, di Giuseppe D, Wolk A, Westerlind H, Klareskog L, Alfredsson L, et al. Dietary Intake of Polyunsaturated Fatty Acids and Pain in Spite of Inflammatory Control Among Methotrexate-Treated Early Rheumatoid Arthritis Patients. *Arthritis Care Res (Hoboken)*. 2018 Feb 29;70(2):205–12.
35. Gioxari A, Kaliora AC, Marantidou F, Panagiotakos DP. Intake of ω -3 polyunsaturated fatty acids in patients with rheumatoid arthritis: A systematic review and meta-analysis. *Nutrition*. 2018 Jan;45:114-124.e4.
36. Rajaei E, Mowla K, Ghorbani A, Bahadoram S, Bahadoram M, Dargahi-Malamir M. The Effect of Omega-3 Fatty Acids in Patients With Active Rheumatoid Arthritis Receiving DMARDs Therapy: Double-Blind Randomized Controlled Trial. *Glob J Health Sci*. 2015 Nov 3;8(7):18.
37. Veselinovic M, Vasiljevic D, Vucic V, Arsic A, Petrovic S, Tomic-Lucic A, et al. Clinical Benefits of n-3 PUFA and γ -Linolenic Acid in Patients with Rheumatoid Arthritis. *Nutrients*. 2017 Mar 25;9(4):325.
38. Dourado E, Ferro M, Sousa Guerreiro C, Fonseca JE. Diet as a Modulator of Intestinal Microbiota in Rheumatoid Arthritis. *Nutrients*. 2020 Nov 14;12(11):3504.

39. Lynch S v., Pedersen O. The Human Intestinal Microbiome in Health and Disease. *New England Journal of Medicine*. 2016 Dec 15;375(24):2369–79.

8. Figures/Tables

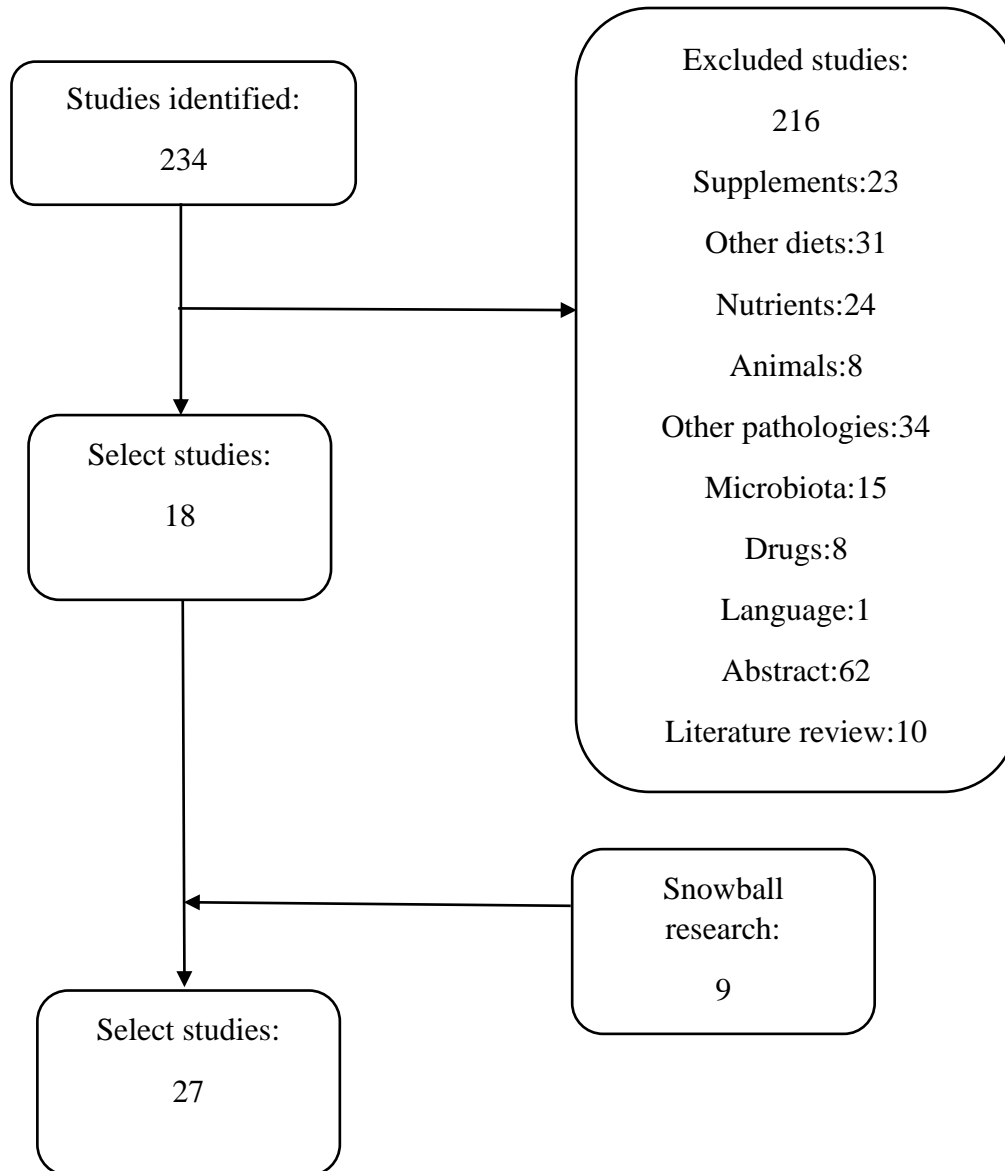


Figure 1. Flow diagram of the studies included in this review.

