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Invited Review

A Literature Review on Plant-Based Foods and Dietary Quality in Knee Osteoarthritis

Zhaoli Dai[1,2]

Abstract

This literature review summarizes the role of plant-based foods and diet quality in osteoarthritis, particularly knee osteoarthritis, in observational studies and clinical trials published during 2015-2020. The included studies have suggested favorable results on reducing the prevalence, pain, and cartilage changes related to osteoarthritis and inflammatory and oxidation markers such as interleukin-1, interleukin-6, tumor necrosis factor, and lipid peroxidation. Due to the lack of large longitudinal cohorts to study whole foods or diets concerning knee osteoarthritis, findings from the cross-sectional studies or clinical trials require further validation, particularly in well-designed clinical trials and a more extended follow-up period. Potential mechanisms on the role of plant-based foods in body weight, inflammation, and microbiome were explored to explain their protective associations with osteoarthritis. However, most evidence examining the relationship between the microbiome and osteoarthritis joint pain is conducted in preclinical animal studies, and few observational studies show a positive association between *Streptococcus* species and local joint inflammation in the knee. Given the close links of plant-based foods on obesity, inflammation, and microbiome, data on the role of whole foods or diets in the change in knee osteoarthritis pain through the lens of microbial composition can provide more certainty regarding the utilization of microbiome as a potential therapeutic target.

Keywords: Plant-based foods, dietary patterns, knee osteoarthritis, osteoarthritis

Introduction

Knee osteoarthritis (OA), affecting 330 million people globally, is a leading cause of functional limitation and disability.[1,2] With global aging and nearly 40% of the world population being overweight and obese,[3] OA is a common age-related chronic condition that contributes to the global burden of disease.[4] Moreover, a well-established risk factor, overweight/obesity, significantly increases the risk of the onset and progression of OA.[5] This increased risk is partly due to bodyweight affecting the joints through mechanical loading. Furthermore, excessive adipose tissue also increases oxidative stress and pro-inflammatory markers such as tumor necrosis factor (TNF) α and interleukin (IL)-6 locally in the joints and systemically in the blood.[6,7]

People with knee OA often develop structure-damaged joints, including joint space narrowing and osteophytes and the associated symptoms such as pain, stiffness, and ache. Structurally, OA is characterized by cartilage loss and modification of the structural and material properties of the subchondral bone.[8] Due to aging, obesity, and injury, cartilage loss in the joints gradually reduces the protective space between the bones, ultimately causing bone rubs against the bone. Earlier studies have suggested that knee cartilage in persons with knee OA tends to deteriorate more rapidly than those without the disease and have nearly double the rate of tibial cartilage loss among those with symptomatic knee OA than the healthy controls without knee pain.[9,10] These studies suggest a close relationship between cartilage loss and the progression and pain of knee OA.

Furthermore, a study by Hunter et al[11] suggested that meniscal damage was strongly associated with cartilage loss. The authors found that less meniscal coverage and reduced meniscal height were significantly associated with cartilage loss.[11] Consistent with this, another study reported that the morphology of the meniscal damage, especially root tear, was associated with the highest score of Western Ontario and McMaster Universities Osteoarthritis (WOMAC) pain score in the knees.[12] Again, these studies have illustrated meniscal damage as part of knee OA structural progression pathophysiology.

ORCID iD of the author:
Z.D. 0000-0003-0809-5692.

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[1] Charles Perkins Centre, School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, Australia
[2] College of Medicine & Public Health Flinders University, Australia

Corresponding author:
Zhaoli Dai
E-mail: zhaoli.dai-keller@sydney.edu.au

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Osteophytes, another structural change of the joints, are often used to define the presence of OA radiographically. These bone spurs are most often present at the margins of the joint, as outgrowths of cartilage originally and subsequently undergo endochondral ossification.[13] Although osteophytes may not increase the risk of OA structural progression, they have been shown to be strongly associated with malalignment to the side of the osteophytes.[13] Other studies in the well-adjusted cross-sectional analyses also suggested that osteophyte size was associated with the presence[14] but not the severity of pain in knee OA.[15]

