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The role of dietary polyphenols in patients with rheumatoid arthritis – a review of literature

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Abstract:

Introduction and purpose: Rheumatoid arthritis (RA) is a systemic, autoimmune disease of the connective tissue, affecting predominantly symmetrical synovial joints. RA is characterized by a complex, multifactorial etiology, including genetic and environmental factors, the latter of which have been scrutinized in the recent years. One of the modifiable factors affecting the disease is diet. The purpose of this review is to present current data on the role of polyphenols in diet in patients with RA.

A brief description of the state of knowledge: The etiology of rheumatoid arthritis includes genetic predispositions along with environmental factors – such as diet. There have been numerous studies analysing different types of diet and particular compounds which may alleviate disease activity in patients and lower its burden. However, currently there are no standardised recommendations proposed for physicians, or patients regarding the advised dietary measures. Polyphenols are natural compounds found in plants which have been frequently investigated for their anti-inflammatory properties and impact on autoimmune disorders. Studies have found that some polyphenols, such as curcumin, resveratrol, quercetin, and more, lower the disease activity score (DAS-28) in patients with RA, or lighten reported symptoms, by interacting with several pathways of the disease and attenuating oxidative stress.

Summary: RA is an autoimmune disorder, affecting increasingly more patients. The burden of the disease is paramount, thus encouraging research into beneficial methods of conventional and adjuvant treatment. Diet is one of the crucial focal points for further exploration. Current data provide promising evidence on the effects of polyphenols on RA activity but further research, especially clinical trials, is required.

Key words: rheumatoid arthritis diet, polyphenols, disease activity

Introduction and purpose:

Rheumatoid arthritis is a systemic, autoimmune disease of complex pathophysiology. It primarily affects synovial joints, causing chronic inflammation with distortion of the cartilage. Common symptoms of the disease include joint stiffness, pain, chronic fatigue, swelling of the joints and even degradation of cartilage. Rheumatoid arthritis (RA) can ultimately result in severe disability, both physically, in deformation of joints and from a socioeconomic standpoint, in impairment of the quality of everyday life as well as work performance. Its global burden is a serious public health issue, thus encouraging further research into effective methods of treatment. Although many advancements in the treatment of RA have been obtained and current regimen consisting of disease modifying anti-rheumatic drugs (DMARDs), steroids, non-steroidal anti-inflammatory drugs (NSAIDs) and biological therapies has been widely acclaimed, there is still room for improvement. Current strategies, though oftentimes effective, have their limitations regarding significant side effects or availability.

The pathophysiology of rheumatoid arthritis is multifactorial, encompassing genetic predispositions as well as environmental risks. One of the easily modifiable lifestyle factors, thoroughly researched in recent years, is diet. Many types of diets have been studied and numerous dietary recommendations have been suggested so far. One of the more promising findings in research is the role of polyphenolic compounds in diet in patients with RA. Dietary polyphenols are commonly found in various fruits, legumes, tea leaves and spices.

They prove to have many beneficial effects, mostly anti-inflammatory and antioxidant and have been utilized in many autoimmune diseases for their immunomodulatory properties. Research shows that their influence on disease activity in rheumatoid arthritis is noteworthy and warrants further investigations into implementing adjuvant diet therapy into current management of the disease accordingly.

The aim of this paper is to present current state of knowledge on the role of dietary polyphenols as part of the holistic treatment of rheumatoid arthritis. A comprehensive review of literature has been performed by authors in databases such as PubMed and Google Scholar. Key search terms used in the investigation were: “rheumatoid arthritis diet”, “dietary polyphenols”, “RA disease activity”. Found articles were screened to exclude irrelevant studies. Only articles published in English were included in this review.

