Oral intake of purple passion fruit peel extract reduces pain and stiffness and improves physical function in adult patients with knee osteoarthritis

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Knee osteoarthritis (OA) is a common degenerative joint disorder and a major cause of pain and disability. The hypothesis tested in this study was that the passion fruit peel extract (PFP), a flavonoid-rich dietary supplement, would reduce symptoms due to knee OA. Thirty-three OA patients were enrolled in a randomized, double-blind, placebo-controlled trial with parallel-group design. Patients received either placebo or PFP pills (150 mg, daily) in a double-blinded fashion for 2 months. The OA clinical symptoms were evaluated monthly with Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index. In the PFP group, there was a significant improvement in total WOMAC score and WOMAC subscale score of physical function after 30 days and pain after 60 days. At 60 days, reductions of 18.6%, 18%, 19.6%, and 19.2% in pain, stiffness, physical function, and composite WOMAC score, respectively, were self-reported in the PFP group. Whereas, in the placebo group, the self-reported WOMAC scores increased in every category. The results of this study show that PFP substantially alleviated osteoarthritis symptoms. This beneficial effect of PFP may be due to its antioxidant and anti-inflammatory properties.

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Keywords: Osteoarthritis; Knee; Passion fruit; Flavonoid; Antioxidant; Pain
Abbreviations: MMPs, matrix metalloproteinases; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, knee osteoarthritis; PFP, passion fruit peel extract; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

1. Introduction

Osteoarthritis (OA) represents the most common joint disorder among adults and affects most of the population older than 70 years in the United States [1]. Osteoarthritis is generally considered a degenerative disorder involving cartilage degradation, accompanied by local inflammation that accelerates the joint destruction. For countries with aging populations, the prevalence of OA is expected to increase [1]. In addition, OA should become more common as more of the global population becomes obese due to the
relationship between increased incidence of OA and increased proportion of adipose tissue and elevated body mass index [2]. Knees are more often affected with OA than other joints as the knees are the primary weight-bearing joints, and injury after the age of 30 may increase the risk for developing OA in the United States [1,3]. The elevated risk for the promotion of knee OA is clear as more than 21.1% of adults older than 60 years experience symptomatic osteoarthritis in the knee, compared to 8% in the hand and 4.4% in the feet. This highlights the burden of knee OA in the population older than 60 years in the United States [1,4,5].

The mechanisms that promote OA of the knee are similar to those that allow OA to develop in other joints, with the knee being slightly more affected by trauma and stress than other joints due to the increased strain experienced by the knee. Besides increased mechanical strain and microinjuries more commonly experienced by the knee, cellular mechanisms also act to degrade cartilage in the knee and other joints affected by OA. Matrix metalloproteinases (MMPs) are expressed in joint tissues and have been shown to contribute to cartilage destruction that promotes the further development of OA and joint degradation [6]. Besides MMPs, other inflammatory mediators have been associated with the cartilage destruction that characterizes OA and act specifically after mechanical injury. These proinflammatory mediators have been found to include prostaglandins, cytokines, nitric oxide, and proteases and act to perpetuate mediators have been found to include prostaglandins, cyclooxynge activity with a potential role in OA [12,13]. In vitro. Anthocyanins and flavonoids in PFP [10,13] may also act as important antiinflammatory mediators to improve OA and, thus, may alleviate symptoms. The PFP reduced symptoms of asthma in patients after just 4 weeks of treatment [10], in partial, because of the antiinflammatory effects of the flavonoids present in PFP along with other components that scavenge free radicals and act as antioxidants [10]. This effect shown for the treatment of asthma may indicate the propensity for PFP to act as an antiinflammatory agent in OA with the ability to inhibit some of the cartilage-degrading processes that occur with OA. The key study objective tested the role of the PFP extract containing bioflavonoids with antioxidant and antiinflammatory activity [10,13] in alleviating symptoms of knee OA in patients.

2. Methods and materials

2.1. Human subjects

Patients were eligible for the study if they fulfilled the American College of Rheumatology criteria for primary knee OA grade 1 or 2, were between 25 and 65 years of age and had a Western Ontario and McMaster Universities (WOMAC) pain subscale index of at least 40 at the baseline. They also had to have intermittent or constant pain in the target knee for at least 50% of the time requiring medical treatment with NSAIDs, or selective cyclooxygenase 2 inhibitors most days for the previous 3 months. Exclusion criteria were as follows: secondary OA (due to a known disorder); arthroscopy, surgery, or a joint injection of the target knee within the previous 6 months; history of knee joint replacement; any serious systematic disease; any other chronic inflammatory disease; or taking any other supplement other than a single daily multivitamin. The WOMAC tests and study design were done and used as previously described by us [7].