Besides structural damages found in OA, a growing body of evidence supports the notion that inflammation, both locally found in the joints as well as the low-grade systemic inflammation due to obesity or other metabolic diseases, may contribute to the structural progression of OA joints, pain, and symptoms.[16] As a form of local inflammation, synovitis is commonly found in the synovial membrane and it has been increasingly recognized as a pathophysiological mechanism of OA progression.[17] In support of this, evidence on analgesic therapies supports the anti-inflammatory agents for the benefits of targeting synovial inflammation to reduce knee pain.[18] Overall, this body of evidence suggests that synovial inflammation is associated with progressive joint failure,[19,20] incident OA,[21,22] and OA symptoms, particularly knee pain.[23,24]

Main Points

- Plant-based food consumption such as fruit, vegetables, and legumes is likely to have a favorable outcome in knee osteoarthritis (OA), although the quality of the evidence is low.
- Studies on dietary quality measured by the Mediterranean diet, alternative healthy eating index, or the dietary inflammatory index also suggest possible protective associations with different clinical or pathophysiological indicators of OA.
- Potential mechanisms for associating these dietary components with knee osteoarthritis are likely contributing to the dietary effects on obesity, inflammation, and the gut microbiome. Human data in the microbiome–joint pain association are lacking but suggest that microbial composition could be a target to reduce inflammatory pain in OA.

Together, the interlinks of local (synovitis) and systemic inflammation with cartilage damage in knee OA joints demonstrate the potential of an anti-inflammatory intervention in managing the structural progression and knee pain related to knee OA.

Non-pharmacologic treatment options including physical activity, safe and monitored weight loss through dietary interventions, and physical therapy should be the first-line treatment options to manage knee OA.[25] The American College of Rheumatology guidelines strongly recommend weight loss to overweight or obese individuals with knee and hip OA.[25] This recommendation is based on a dose–response relationship between weight loss and improved symptoms and functions in patients with knee OA.[26] Later studies and reviews also have suggested that over 7.7%-10% of body weight loss has clinically meaningful outcomes in OA in the knees.[27-29]

Dietary quality plays a crucial role in overweight and obesity. The World Health Organization[3] and different countries' dietary guidelines recommend increased consumption of plant-based foods, including whole grains, fruit and vegetables, and legumes and nuts, as an effective way to control weight gain and reduce obesity. Furthermore, emerging evidence has suggested that plant-based foods or healthy diets may reduce chronic musculoskeletal pain,[30] including fibromyalgia[31] and rheumatoid arthritis.[32]

Earlier studies using data from different population-based longitudinal cohorts have shown the health benefits of fiber-rich foods in lowering the risk of symptomatic knee OA and knee pain severity.[33] This protective association is partly explained by the mechanism where fiber lowers bodyweight that might precede its effect on the symptoms due to knee OA. Furthermore, this protective association is potentially mediated by reducing inflammation, such as C-reactive protein (CRP).[34] Consistent with our findings, several healthy dietary patterns in the published systematic reviews, including a low inflammatory diet[26] and the Mediterranean diet,[35] have suggested a protective association with knee OA in observational studies or clinical trials. However, it should be noted that the heterogeneity of these studies included in these reviews is high.

To my knowledge, no review has synthesized the evidence on plant-based foods such as fruit, vegetables, nuts/legumes, whole grains, and diets that are rich in these components regarding their roles in the prevention and treatment of knee OA. Therefore, the first part of the review summarizes these empirical findings. The second part explores the potential mechanisms that affect knee OA outcomes via body weight, inflammation, and the gut microbiome.

Briefly, a literature search using keywords, including osteoarthritis, plant-based, dietary quality, healthy diet, food, and knee osteoarthritis, were conducted in PubMed via Ovid to search articles published in 2015-2020. The inclusion criteria are human observational studies or clinical trials. The exposures or interventions are plant-based foods mentioned above or a healthy dietary pattern such as a Mediterranean diet or a diet based on a dietary quality index. The clinical outcomes must relate to structures or symptoms of knee OA. Studies on nutrients, such as dietary magnesium or vitamins including K and B complex, were excluded, as these nutritional sources vary and include both plant-based and animal foods. Studies focusing on nutrient supplements are also excluded. All included studies were written in English.

Evidence on the Association of Diet and Knee OA

A total of 14 studies were included in this review. In addition, a narrative summary was provided based on study design, dietary exposures or interventions, and outcome measures. Table 1 describes the studies focusing on plant-based dietary components and their association with OA, and Table 2 summarizes studies focusing on dietary patterns with OA.