Description of the state of knowledge

What is rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, systemic disease characterized by persistent inflammation of the symmetrical synovial joints. RA affects 0.1-2.0% of the population, predominantly middle-aged women. It is an autoimmune disorder which results in the destruction of the joints, leading even to severe deformation and temporary or permanent disability of the affected areas. Other common symptoms of RA include chronic fatigue, stiffness, tenderness and pain of the joints as well as fever, weight loss and rheumatoid nodules under the skin (1–3)

The burden of the disease is paramount, both on a global scale and in regard to individual patients managing disability, lower quality of work and life and compromised overall wellbeing. Even 20% of patients become permanently disabled in the first two decades of the diagnosis, especially if left untreated. Constant pain, swelling and compromised mobility of the joints results in impaired everyday functioning of the patients, leaving significant mark on the quality of their work and life activities. (4–6) Many patients report substandard energy levels and significantly worsened emotional state, amplified by side effects of the applied treatment and comorbid conditions. Rheumatoid arthritis is also linked with higher premature mortality due to increased risk of cardiovascular incidents. Therefore, patients with RA can experience a reduction in life expectancy and healthy life years. (4,6,7)

The etiology of rheumatoid arthritis is multifactorial and complex, consisting of genetic components and many pathophysiological mechanisms leading to inflammation of the synovial membrane of the joints. There is a genetic component in the etiology of the disease, making rheumatoid arthritis hereditable. Genetic factors such as HLA-DR4, HLA-DR1 have been shown to significantly increase the risk of developing RA.

There have also been studies confirming juvenile idiopathic arthritis (JIA) as a risk factor for RA later in life. (3) Furthermore, RA is an autoimmune disease, meaning that the immune system of the patient is attacking itself. Therefore, a major role in the development of RA is attributed to T lymphocytes and activation of inflammatory cytokines such as TNF-α (tumour necrosis factor alpha) and interleukins: IL-1, IL-6, IL-17. The enabled inflammatory factors mediate the response of the fibroblast-like synoviocytes (FLS) which proliferate and turn into aggressive phenotypes. Along with activated lymphocytes and macrophages, they go on stimulate osteoclasts which ultimately leads to demolition of the joint cartilage, synovium and

even bones of the joint. (5,8,9) Further progression of joint destruction has been linked to increased levels of intracellular reactive oxygen species. Oxidative stress proves to be an important factor in the pathogenesis of many diseases, including rheumatoid arthritis, alongside inflammation. Reactive oxygen species (ROS) are highly reactive chemicals which can lead to DNA damage, and their high concentrations have been found to influence the apoptosis of osteocytes, osteoblasts and chondrocytes. Excessive ROS amount can be detrimental to the cells of the body, however under normal circumstances, their production is controlled and contained by a broad variety of oxidant defence systems of the body. (10–12) There have been many investigations into the influence of lifestyle factors on the morbidity and progression of RA. It has been found that cigarette smoke, even passive exposure to it, obesity and diet have the most prevalent effect on the disease. Diet is one of the easily modifiable lifestyle factors and therefore, dietary interventions including anti-inflammatory diets have been studied thoroughly in terms of prevention and alleviating symptoms of the disease. (13–16)

Treatment of rheumatoid arthritis

Many advances in treatment of rheumatoid arthritis have been made in the last years. Modern approach towards RA treatment consists of management of pain, swelling and other symptoms of the disease, as well as immunosuppression obtained by disease modifying anti-rheumatic drugs (DMARDs), steroids and increasingly more common biological therapies. These treatments have had tremendous success in decreasing the mortality and disability of patients. However, there is still a considerable group of patients who have not benefited from aforementioned therapies, including achieving remission of the disease, enduring severe symptoms or experiencing side-effects of the applied treatment. Therefore, further investigation of the influence of non-pharmacotherapeutic interventions is required. (4,11)

Current approach to treatment according to ACR (American College of Rheumatology) and EULAR (European Alliance of Associations for Rheumatology) guidelines includes disease-modifying drugs (DMARDs) and symptomatic treatment using glucocorticoids and non-steroidal anti-inflammatory drugs). Symptomatic therapy reduces inflammation and pain and is especially effective in acute phase of the disease. DMARDs are the backbone of the treatment and are used to induce remission of the disease by reducing the autoimmune activity. There are both conventional synthetic DMARDs as well as biologic alternatives when synthetics are not tolerated well by the patient. Recently, an important role in the management of RA has been assigned to TNF-α inhibitors such as Adalimumbab,

