HHS Public Access

Author manuscript

*Food Funct*. Author manuscript; available in PMC 2019 January 24.

Published in final edited form as:

*Food Funct*. 2018 January 24; 9(1): 70–77. doi:10.1039/c7fo01435j.

# Dietary fruits and arthritis

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## Abstract

Arthritis is a global health concern affecting a significant proportion of the population and associated with reduced quality of life. Among the different forms of arthritis, osteoarthritis (OA) and rheumatoid arthritis (RA) are the most common and lacking a definite cure in the affected individuals. Fruits, such as berries and pomegranates are rich sources of a variety of dietary bioactive compounds, especially the polyphenolic flavonoids that have been associated with antioxidant, anti-inflammatory and analgesic effects. Emerging research demonstrates a protective role of fruits and their polyphenols in pre-clinical, clinical and epidemiological studies of OA and RA. In this context, commonly available fruits, such as blueberries, raspberries and strawberries, and pomegranates have shown promising results in reducing pain and inflammation in experimental models and in human clinical studies of arthritis. There is also some evidence on the role of specific fruit polyphenols, such as quercetin and citrus flavonoids in alleviating RA symptoms. These emerging data deserve further investigation in rigorous scientific studies to determine the mechanisms, dosing and selection of fruits and fruit extracts in arthritis management.

### Keywords

Berries; pomegranates; polyphenols; osteoarthritis; rheumatoid arthritis; pain; inflammation

## Arthritis: a public health burden

Arthritis, a chronic condition referring to joint pain or joint disease is the leading cause of disability in the US and other global populations.[1,2] Osteoarthritis (OA) is the most common form of arthritis affecting a significant proportion of older adults. OA is a progressive and degenerative joint disease characterized by inflammation, chronic pain, functional limitation

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and reduced quality of life in the affected population.[3,4] Rheumatoid arthritis (RA) is an autoimmune disorder, also affecting a significant proportion of the general population.[5] Although the etiology and underlying mechanisms of OA and RA are complicated, a body of evidence suggests that the progression of these conditions in patients may be primarily driven by an increase in oxidative stress and inflammation.[6,7] Among the non-pharmacological approaches, weight loss diets and exercise interventions are the commonly recommended strategies in OA management,[8,9] whereas anti-inflammatory foods and supplements and specific vitamins, such as vitamin D have been shown to reduce recurrence of RA.[10,11] However, arthritis still remains an incurable condition, and there exists an urgent need to identify new and effective therapies for management of different forms of arthritis and associated symptoms of pain and disabilities.

In recent years, the role of dietary antioxidants in arthritis management is increasingly being addressed by researchers in reported studies. In context of dietary compounds, polyphenol-rich fruits, such as berries show promise in OA and RA management in emerging scientific studies. A recently reported cross-sectional study from Korean National Health and Nutrition Examination Survey revealed higher intake of fruits and vegetables to be significantly associated with lower prevalence of keen pain in older adults with knee OA.[12] In another cross-sectional report among patients with RA, 20 commonly consumed foods were associated with varying levels of pain and RA symptoms. Interestingly, among these foods identified by the participants to be associated with improving RA symptoms, blueberries and strawberries were ranked high on the list of ‘anti-inflammatory foods’ based on Disease activity scores.[13] These significant associations persisted when researchers accounted for confounding factors, such as exercise, sleep, vitamin use and warm room temperature in the cohort. These emerging observational data support the role of dietary fruits and berries in alleviating arthritis symptoms and the need for further clinical investigation. The aim of this mini-review is to examine the role of dietary fruits and fruit polyphenols in the management of arthritis based on pre-clinical and clinical reports in the recent timeframe of three to five years.

## Dietary berries and OA: overall mechanisms

Dietary fruits, especially berries are a rich source of several phytochemicals and nutrients which may explain much of their physiological effects as antioxidants and anti-inflammatory agents. Commonly consumed berries, such as blueberries, raspberries and strawberries are a rich source of several polyphenols including anthocyanins, quercetin, and various types of phenolic acids.[14-16] Emerging pre-clinical studies provide evidence on the role of whole berries and berry polyphenols in reversing the pathological changes in arthritis including OA (Table 1). In a rat model of collagen-induced arthritis, treatment of animals with 15mg/kg/day raspberry extract was demonstrated to improve the clinical symptoms of arthritis including tissue swelling, osteophyte formation and decreased articular destruction when compared to the control animals.[17] In another study by the same group of researchers, blueberry extracts (12.5mg/kg/day) was shown to cause approximately 30% decrease in tissue swelling and edema and a concomitant decrease in inflammatory molecules assessed by histological scores when compared to the control animals. Analysis of the administered blueberry extract using HPLC techniques revealed greater than 40 phenolic compounds of