Role of Plant-Based Foods in OA

In studies focusing on plant-based foods, there are 3 cross-sectional studies[36-38] and 5 randomized, controlled trials.[39-43] The exposures include soymilk (once a day vs. less than once a day), fruit or vegetables (times/day), and fruit and vegetable intakes in quantiles in the observational studies. The interventions include pomegranate juice (200 mL daily vs. usual lifestyle), broccoli (100 g/day vs. regular diets), freeze-dried strawberries (50 g/day vs. placebo), and freeze-dried blueberries (40 g/day vs. placebo). The clinical outcomes include cartilage structure parameters such as osteophytes (OST), joint space narrowing (JSN), cartilage defects, bone marrow lesions (BML), knee pain, WOMAC scores, and inflammatory markers such as IL-6, IL-1β, and matrix metalloproteinase (MMP-3). One study shows a higher level of synovial isothiocyanates in the broccoli treatment group than the control group as proof of concept of showing isothiocyanates

Table 1. Studies on the Health Benefits of Plant-Based Food Components in Knee or Hip Osteoarthritis

Study	Study Design	Populations	Food Components	Duration	Outcome Measures	Results	Favorable Outcomes or Not
Observational studies							
Li et al. 2016 (37)	Cross-sectional study	5764 people included	Soymilk intake	n/a	Prevalence of radiographic knee JSN and OST.	Significant associations found in those who had soymilk "≥once a day" vs. never: OR: 0.49, 95% CI: 0.26-0.92, $P = .026$ and those who had soy milk <once a day vs. never: OR: 0.79, 95% CI: 0.67-0.94, $P = .009$) and the P for trend was .001	Yes with OST but no association with JSN.
Wang et al. 2016 (38)	Cross-sectional study	214 participants without diagnosed hip OA	Fruit and vegetables	n/a	Femoral head BML and cartilage defects	Vegetable consumption (times/day) was associated with reduced prevalence of femoral head cartilage defects and BML. No associations for fruit consumption.	Yes for vegetable consumption with prevalence of femoral head cartilage defects and BML but no protective association with fruit consumption.
Han et al. 2017(39)	Cross-sectional study	6588 people aged ≥50 years	Fruit and vegetable intake	n/a	Pain scores of knee decreased significantly with increasing fruit and vegetable intake by quartile.	Fourth versus the first quartile of vegetable and fruit consumption: decreased prevalence of severe knee pain (OR: 0.59, 95% CI: 0.48-0.73)	Fruit and vegetable intake decreased pain score.
Clinical trials							
Ghoochani et al. 2016 (40)	Randomized clinical trial	38 patients with knee OA	200 mL sugar- and additive-free pomegranate juice daily versus usual lifestyle (placebo)	6 weeks	Clinical signs on stiffness and functions, inflammation and antioxidant status.	Group differences were found for lower levels of MMP1, MMP13, and glutathione peroxidase in the treatment group versus the control group after the intervention. No group differences in WOMAC pain or other WOMAC scores. However, WOMAC pain score and stiffness were lower after the intervention in the treatment group.	Pomegranate juice may contain phytochemicals, such as anthocyanins and ellagic acid which may inhibit proteoglycan breakdown in cartilage, evident by decreasing MMPs; they may also exert anti-inflammatory and antioxidant properties.
Davidson et al. 2017(41)	Randomized clinical trial (crossover)	40 patients with knee OA undergoing total knee replacement	7 days_ washout_100 g of broccoli/d versus no such diet	14 days before TKR	Synovial isothiocyanates	Synovial ITC was detected in the high glycosylate diet but not in the low group; however, mean total ITC levels were 4.47-fold lower in the synovial fluid than in the plasma.	Bioactive constituent ITCs reach the synovial fluid at concentrations with biological impact on the articular joint tissues and alter the synovial fluid protein profile, showing that a dietary bioactive with chondroprotective properties can penetrate the knee in osteoarthritis.