Certolizumab or Infliximab, to name a few. These therapies have shown great results in decreasing inflammation and most bothersome symptoms of RA. (3,17)

However, these treatments can be ineffective in many patients or cause adverse side effects which may lower the quality of life or lead to decrease in compliance. Therefore, there still is a demand to study adjuvant non-pharmacological therapies. It is crucial to include patient education as well as lifestyle management consisting of exercise, physical therapy and anti-inflammatory diet as part of the therapeutic process. (2,6,16) There has been extensive research done into the protective role of diet in both prevention and minimizing the aggravating symptoms of the disease. One of the promising areas of dietary interventions in patients with rheumatoid arthritis is a diet rich in polyphenolic compounds.

Polyphenolic compounds

Dietary polyphenols have been subject to comprehensive research for a long time. Their potential to impact the immunomodulation and, in consequence, prevent or suppress autoimmune disease has been widely reviewed. (18) Polyphenols are bioactive metabolites found in various plants, herbs, spices, vegetables and fruits. There have been over 8000 polyphenols found. They can be categorized based on their chemical structure and properties into phenolic acids, stilbenes, flavonoids, tannins and others, however they are alike in key structure of the compound – the aromatic ring and at least one hydroxyl group. Their chemical structure is directly linked with their most prominent property utilized in management of oxidative stress as they can interact with reactive oxygen species (ROS) forming relatively stable compounds, preventing further oxidation. For that reason, they have been identified as antioxidant compounds and, therefore, used in pertinent autoimmune diseases. Polyphenols have been scrutinised for their immunomodulatory properties mostly due to their ability to impact many immunological processes on cellular level, affecting signalling, proliferation or apoptosis, and so on. Some studies suggest that flavonoids, one of the groups of polyphenols, exhibit hepatoprotective, antibacterial and antiviral activity on top of aforementioned antioxidant effect. (8,18–21) Furthermore, polyphenolic compounds affect many inflammatory pathways. It has been found that polyphenols such as kaempferol, galangin, quercentin inhibited the activity of PLA2 enzyme responsible for arachidonic acid inflammation pathways. Moreover, resveratol, genistein, quercetin have been shown to suppress NF-kB signalling pathway which holds an important role in controlling the activity of pro-inflammatory cytokines such as TNF-α or IL-6. But the role of polyphenols in

inhibiting inflammatory pathways does not end there. Numerous papers have also established that polyphenols affect mitogen activated protein kinase pathway (MAPKs). (6)

Dietary polyphenols have been therefore shown to impact the activity of immunological processes in the body, raising a question on their benefits in adjuvant treatment or even prevention of autoimmune diseases. Some of the more frequently studied polyphenols include resveratol – found mostly in berries and grapes, quercetin – found in berries, apples, onions and tea, and curcumin – found in tumeric (*Curcuma longa).* (9,11,22)

Diet in rheumatoid arthritis

Rheumatoid arthritis has a multifactorial etiology, consisting of genetic predisposition and environmental factors. One of these environmental factors impacting the disease is diet. Diet has been shown to influence the risk of RA prevalence and the modulation of the disease activity. It is a highly scrutinised factor, mostly due to its modifiability and substantial data, in many autoimmune diseases, including rheumatoid arthritis. Many approaches have been studied, from restrictive diets – such as vegetarian, vegan or diets requiring a calorie deficit, to diets based on specific products, such as Mediterranean diet or anti-inflammatory diet rich in polyphenolic compounds. (16,23) Even though various diets have been researched, and the results of studies are promising, there are no standardized RA-specific recommendations for patients, or their physicians. Currently, the consensus is that patients should follow a healthy, nutritious diet similar to general population. When contemplating the diet for patients with RA, it is also important to consider that some patients may present an issue with preparation of healthy food, due to distressing symptoms such as pain or deformity of the joints, restricting their ability to process their food, for example peel or cut. For all these reasons, it is crucial for physicians treating patients with rheumatoid arthritis to focus on patient education, regarding not only the disease itself, but also necessary lifestyle adjustments like parameters of healthy diet and limitations in preparation of the food. (4,7)