which chlorogenic acid, malvidin, peonidin and cyanidin were the major polyphenols that may synergistically confer anti-arthritic effects in these animals.[18] In addition to these commonly consumed berries, pomegranates, also classified as berry fruits are rich in ellagitannins and hydrolysable tannins, and have been shown to confer antioxidant and anti-inflammatory effects in various experimental models of chronic diseases including a few on arthritis.[19] In an experimental OA model of New Zealand white rabbits, treatment with pomegranate fruit extracts was demonstrated to induce several chondroprotective effects, especially, decreasing mRNA expressions of matrix metalloproteinases (MMPs), a group of cartilage degradation enzymes, as well as decreasing synovial fluid and plasma levels of inflammatory interleukins and prostaglandins in these animals.[20] Emerging evidence also suggests a role of citrus fruit polyphenols, such as hesperidin and naringenin in decreasing expressions of inflammatory molecules that have been associated with aggravating RA symptoms. In a murine model of collagen-induced arthritis, naringenin treatment was shown to decrease levels of anti-collagen Type II immunoglobulin factor and corresponding maturation of dendritic cells, thereby improving inflammation and RA symptoms in these animals.[21] In another recent study, hesperidin treatment in a murine model of arthritis was shown to down regulate several inflammatory pathways, such as Wnt signaling leading to reduced proliferation of fibroblast-like synoviocytes that have been shown to contribute to RA symptoms.[22] Emerging studies also support a role of traditional fruits, such as Russian olives and purple passion fruits in alleviating RA in experimental animal models.[23,24] These fruits, though not commonly consumed in the Western population, have been traditionally grown and used in middle east and south American countries, respectively, for relieving arthritis symptoms, and thus deserve further attention as potential fruit nutraceuticals in arthritis therapy. Thus, while previous studies support a protective role of dietary polyphenols in the management of arthritis,[25] the reported studies on fruits and fruit-derived polyphenols and arthritis in recent years provide more promising evidence in pre-clinical models that can then be translated in human clinical trials of arthritis.

## Comparative mechanisms and composition underlying the role of fruits in arthritis

Emerging research in animal and human studies is increasingly identifying the role of specific whole fruits, such as berries and pomegranates and their bioactive polyphenols in alleviating symptoms of arthritis. In a comparative study of antioxidant potential among commonly consumed polyphenol-rich fruit juices in the US, pomegranate juice was assigned the highest antioxidant activity when compared to red wine, and juices derived from grapes, blueberries, cranberries, cherries, apples and oranges.[26] Comparative data among the berry fruits show various categories of phenolic compounds which differ based on their structural properties (phenolic acids, flavonoids, such as anthocyanins and flavonols, and tannins), and these explain much of the protective effects of berries in inflammatory conditions such as arthritis.[27] In terms of anthocyanin content, the best studied bioactive compounds in berries, our group previously published a report comparing USDA data on berry flavonoids which show the darker colored berries, such as blueberries, bilberries and black raspberries have higher anthocyanin content (163, 430, and 324 mg/100g edible portion, respectively) compared to dried cranberries, red raspberries and strawberries (0.72, 38, and 33 mg/100g

edible portion, respectively).[28] Pomegranates have higher antioxidant activity than other fruits, and this has been mostly attributed to their ellagitannins and phenolic acid content (range: approximately 1200-9000mg/L aril juice).[29] Lesser known fruits that emerge as of benefit in arthritis, such as Russian olives grown in Middle east countries, or traditional fruits such as olives, olive oil and figs grown in Mediterranean countries are also high in several bioactive compounds. The most abundant phenolic compounds found in Russian olives are several derivatives of flavonoids, such as isorhamnetin and kaempferol, and phenolic acids, such as 4-hydroxybenzoic acid and cinnamic acid, and these have been shown to explain much of their anti-inflammatory, antioxidant and pain relieving effects[30]. In figs, the polyphenol content is lower than in berries, and the most abundant phenolic acid is rutin (29 mg/100g), followed by catechin (4 mg/100g) and chlorogenic acid (1.7 mg/100g).[31] Interestingly, the phenolic content of olive oil is lower than that of berries, pomegranates and figs, and the major phenolic compounds are oleuropein which undergoes hydrolysis to yield hydroxytyrosol, the major phenol in olive oil (1.4 mg/100g edible portion).[32] Hydroxytyrosol has been associated with multiple health benefits including antioxidant, anti-inflammatory and anti-diabetic effects, and also with alleviating arthritis in animal models and as part of Mediterranean diet in humans.[33, 34]