(*Continued*)

Table 1. Studies on the Health Benefits of Plant-Based Food Components in Knee or Hip Osteoarthritis (*Continued*)

Study	Study Design	Populations	Food Components	Duration	Outcome Measures	Results	Favorable Outcomes or Not
Schell et al. 2017 (42)	Randomized clinical trial (crossover)	17 adults with knee OA	Freeze-dried strawberry beverage (50 g/day) or control beverage daily	12 weeks	IL-6, IL-1, MMP-3, pain score, and disability index	Interleukin (IL)-6, IL-1β, and MMP-3 were significantly decreased after consumption of strawberry beverage versus control (all $P < .05$). In addition, the strawberry group also significantly reduced constant, intermittent, and total pain as evaluated by the ICOAP questionnaire and the HAQ-DI scores as a disability index (all $P < .05$), compared with the control group.	Yes, with a reduction on IL-6, IL-1, MMP-3, pain score and disability index. No effects on CRP, lipid profiles.
Basu et al. 2018 (43)	Randomized clinical trial (crossover)	4 men and 13 women aged 57 ± 3 year	Dietary freeze-dried strawberries vs. control, 50 g/day (match for kcal and fiber)	12 weeks, washout 2 weeks, 12 weeks	Obesity-related hormones, biomarkers of inflammation and lipid peroxidation	TNF-α and lipid peroxidation markers, hydroxy-2-nonenal (4-HNE) and conjugated dienes. decreased; but not body weight	Yes to TNF-α and lipid peroxidation markers but no effect on body weight.
Du et al. 2019 (44)	Randomized clinical trial	63 adults aged 45-79 with symptomatic knee OA	Freeze-dried whole blueberries (40 g/day) versus placebo on pain, gait performance, and inflammation in individuals with symptomatic knee OA	4 months	WOMAC pain, walking speed, and inflammation markers include IL-1, IL-6, IL-10, IL-13.	WOMAC total score and sub-groups, including pain, stiffness, and difficulty to perform daily activities, decreased significantly in the blueberry treatment group ($P < .05$) but no difference from the control group. No effect was found on reducing inflammatory markers such as IL-1, IL-13, IL-6, and IL-10 or MCP-1 between time points in the same group or between groups.	No differences between groups.

OST, osteophytes; JSN, joint space narrowing; BML, bone marrow lesion; MMP, matrix metalloproteinase; OR, odds ratio; WOMAC, Western Ontario and McMaster Universities Osteoarthritis pain score; TKR, total knee replacement; ITC, iothiocyanates; CRP, C-reactive protein; MCP, monocyte chemoattractant protein-1; TNF, tumor necrosis factor; OA, osteoarthritis.

Table 2. Studies on Dietary Patterns in Association with Knee Osteoarthritis

Study	Study Design	Populations	Food Or Nutrients	Duration	Outcome Measures	Results	Favorable Outcomes Or Not
Veronese et al. 2016 (45)	Cross-sectional studies	4470 participants aged 61 years on average	aMED	n/a	Quality of life by SF-12, WOMAC pain, and CES-D	Higher aMED was significantly associated with a higher SF-12 physical composite scale value (beta: 0.10; 95% CI: 0.05, 0.15; $P < .0001$), lower WOMAC scores (except for stiffness), and lower CES-D scores (beta: −0.05; 95% CI: −0.09, −0.01; $P = .01$)	Yes, to quality of life scores, WOMAC pain, and CES-D (mental health) score.
Veronese et al. 2017 (46)	Cross-sectional studies	4358 community-dwelling participants (2527 females; mean age: 61.2 years) from OAI	aMED	n/a	Prevalence of knee OA	Participants with the highest aMED had a significant reduction in the presence of knee OA (OR, 0.83; 95% CIs: 0.69-0.99, $P = .04$). In addition, higher use of cereals was associated with lower odds of having knee OA (OR: 0.76; 95% CI: 0.60-0.98; $P = .03$).	Yes, to lower the prevalence of knee OA.
Mears et al. 2018 (47)	Cross-sectional studies	122 older overweight and obese African American females with self-reported OA	Alternative Healthy Eating Index 2010 (AHEI-2010)	n/a	WOMAC, IL-6	Interleukin-6 was negatively correlated with AHEI-2010	Yes, to IL-6
Veronese 2018 (48)	Cross-sectional studies	783 participants with an MRI assessment	MED	n/a	Knee cartilage morphology	Per standard deviation in the MED corresponded to a significant increase in the central medial femoral cartilage volume (beta = 0.12; 95% CI: 0.09-0.15), in the mean central medial femoral cartilage thickness (beta = 0.13; 95% CI: 0.01-0.17), in the cartilage thickness of the mean central medial tibiofemoral compartment (beta = 0.12; 95% CI: 0.09-0.15), and in the cartilage volume of the medial tibiofemoral compartment (beta = 0.09; 95% CI: 0.06-0.12).	Yes, to increase cartilage volume and cartilage thickness.
Veronese et al. 2019 (49)	Cross- sectional studies	4358 participants	DII	n/a	Radiographic, symptomatic knee OA	Participants with the highest versus lowest quartile DII, had a significantly higher probability of experiencing radiographic symptomatic knee osteoarthritis (OR: 1.40; 95% CI: 1.14-1.72; $P = .002$).	A negative effect of an inflammatory diet to knee OA
Clinical trials							
Dyer et al. 2017 (50)	Randomized trial	99 volunteers with OA (aged 31-90 years) (med diet: n = 50 versus normal diet n = 49)	Mediterranean diet	16 weeks	AIMS2 and inflammatory cytokines	There was no difference in AIMS2 and most inflammatory markers between the groups, except IL-1 alpha and sCOMP decreased in the diet group, but a significant improvement in the hip rotation in the diet group versus the control group.	Yes, to IL-1 and sCOMP and hip rotation. No effects on most inflammatory markers or arthritis impact measurement scale.