Table 1. Summary of the studies included in the review

Author and Year	Study design	Sample	Results
Vadell, A et al. (2020)	Randomized controlled crossover trial	50 participants with RA, 47 completed ≥ 1 diet period and 44 completed both diet periods	The DAS28-ESR of the participants significantly decreases after the intervention
Hulander, E et al. (2021)	Randomized controlled crossover trial	50 RA participants (18-75 years old) and with at least 2 years of disease duration	After the two diet periods, there was a significant effect on disease activity Reduced the systemic inflammation in patients with RA that had a high compliance to the dietary intervention
Bustamante, M et al. (2020)	Randomized controlled crossover trial	30 RA patients who meet the 2010 ACR/EULAR classification criteria for RA	High adherence of RA patients to a diet that includes a high intake of potentially anti-inflammatory foods
Genel, F et al. (2020)	Systematic review and meta-analysis	5 randomised and 2 prospective trials involving 468 participants with either osteoarthritis or rheumatoid arthritis	Very low quality evidence indicates that the anti-inflammatory diet is associated with decreased inflammation, improved physical function, reduced joint pain and weight loss
Wadell, A et al. (2021)	Randomized controlled crossover trial	50 RA patients (18 to 75 years), with a disease duration of at least 2 years	Significant improvements in physical functioning

Schönenberger, K et al. (2021)	Systematic review and meta-analysis	7 randomized clinical trials, involving 326 participants	A decrease in the subjective pain rating of patients on anti-inflammatory diets compared to patients on standard diets was clinically relevant
Tedeschi, S et al. (2017)	Prospective longitudinal study	300 RA patients registered in the Brigham RA Sequential Study	Nearly a quarter of RA patients with long-term illness reported that diet had an effect on symptoms, blueberries and spinach improved symptoms, sodas and sweet desserts worsened symptoms
Raad, T et al. (2021)	Systematic review	20 studies with a total of 1063 participants	Dietary interventions such as the anti-inflammatory diet may be effective in adults with RA who are seeking complementary treatments and may improve RA symptoms, but their role and effectiveness are still unclear
Forsyth, C et al. (2017)	Systematic review	2 prospective studies 2 clinical trials	Mediterranean diet demonstrates beneficial effects in reducing pain and increasing physical function in patients with RA, however these results show limitations

Anti-inflammatory diet and rheumatoid arthritis: overview on the current evidence

Mateen, S et al. (2017)	Randomized controlled crossover trial	100 RA patients (24 to 60 years) who visited the orthopedic OPD at Jawaharlal Nehru Medical College, Aligarh	In RA patients, the level of 25-hydroxy vitamin D was reduced and the level of ROS and inflammatory cytokines increased
Nelson, J et al. (2020)	Systematic review	27 Randomized Controlled Trials	Interventions with Mediterranean diet, spices, antioxidants and probiotics containing Lactobacillus Casei, showed moderate strength evidence for positive effects on disease activity
Giuseppe, D et al. (2014)	Prospective cohort study	32.232 women born between 1914 and 1948 and living in Uppsala and Västmanland	205 RA cases identified during a mean follow-up of 7.5 years An intake of long-chain n-3 PUFAs (>0.21g/day) in the diet reduces the risk of developing RA by 35% Long-term intake consistently greater than 0.21 g/day was associated with a 52% reduced risk Long-term fish consumption (≥ 1 serving/week) was associated with a 29% decrease in risk

Lourdudoss, C et al. (2018)	Population-based prospective case-control study	1296 newly diagnosed RA patients (disease duration \leq 12 months), of 591 were on methotrexate monotherapy (MTX) for at least the first 3 months from baseline	Omega-3 polyunsaturated fatty acid (FA) was inversely, and the omega-6:omega-3 FA ratio was directly associated with both unacceptable and refractory pain after 3 months of MTX treatment
Philippou, E et al. (2021)	Systematic review	70 clinical trials	Some dietary approaches may improve the symptoms of RA
Khojah, H. et al. (2018)	Randomized controlled clinical trial	100 RA patients (68 female, 32 male)	The co-administration of oral resveratrol to RA patients has improved the disease management by reducing its activity as well as some of its clinical and biochemical markers
Nachvak, S et al. (2019)	Randomized, double-blind, placebo-controlled trial	54 RA patients (18-45 years old), diagnosed at least 6 months ago and with DAS-28 $>$ 3.2	Significant reduction in ERS, pain score, and swollen and tender joint counts after intervention
Javadi, F et al. (2017)	Randomized, double-blind, placebo-controlled clinical trial	50 women with RA	Quercetin 500 mg/day for 8 weeks resulted in improvements in clinical symptoms, disease activity and reduction in plasma level of hs-TNF α and HAQ scores
Gioxari, A et al. (2017)	Systematic review and meta-analysis	20 randomized controlled trials, involving 717 patients with RA in the intervention group and 535 RA patients in the control group	Consumption of ω -3 fatty acids was found to significantly improve eight disease activity-related markers

Rajaei, E et al. (2015)	Double-blind randomized controlled trial	60 patients with active rheumatoid arthritis (49 female and 11 male)	Omega-3 consumption significantly improved the patient's global assessment and reduced the need for concomitant analgesic medication
Veselinovic, M et al. (2017)	Prospective, double-blind randomized-controlled trial	60 female patients (mean age 63.1 ± 9.6 years) with RA	The disease activity score 28 (DAS score 28), the number of joints and the visual analogue scale (VAS) decreased remarkably after intervention with omega-3