2.2. Study design

This randomized, parallel-group, double-blind, placebo-controlled trial was approved by the ethical committee of Mashhad Medical University (Iran). The study was conducted at the rheumatology department of Mashhad Medical University. At the screening visit, after explaining the objective of the study and verifying the inclusion and exclusion criteria, each subject signed a written informed consent, followed by a physical examination and x-ray evaluation. In the second (baseline) visit, patients completed the WOMAC form and were allocated randomly to either the PFP (150 mg, daily) or matched placebo group in a double-blinded manner (refer to Fig. 1). The PFP was an extract of

Passiflora edulis, has shown great promise in reducing hypertension and asthma [10,13]. Therefore, we hypothesized that PFP might mediate the effects of OA [10,11]. Particularly, PFP inhibits matrix metalloproteinase (MMP-2 and MMP-9), a pharmacologic property of PFP capable of limiting the detrimental role of the MMPs in OA [12], in vitro. Anthocyanins and flavonoids in PFP [10,13] may also act as important antiinflammatory mediators to improve OA and, thus, may alleviate symptoms. The PFP reduced symptoms of asthma in patients after just 4 weeks of treatment [10], in partial, because of the antiinflammatory effects of the flavonoids present in PFP along with other components that scavenge free radicals and act as antioxidants [10]. This effect shown for the treatment of asthma may indicate the propensity for PFP to act as an antiinflammatory agent in OA with the ability to inhibit some of the cartilage-degrading processes that occur with OA. The key study objective tested the role of the PFP extract containing bioflavonoids with antioxidant and antiinflammatory activity [10,13] in alleviating symptoms of knee OA in patients.

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the skin of the passion fruit (Passiflora edulis) that had been purified to concentrate the organic constituents with anthocyanins and flavonoids as the principal compounds as shown in the chromatograms from high-pressure liquid chromatography in Fig. 2. The placebo pills contained inactive ingredients with no therapeutic activity and an identical appearance.

After the baseline visit, follow-up visits were scheduled on days 30 and 60. The flow of patients is shown in Fig. 1. At each clinical visit, the effect of the treatment on joint pain, stiffness, and physical function were evaluated using the WOMAC index, a questionnaire containing 24 visual analog scales [7]. Subjects were also supplied with study medication and a diary form, indicating the frequency and dosage of NSAIDs and cyclooxygenase 2 inhibitor use. They were instructed to return the diary form and unused pills at the monthly follow-up visit. Participants’ compliance was evaluated by counting the pills at each visit. All changes in concomitant medications and clinical adverse events, either volunteered or elicited by questioning at follow-up visits, were recorded. For safety evaluation, blood samples were obtained at the baseline and day 60 to determine the biochemical parameters including fasting plasma glucose, alanine aminotransferase, aspartate aminotransferase, urea, and creatinine level. All were analyzed by the clinical laboratory of Mashhad Medical School.

2.3. Preparation of PFP extract

The PFP was an extract of the skin of the passion fruit that has been purified to concentrate the organic constituents with anthocyanins and flavonoids as the principal compounds as shown in the high-pressure liquid chromatography in Fig. 2. The placebo pills contained inactive ingredients with no therapeutic activity and an identical appearance.

2.4. Statistical analyses

The data are expressed as mean ± standard deviation. Statistical analyses were performed with SPSS version 11.5 (SPSS Institute, Chicago, Ill). Values obtained from the PFP group were compared with the placebo group using the Student *t* test. Comparable nonparametric tests (Kruskal-Wallis and rank sum test) were substituted when tests for normality and equal variance failed. A value of *P* < .05 was used as a criterion for statistical significance. Analysis was performed according to the intention-to-treat principle. A per-protocol analysis was also conducted.

3. Results

A total of 40 subjects met the inclusion and exclusion criteria. During the study, 7 subjects declined to continue to participate. The four that were lost from the placebo group was due to their perceived lack of efficacy. There were three in the PFP group who failed to return during the study (Fig. 1). The OA group had 5 males and 12 females, whereas the placebo group had a similar sex ratio of 3 males and 13 females. The groups had similar demographics and clinical characteristics at the baseline, and no significant differences were observed at the baseline (Table 1). No side effects were reported during the study, as was also found in previous PFP studies [10,13]. The results of the hematology and blood chemistry tests performed at the baseline and at the end of the treatment showed no changes, and there was no statistically significant difference between the control and treatment groups (data not shown).