CES-D, Center for Epidemiological Studies Depression; aMED, alternative Mediterranean diet; WOMAC, Western Ontario and McMaster Universities Osteoarthritis pain score; OR, odds ratio; OA, osteoarthritis; MRI, magnetic resonance imaging; DII, Dietary inflammatory index; IL, interleukin; sCOMP, serum cartilage oligomeric matrix protein; AIMS2, Arthritis Impact Measurement Scale; SF-12, Short Form Survey 12.

could penetrate to the synovial fluid. However, this study did not mention its effect on OA outcomes.[40]

Half of the studies have suggested favorable outcomes on symptoms (knee pain, stiffness, or symptomatic knee OA) or structure (JSN, OST, and radiographic knee OA). To be noted, the sample size of the intervention studies is generally small, ranging from 17 to 63 individuals with a trial period of 14 days to 4 months. In addition, although significant effects were reported on reduced pain or other symptoms[39,43] or lower levels of IL-1, IL-6, TNF, and MMP-3 markers,[41,42] no consistent findings were reported across the studies.

Role of Dietary Patterns/Diet Quality in OA

In studies focusing on dietary patterns and their associations with or effects on knee OA-related outcomes, there are 5 cross-sectional studies[44-48] and 1 RCT[49] (Table 2). The majority of the studies examined the Mediterranean diet (n = 5). Two studies assessed diet quality, one on the Alternative Healthy Eating Index 2010 and the other examined the dietary inflammatory index (DII). The outcomes include the prevalence of OA, quality of life using the 12-Item Short Form Survey (SF-12), WOMAC pain, Center for Epidemiological Studies Depression (CES-D), levels of inflammatory cytokines such as IL-1, serum cartilage oligomeric matrix protein (sCOMP), and structural outcomes on cartilage volume/thickness. All studies found significant associations for all or partial indicators of OA. The only RCT among 99 participants suggests that those who consumed the Mediterranean diet had a reduction in IL-1 and sCOMP and a significant improvement in hip rotation than those on the control diet after a 16 week of intervention.[49]

Clinical Relevance of the Included Intervention Studies

Although the results of the 6 included intervention studies have indicated certain health benefits of the dietary patterns to manage OA, the statistically significant differences between the control and the treatment groups were primarily found based on the change in the inflammatory or oxidative markers.[39,41,42,49] However, no statistical significance was found in group differences for WOMAC pain,[39] bodyweight,[42] or Arthritis Impact Measurement Scale.[49] Furthermore, in some studies, the authors only presented the changes between different time points in the treatment group instead of comparing the group differences.[43] Interestingly, the analysis by Davidson et al[40] has detected a higher concentration of isothiocyanates in the group of people who consumed broccoli, suggesting specific dietary components may penetrate the articular joint tissue to alter the protein profile in the synovial fluid.