Comparative data on the effects of berries and other fruits in arthritis are lacking, but data in cancer cells show black raspberries and strawberry extracts to exert the most significant pro-apoptotic effects vs. blackberries, blueberries, cranberries and red raspberries.[35] Thus, these data show that while black raspberries and strawberries differ in their polyphenol composition, each are equally potent in exerting anti-carcinogenic effects. This may be explained by the unique composition of bioactive compounds in each berry which must be further studied in context of arthritis. In another recent review on the role of polyphenols in arthritis, researchers revealed that epigallocatechin gallate, carnosol, hydroxytyrosol, curcumin, resveratrol, kaempferol and genistein were the most widely studied polyphenols in pre-clinical models, but no comparative data were provided to identify any hierarchy of biological, including antioxidant activities among these polyphenols.[36] Overall, these emerging data show the unique make-up of dietary bioactive compounds in each fruit that may explain their anti-arthritic effects, and based on antioxidant comparisons, pomegranates score high among other habitually consumed fruits and their products.

## Clinical studies: commonly consumed fruits and arthritis

Emerging evidence supports the role of fruits including berries in alleviating inflammation and pain in knee OA. As summarized in Table 2, these studies involve commonly consumed fruits and berries, such as pomegranates and strawberries, as well as less commonly consumed traditional fruits, such as Russian olive and fig fruits grown in Iran that have been used in various complementary medicinal practices. Among the berry fruits, strawberries are widely consumed as whole fruits and processed fruit products, and thus have been studied for their health effects, especially in reducing oxidative stress and inflammation and subsequent disease risks. Our group was the first to report a 26-week cross over study in which adults with radiographic evidence of knee OA were randomized to consume a strawberry beverage (50g freeze-dried strawberry powder reconstituted in water) or calorie and fiber-matched control beverage each for 12 weeks. The strawberry beverage provided a

daily dose of approximately 1500 mg total polyphenols and 66mg anthocyanins. Our study findings revealed a significant decrease in knee pain scores and biomarkers of inflammation, especially interleukin-6 and 1β, and MMP-3 at the end of the strawberry vs. the control phase in these participants.[37] In recent years, evidence also supports the role of pomegranate fruits in improving symptoms of OA and RA. In a study involving patients with knee OA, consumption of pomegranate juice (200ml/day) for six weeks was shown to improve stiffness and physical function scores, and decrease serum MMP-13 in these adults.[38] Serum levels of MMPs, especially MMP-3 has been implicated in the progression of knee OA,[39] and these data support a role of pomegranate juice in benefit of OA. In a second clinical trial, pomegranate extract supplementation (250mg) for eight weeks was shown to significantly improve disease activity scores leading to less pain and joint swelling, as well as improved quality of life scores in adults with RA.[40] On the contrary, pomegranate supplements did not decrease serum biomarkers of inflammation, especially C-reactive protein and MMP-3 in these patients.[40] This could be explained by the low dose of polyphenols used in their study when compared to our study dose of strawberry polyphenols in OA, and also the differential effects of polyphenol sub-types in dietary fruits and berries.