Many studies show that nutritious diet rich in fiber, polyphenols, omega-3 polyunsaturated fatty acids (PUFAs) is encouraged in management of rheumatoid arthritis, mostly for their anti-inflammatory and gut-modulating effect. Therefore, Mediterranean diet which in its core consists of products rich in aforementioned nutrients, has been widely studied. (1,18) Mediterranean diet (MD) is based mostly on olive oil, whole grain, fruits, vegetables, nuts and, less frequently, fish, dairy and legumes. Salt, red meat and highly processed food consumption is limited. It has been proven that such a balanced diet can improve the quality of life of patients with RA and progression of the disease. MD is also filled with polyphenolic

compounds which proves its anti-inflammatory and antioxidant properties. Some studies show that adherence to MD lowered DAS-28 (disease activity score) and relieved some of the symptoms such as morning stiffness, however some found no correlation between adherence to MD and development of rheumatoid arthritis. (24,25) It has been found that higher intake of omega-3 polyunsaturated acids in diet is beneficial in relieving pain and morning stiffness of joints, resulting in lowered amount of NSAIDs taken by patients. (3) However, not only Mediterranean diet has been studied in regard to its beneficial effects. Various experimental studies showed that cohesive vegan and vegetarian diets resulted in lowered pain and inflammation. In some cases, a calorie restriction or even controlled fasting presented with the same benefits. It is also crucial to highlight the significance of correct BMI (Body Mass Index) in patients with rheumatoid arthritis. It has been confirmed that for every 5 kg/m2 increase of BMI, there was a 13% increase in RA risk. Obesity, defined as BMI > 30 kg/m2, has also been documented to agitate symptoms of RA, resulting in worsened DAS-28, pain, tenderness of the joints as well as physical function scores. (16,23,26) Numerous reviews suggest that enhancing the share of vegetables and fruits in diet reduce the risk of diseases associated with oxidative stress due to the abundance of antioxidant compounds, such as polyphenols, in natural, non-processed food. Some of the dietary components found to decrease mortality risk in rheumatoid arthritis are high intake of fiber, zinc, PUFAs, vegetables, fruits and wholegrains and low intake of saturated fats. Some of the dietary habits linked with higher prevalence of RA are high free fructose-rich beverages, red meat, butter and pastries consumption. (13,16,25)

Polyphenols in diet in RA

Many promising findings have been recently identified in research on dietary polyphenolic compounds in management of rheumatoid arthritis. Their antioxidant, anti-inflammatory properties have held high promises for their application in RA-specific diet. As mentioned before, dietary polyphenols have been proven to diminish oxidative stress on a cellular level, resulting in a decrease in inflammation and, overall, lessening symptoms of rheumatoid arthritis. Their mechanism of action includes neutralising ROS, modulating inflammatory pathways such as NK-kB signalling, MAPKs and arachidonic acid pathways. (6,14,20,23)
One of the polyphenols which has been frequently regarded for its benefits in treatment of rheumatoid arthritis is resveratrol. It is a stilbene compound which appears mostly in grapes,

peanuts and berries such as mulberry. Its main mechanism of action includes neutralising reactive oxygen species (ROS) and, therefore, attenuating oxidative stress. Its properties have been linked with prevention of inflammatory diseases like RA or even diabetes, obesity, cardiovascular diseases and neurodegenerative diseases such as Alzheimer's. (11,27)

The effects of resveratrol were investigated in a clinical trial in which 1000 mg of resveratrol was administered for 3 months, alongside traditional treatment of RA. The trial proved that DAS-28 was significantly lowered in patients who took resveratrol. What is more, some biochemical markers of the disease such as C-reactive protein or TNF-α, IL-6 had decreased serum levels in resveratrol group, compared to control group and the levels measured before the trial. Resveratrol has also been studied in animal models, the results of which reported reduction in damage of the cartilage and bones in mice. (8,27,28)