Because of the small sample size and a short intervention period, it remains to be determined whether these plant-based components have clinically meaningful benefits in OA parameters, such as cartilage degradation, joint space narrowing, pain, and stiffness. However, as pomegranate juice and berries contain polyphenols such as anthocyanins and ellagic acids that were shown to have anti-inflammatory and antioxidant functions, they were likely to inhibit various interleukine cytokines, serum cartilage oligomeric matrix protein (a marker of cartilage degradation), peroxidation in the chondrocytes, synoviocytes, macrophages, and osteoblast to have a downstream effect in reducing cartilage degradation, joint space narrowing, pain, and stiffness in OA.[50]

Comparison with Other Reviews on Food/Diets on OA: This review is unique because it focuses on plant-based foods and dietary patterns and their relationship with OA onset, prevalence, related pain, and other pathophysiological parameters. We did not include nutritional supplements in this review for the following reasons. First, the supplements regulations are usually lax, and the quality of dietary supplements is generally low or unknown. Second, the evidence on the health benefits of supplements to maintain well-being remains controversial in different health conditions, including knee OA.[51] Third, a previous review on the effects of dietary supplements on OA management has pointed to low quality of evidence. In the review led by Liu and colleagues[52], the authors reported that several unusual supplements such as *Boswellia serrata* extract and pycnogenol had significant effects on pain reduction in hand, knee, or hip OA. However, the most widely used supplements such as glucosamine, chondroitin, vitamin D, or vitamin E did not provide clinically meaningful long-term effects to improve pain symptoms.[52]

Another review on polyphenols primarily conducted in animal studies has provided evidence of their potential benefits on reducing levels of IL-1, IL-6, TNF, and MMP.[53] Consistent with this review, a meta-analysis on mice induced with OA by surgical procedures has suggested adverse outcomes on OA in the mice fed a high-fat diet, including worsened progression of OA and increased levels of TNF-α, IL-1β, and leptin.[54] However, there is only one systematic review on the Mediterranean diet,[35] which only includes two cross-sectional studies[44,45] and one RCT.[49] Due to the high heterogeneity of the studies, no meta-analysis was conducted. Another systematic review focused on the inflammatory aspect of diets, including the Mediterranean diet and diet supplemented with blueberry or strawberry powders on knee pain related to rheumatoid arthritis and OA.[26] In this review, the meta-analysis has suggested statistically significant differences in weight change and inflammatory biomarkers, such as in CRP, IL-6, and IL-1β; but no significant effects on physical function or pain score were detected. Again, heterogeneity across the studies was high (>70%). Overall, the quality of the evidence was rated low, and each meta-analysis included only 3 studies.[26]

Potential Mechanisms for Plant-Based Foods and Diet Quality on Knee OA

Overweight and Obesity

Overweight and obesity are the causative risk factors for knee OA. The weight-induced mechanical loading further exacerbates the age-related "wear and tear" process of structural changes in joint cartilage. Knee OA shares similar metabolic risk factors such as body weight and inflammation with several cardiometabolic conditions, including obesity, type 2 diabetes, and cardiovascular diseases.[55] The lifetime risk of diagnosed knee OA was estimated as 20% for obese people compared to 11% for non-obese people, with the highest risk (24%) found in obese females.[56]

The effect of a low-calorie diet, including high consumption of vegetables, on knee OA, was well illustrated in an 18-month intervention, which found that a very low-calorie diet (500-700 kcal/day, high in vegetables) reduced knee joint compressive force in the diet arm or the diet + exercise arm and comparable lower levels of IL-6 than the exercise arm.[57] This evidence suggests that a diet rich in plant-based foods or food components with weight control effects is likely to relieve pain symptoms related to OA. Furthermore, a network meta-analysis has indicated that the most effective interventions to alleviate arthritis pain were bariatric surgery, low-calorie diet and exercise, and intensive weight loss and exercise.[58] For most people, consuming a diet rich in plant-based foods may offer a safe, economical, and sustainable option to prevent and manage OA if that is feasible.

Inflammation

Evidence on the health benefits of plant-based foods, such as fruit, vegetables, whole grains, nuts, and legumes lowering systemic inflammatory cytokines, has been studied

extensively.[59,60] For different healthy diets, such as the Mediterranean diet [emphasizing on fruits, vegetables, olive oil, cereals, nuts and legumes, and limited consumption of red meat, processed meat and full-fat dairy[61]], the alternative healthy eating index 2010 [focusing on fruits, vegetables, whole grains, nuts and legumes, and long-chain unsaturated fatty acids, and minimized red meat and processed meat consumption[62]], and the DII [including several herbs and spices, dietary fiber, vitamins, fatty acids, polyphenols such as genistein, daidzein, and anthocyanin, carbohydrates, and alcohol; with the higher the score, the more pro-inflammatory the diet is[63]], several systematic reviews have demonstrated their health benefits in mortality,[64,65] cardiovascular diseases, and type 2 diabetes.[65] In addition, higher DII is related to a higher risk of developing central obesity[66] and mortality.[67] These specific dietary patterns (for DII, a diet with a low inflammatory score) may affect inflammation through multiple pathways, such as DNA methylation to modulate gene expression,[68] lower oxidative stress,[69] improve autophagy,[70] and regulate helper T cells in the immune response[71] that lead to a downstream effect to reduce inflammation.