## Clinical studies: ethnic fruits and arthritis

Persian or Russian olive (Elaeagnus angustifolia L.) is a nitrogen-fixing thorny shrub extensively used in traditional medicine to alleviate pain and treat RA, OA, gastrointestinal problems, fever, and asthma. Anti-inflammatory effects of Russian olives have also been reported in a few clinical studies of arthritis. Russian olive fruit powder (15mg/day) for eight weeks was shown to decrease tumor necrosis factor-alpha and MMP-1, and increase IL-10, an anti-inflammatory cytokine in adults with OA.[41] In a similar study reported from Iran, a combination of olive oil, Russian olives and figs was shown to delay RA recurrence in patients, thus adding to the clinical evidence of the synergistic effects of traditional and conventional fruits in improving arthritis progression.[42] The most abundant phenolic compounds found in Russian olives are known to be 4-hydroxybenzoic acid from the benzoic group, and caffeic acid from the cinnamic group[30] and these have been shown to explain much of their anti-inflammatory, antioxidant and pain relieving effects. Olive oil, and fresh and dried figs are important components of the Mediterranean diet. These foods are high in polyphenolic compounds, such as oleuropein and hydroxytyrosol, and chlorogenic acid, protocatechuic acid and rutin, respectively that underlie their biological effects and clinical symptom alleviation in arthritis.[31, 32] Though promising, these results need further investigation in larger controlled studies and further identification and standardization of their bioactive compounds for clinical recommendations.

## Clinical studies: fruit polyphenol supplements and arthritis

In addition to whole fruits and juices, emerging clinical studies also suggest a role of individual fruit polyphenols, such as quercetin in improving arthritis. Quercetin is one of the most important phenolic compounds and most abundant bioflavonoids in foods of plant origin such as fruits and vegetables. While fruit-derived polyphenols have been extensively studied in modulating arthritis in pre-clinical models, clinical studies are lacking and to the best of our knowledge only a single clinical study has been reported in recent years on the

effects of quercetin per se in arthritis.[43] In this placebo-controlled trial, quercetin supplementation (500mg/day) was demonstrated to improve RA symptoms and biomarkers of inflammation in affected adults.[43] In an earlier clinical study reported in 2012, quercetin (45mg/day) co-supplemented with glucosamine and chondroitin, the commonly used dietary supplements in arthritis, was shown to significantly improve knee pain symptoms in OA.[44] These data deserve further investigation in adults with OA and RA, and should address comparative analyses among supplementation of whole fruits vs. individual bioactive compounds and with other dietary supplements used in arthritis treatment.

## Conclusion

Based on these emerging data, one has to make careful and informed decisions on the selection of the type of fruits and berries as well as their encapsulated extracts in arthritis management. While emerging epidemiological and clinical studies support whole fruits and specific fruits extracts to be effective, further studies are needed to identify most effective berries and fruits in affecting OA and RA development and progression. In this context, survey data show contrary results where commonly consumed fructose-sweetened juices, including apple juice and fruit drinks, have been positively associated with RA in young US adults of 20 to 30 years of age.[45] In this report, the authors discuss the role of ingested fructose leading to the formation of advanced glycation end products that travel beyond the intestinal boundaries to other tissues and may play a role in the etiology of auto-immune arthritis.[45] In addition to clinical studies showing some protective effects of specific fruits including berries and their extracts, epidemiological data is further substantiating the protective associations of a dietary pattern, such as the Mediterranean diet rich in a combination of dietary polyphenols derived from fruits, vegetables, olives and red wine in OA.[46,47]

In conclusion, on the basis of emerging pre-clinical, epidemiological and clinical data, blueberries, raspberries and strawberries, as well as pomegranates are among the commonly available fruits that may offer some protection against arthritis. The role of traditional fruits in protecting against arthritis, though significant needs further clinical investigation to determine their dosing, as well as safety issues when consumed as nutraceuticals in the general and western society. Overall, these studies continue to support the role of whole fruits, especially berries and their bioactive compounds in arthritis prevention and management.

## Acknowledgments

Support for work cited in this review was obtained from the Jim and Lynne Professorship Endowments at OSU and the NIH grant U54GM104938 (Oklahoma Shared Clinical and Translational Resource), OUHSC.