Another polyphenolic compound thoroughly researched for its beneficial effect on RA progression is curcumin. Curcumin is a cucuminoid compound found in the rhizome of turmeric (*Curcuma longa).* It has been studied for its anti-inflammatory properties and have been found to inhibit activation of IL-6 and NF-kB pathway, as well as induce apoptosis of fibroblast-like synoviocytes (FLS). Curcumin was also a subject of a randomised clinical trial in which one group was treated with 500 mg curcumin, the second group with 50 mg of diclofenac sodium and the third with both. The curcumin-treated group showed a great improvement of patients' symptoms with no side effects. (6,18,22,28)

There is also evidence supporting quercetin as a valuable component of dietary adjuvant therapy of RA. Quercetin is a flavonol found in various plants and vegetables such as *Mentha pulegium,* but also apples, onions, cranberries or tea. Its mechanism of action involves attenuating NF-kB signalling and inhibiting enzymes like cyclooxygenase and lipoxygenase which take part in arachidonic acid pathway of inflammation. Studies show that quercetin supplementation of 500 mg per day alleviated some of RA symptoms like morning stiffness and pain. What is more, intake of cranberry juice, rich in quercetin, has been proven to lower inflammatory biomarkers such as C-reactive protein and IL-6 and disease activity (DAS-28) as well as anti-CCP levels in patients with rheumatoid arthritis. Altogether, quercetin has been evidenced to improve the quality of life in patients with RA mainly by decreasing symptoms and disease activity. (9,19,28–30)

Moreover, research concerning the role of polyphenols in diet in patients with rheumatoid arthritis highlights the importance of other compounds, like the extract of EVOO (extra-virgin olive oil), ellagitannins present in pomegranates or epigallocatechin-3-gallate (EGCG) found commonly in green tea, all play a part in reducing inflammation. Research into flavanones,

including hesperidin, naringin and eriodyctiol which are present in various herbs and fruits such as dried peppermint, clementines, sweet orange, rosemary, oregano or lemons, shows that their increased consumption has an effect on reducing the prevalence of rheumatoid arthritis. The anti-inflammatory effects of flavonoids, resulting in alleviated RA symptoms show great promise in terms of possible adjuvant treatments. (15,16,18,31) Another example of polyphenolic compound which greatly affects patients with RA is kaempferol – a flavonol found mostly in grapefruits, onion leaves, papaya shoots, pumpkins, carrots and black tea. It has been shown that kaempferol has anti-inflammatory properties and inhibits the NF-kB pathway as well as suppressed inflammatory cytokines such as IL-1β. It also showed anti-rheumatic effects in synovial tissues. (2,5,6)

On the other hand, the use dietary polyphenols faces some limitations, for example limited solubility and stability of these compounds. Bioavailability of these compounds depends on many factors including digestive stability and absorption. There is a possibility of using nanoscopic drug delivery systems, however, at the moment, specific solutions are still being worked on. (8,28)

Conclusions

Rheumatoid arthritis is still an important public health issue with a significant global burden of the disease. Although immense progress has been obtained in terms of treatment of rheumatoid arthritis, there is still room for improvement. Diet can influence the prevalence and progression of the disease; therefore, it is an important area for further research and, ultimately, creating cohesive guidelines for patients and physicians. Polyphenolic compounds hold much promise in terms of natural, adjuvant therapy of RA due to their anti-inflammatory properties. However, further research should be encouraged on advancing bioavailability of these compounds in order to provide safe and effective treatment of rheumatoid arthritis.

Disclosure:

Authors' contribution

Conceptualization: AD and BR;

Methodology: AD and MJ;

Software: BR and JMM;

Check: NK, MJ and KS;

Formal analysis: BR;
Investigation: MJ and KS;
Resources: JMM and NK;
Data curation: AD;
Writing - rough preparation: AD and BR;
Writing - review and editing: KS, MJ and JMM;
Visualization: BR and MJ;
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