Microbiome

Diet and Microbiome

Another potential mechanism is the effect of plant-based diets on the microbiome's composition. The relationship between diet and the microbiome has been established with convincing evidence.[72-75] Several reviews have also reported that plant-based diets, especially those containing higher contents of dietary fiber and polyphenols, may promote a more diverse and stable microbial system. The health benefits were seen as higher counts of microbes with anti-pathogenic and anti-inflammatory effects, including the lactic acid bacteria (e.g., *Ruminococcus*, *Eubacterium rectale*, and *Roseburia*), *Bifidobacterium* and *Lactobacillus*, and reduced counts of Clostridium and Enterococcus genera. Furthermore, the metabolites of dietary fiber after fermentation, such as short-chain fatty acids (acetate, propionate, and butyrate), can also improve immunity against pathogens and further regulate critical function of the intestine.[75]

In human studies, a cohort has shown a lower relative abundance of the phylum *Actinobacteria* (a group of gram-positive bacteria) in older adults of different ethnic backgrounds after they consumed a high-quality diet based on the Healthy Eating Index, Alternative Healthy Eating Index-2010, the Mediterranean Diet, and the Dietary Approaches to Stop Hypertension.[76] For example, of the 104 bacterial genera tested, 21 (primarily from the phylum *Firmicutes*) were positively associated with at least one dietary index.[76] This evidence suggests that diet quality may link to fecal microbial alpha and beta diversity and different genera. In addition, the increased production of short-chain fatty acids may suppress the activation of effector T cells and abrogate the manifestation of undesirable inflammatory responses.[77] However, whether this is the case in knee OA or OA in general, remains tested.

Microbiome and OA

The gut microbiome concerning health and disease development is still a relatively new research area, particularly OA. One piece of evidence has shown a correlation between dysbiosis of microbiota and the pathogenesis of OA. It should be noted that the majority of the studies were conducted in animal studies. One such review has suggested favorable effects on reduced joint pain and inflammatory markers after feeding either prebiotic or probiotics or *Lactobacillus* to OA-induced mice or rats.[78,79] However, human data in this aspect are limited. A Rotterdam study including more than 1000 participants with hip and knee OA has found a positive relationship between a higher WOMAC score (more pain) and the abundance of the pro-inflammatory Streptococcus taxa.[80] A follow-up of this study, which includes the Rotterdam cohort and the validation cohort of older Canadians, has further confirmed the independent association between greater relative and absolute *Streptococcus* spp. abundance and higher knee pain and local joint inflammation.[81] Additionally, a Chinese cohort of 125 patients with rheumatoid arthritis and 58 patients with OA found abundant diversity of bacterial nucleic acids correlated with the disease condition and that patients with OA had more abundant pro-inflammatory *Haemophilus parainfuenzae*, *Bacteroides fragilis*, *Porphyromonas*, and *Streptococcus* in their synovial tissues or synovial fluid.[82] In summary, these pioneer human observational studies have established a positive relationship between the gut microbiome and OA pathophysiology, suggesting that the microbiome could be a potential therapeutic target for interventions to manage OA pain.

Conclusion

This literature review summarizes the most relevant and updated studies on the role of plant-based food and diet quality in knee OA in observational studies and clinical trials. Although the evidence has shown a protective association with pain, cartilage structural parameters, and inflammatory biomarkers related to OA, the quality of this body of evidence is generally low. Furthermore, as there are considerable variations in the results across the studies, high-quality longitudinal cohort studies and well-designed clinical trials are needed to ascertain the causal effects of plant-based food on clinically meaningful outcomes in OA. In addition, a limited number of observational studies have indicated a potential link between the microbiome and OA. Finally, given the close relationships of plant-based food on obesity, inflammation, and microbiome, evidence on the role of these foods and diet concerning knee OA pain through the changes in the microbial composition can provide more certainty to explore this therapeutic target.

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