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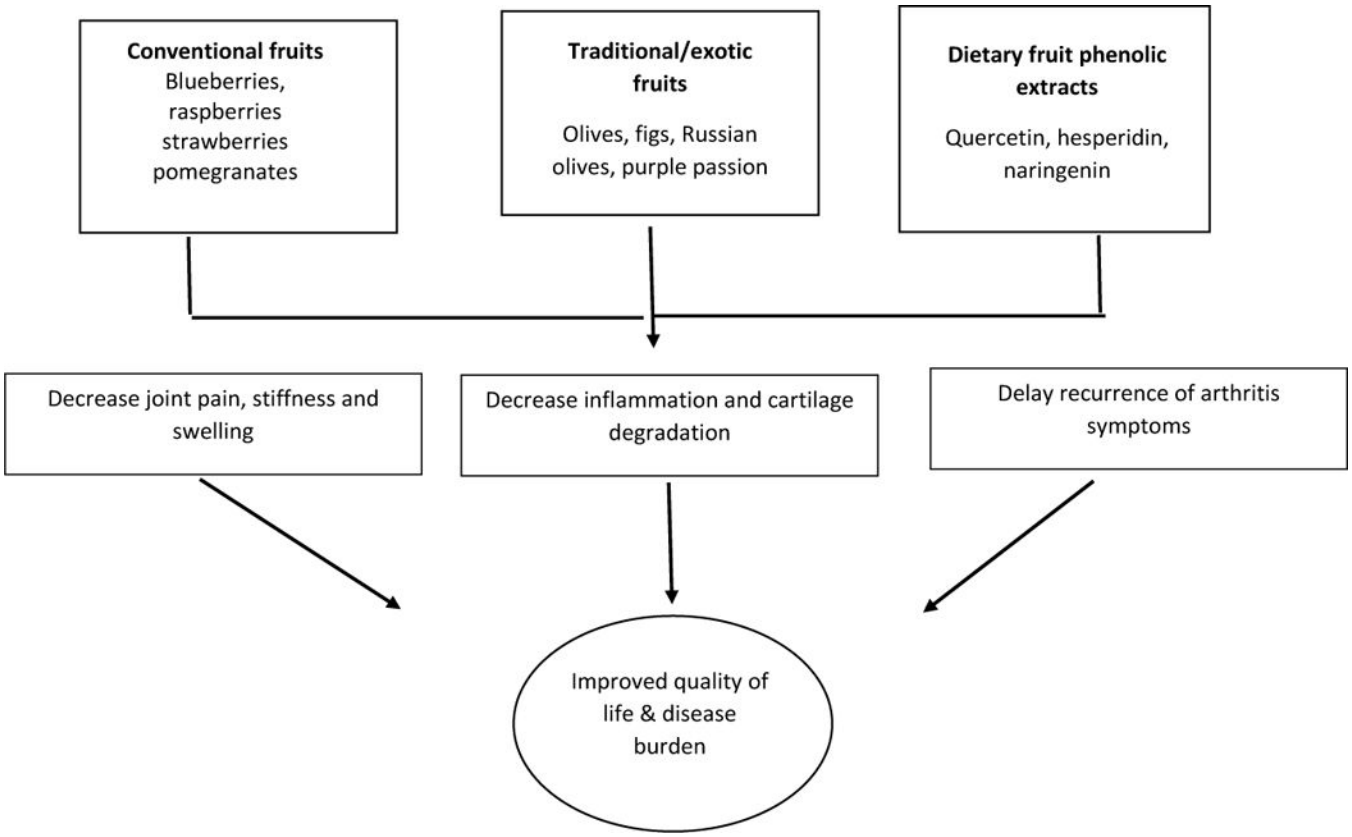


**Figure 1.**
Mechanism of action of dietary fruits on arthritis

## Table 1

Summary of pre-clinical studies on the effects of dietary fruits and berries on arthritis

| Authors (year) | Animal model | Intervention | Significant findings vs. control animals |
|---|---|---|---|
| Hadipour (2010)[48] | Rodent model of Mono-iodoacetate-induced OA | PJ (4, 10, and 20 mL/kg), orally for 2 wk | Decreased chondrocyte damage<br>Decreased inflammation in synovial fluid |
| Figueira et al. (2014)[17] | Rodent model of collagen-induced arthritis | Raspberry fruit extract (15 mg crude extract/kg/day intraperitoneally and per os) every 24 h for 12 days | Inhibited paw edema<br>Decreased histological damage score and articular destruction<br>Improved overall clinical features of arthritis |
| Li et al. (2015)[21] | Rodent model of collagen-induced arthritis | Naringenin (100 or 200 mg/kg, dissolved in corn oil) once daily for 21 days | Decreased inflammation; MAPK and NF-Kb signaling pathways<br>Decreased proliferation of T cells & levels of anticollagen IgG |
| Figueira et al. (2016)[18] | Rodent model of collagen-induced arthritis | Blueberry fruit extract (12.5 mg crude extract/kg/day by gavage) every 24 h for 12 days | Inhibited paw edema<br>Decreased histological damage<br>Decreased Cox-2 and iNOS<br>Improved overall clinical features of arthritis |
| Akhtar et al. (2017)[20] | Rabbit model of surgically-induced OA | PEE (34 mg/kg) in water for 8wk post-surgery | Decreased histological damage score<br>Decreased expressions of MMPs<br>Decreased cytokines in the synovial fluid of PEE-treated animals |
| Liu et al. (2017)[22] | Rodent model of adjuvant arthritis | Hesperidin derivative-11 (50, 100 and 200 mg/kg) for 22 days | Inhibited FLS proliferation and DNMT1 expression<br>Decreased inflammation |
| Motevalian et al. (2017)[23] | Rodent model of collagen-induced arthritis | Fruit extracts of E. angustifolia (100, 300, 700, and 1000 mg/kg) intraperitoneally for 8 days | Decreased edema and inflammation |
| Han et al. (2017)[49] | Rodent model of collagen-induced arthritis | Dried ripe fruit extract of *S. japonicum* (0.5mg/kg) orally for 2 wk | Decreased inflammation and bone/joint damage<br>Decreased gene expressions of pro-inflammatory cytokines |

Cox-2: cyclooxygenase-2; DNMT1: DNA methyltransferase 1; FLS: fibroblast-like synoviocytes; IgG: immunoglobulin G; iNOS: inducible nitric oxide synthase; MAPK: mitogen-activated protein kinase; MMPs: matrix metalloproteinases; NF-Kb: nuclear factor-Kb; OA: osteoarthritis; PEE: pomegranate fruit extract; PJ: pomegranate juice

**Table 2**

Summary of clinical studies on the effects of dietary fruits, berries and polyphenols on arthritis

| Authors (year) | Study design | Duration | Participants | Intervention | Significant findings |
|---|---|---|---|---|---|
| Nikniaz et al. (2014)[41] | Randomized controlled trial | Eight weeks | Adults with OA (N=90); BMI: 32±2 Age:56±8y | E. angustifolia L. (Russian olives) whole fruit and medulla powder (15g/day) vs. placebo | Decreases in serum MMP-1 and TNFα and increase in IL-10 in the fruit group |
| Bahadori et al. (2016)[42] | Randomized controlled trial | 16 weeks | Adults with RA (N=56); BMI: not reported Age:50±12y | Olive oil, olive fruit and fig fruit (2:5:1 w/w semisolid mixture; 15g/day) with conventional RA drugs vs. drugs alone (control) | Decreasing trends in the disease activity scores and improvements in PtGA scores in the fig and olive group |
| Ghoochani et al. (2016)[38] | Randomized controlled trial | Six weeks | Adults with knee OA (N=38); BMI:30±5 Age:54±10y | PJ (200ml/day) vs. control group (usual diet and lifestyle) | Decreases in WOMAC scores; decreases in serum MMP-13 and increase in glutathione peroxidase in the PJ group |
| Schell et al. (2017)[37] | Randomized cross-over | 26 weeks | Adults with knee OA (N=17); BMI:39.1±1.5 Age:57±7y | Strawberry beverage (50g freeze-dried strawberries reconstituted in water) vs. control beverage | Decreases in HAQ-DI, ICOAP constant, intermittent and total knee pain; decreases in serum IL-6, 1β, MMP-3 in the strawberry group |
| Ghavipour et al. (2017)[40] | Randomized controlled trial | Eight weeks | Adults with RA (N=55); BMI:28.7±5.2 Age:48±11y | Pomegranate extracts (250mg/day) vs. control group (cellulose) | Decreases in disease activity scores, joint pain, and ESR; increase in glutathione peroxidase in the Pomegranate extract group |
| Javadi et al. (2017)[43] | Randomized controlled trial | Eight weeks | Adults with RA (N=50); BMI:29±4.5 Age:47±9y | Quercetin (500mg/day) vs. placebo | Decreases in disease activity scores, joint pain, and stiffness; decrease in hs-TNFα in the quercetin group |

BMI: body mass index; ESR: erythrocyte sedimentation rate; HAQ-DI: health assessment questionnaire-disability index; hs-TNFα: high sensitivity tumor necrosis factor alpha; ICOAP: Intermittent and Constant Osteoarthritis IL: interleukin; Pain; MMP: matrix metalloproteinase; PJ: pomegranate juice; OA: osteoarthritis; PtGA: patient global assessment; RA: rheumatoid arthritis; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index