After 30 days of supplementation with PFP, there was a significant reduction in WOMAC pain and physical function scores, as well as composite WOMAC index, when compared to the placebo group (*P* < .001). Table 2 shows the effect of PFP compared to the control groups on pain, physical activity, and stiffness in the joints. The WOMAC scores for the PFP improved at every time point. The WOMAC score for physical function improvement was statistically significant at 30 days (*P* < .05) and 60 days (*P* < .001), and the score for pain was significant at 60 days (*P* < .001). The WOMAC scores in the placebo group did not show any consistent improvement (Table 3). Fig. 2 further demonstrates the effect of PFP supplementation as the WOMAC score decreased for the PFP group consistently, whereas the score in the placebo group worsened.

4. Discussion

Evidence-based dietary supplements are becoming more influential as viable treatments for common chronic diseases involving inflammation [7–10,13]. This study provides initial evidence of a beneficial effect of purple passion fruit peel extract through its reduction of the debilitating symptoms associated with OA. To our knowledge, this is the first randomized clinical trial to show the effectiveness of PFP, a
dietary supplement with known anti-inflammatory activities, in alleviating the clinical symptoms of knee OA. The patients in this study experienced improved physical activity, reduced pain, and less stiffness in affected knee joints, as we hypothesized based upon previous clinical trials [10,13]. Passion fruit peel inhibits MMP-2 and MMP-9 efficiently in vitro, which may improve the condition of knee OA.

Oxidative stress is implicated in knee OA [10,13]. The antioxidant and free radical scavenging activities of constituents of PFP, such as quercetin and other flavonoids, may reduce the propensity for oxidative stress in knee OA and, thus, improve the clinical symptoms in patients with knee OA [11,13]. The study limitations included not defining the effects by sex and the responses to long-term treatment.

The effect of PFP has been explored previously for the treatment of asthma and hypertension [10,13]. Passion fruit peel acts as a significant antiasthmatic because of the free radical scavenging and antioxidant activity of PFP [10], helping explain its actions on OA symptoms. The flavonoid constituents in PFP likely contribute to this antiasthmatic effect. Hypertension was also reduced in patients supplemented with PFP after the production of nitric oxide was reduced [13]. Nitric oxide was modulated by PFP.

Table 1
Baseline characteristics of study subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>PFP group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Age (y)</td>
<td>55 ± 14.1</td>
<td>49.71 ± 14.0</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>5/12</td>
<td>3/13</td>
</tr>
</tbody>
</table>

Values are presented as means ± SD.
Table 2
Effect of purple PFP extract on WOMAC subscales of pain, stiffness, physical function, and composite score over time in subjects with knee OA

<table>
<thead>
<tr>
<th>WOMAC score</th>
<th>Baseline</th>
<th>PFP 30 d</th>
<th>PFP 60 d</th>
<th>Placebo Baseline</th>
<th>Placebo 30 d</th>
<th>Placebo 60 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>22.6 ± 6.9</td>
<td>21.3 ± 6.2</td>
<td>18.4 ± 5.5**</td>
<td>22.8 ± 7.8</td>
<td>25.8 ± 11.0</td>
<td>28.0 ± 5.9</td>
</tr>
<tr>
<td>Stiffness</td>
<td>11.1 ± 4.3</td>
<td>9.8 ± 3.7</td>
<td>9.1 ± 3.3</td>
<td>10.1 ± 4.4</td>
<td>12.4 ± 5.2</td>
<td>10.8 ± 8.7</td>
</tr>
<tr>
<td>Physical function</td>
<td>86.6 ± 16.9</td>
<td>77.2 ± 15.8*</td>
<td>69.6 ± 18.0**</td>
<td>87.9 ± 25.7</td>
<td>115.7 ± 49.0</td>
<td>112.4 ± 33.6</td>
</tr>
<tr>
<td>Composite</td>
<td>120.3 ± 23.4</td>
<td>108.3 ± 20.6</td>
<td>97.1 ± 22.6**</td>
<td>120.9 ± 33.9</td>
<td>125.8 ± 51.1</td>
<td>150.2 ± 42.4</td>
</tr>
</tbody>
</table>

WOMAC was completed at the baseline and at 2 other visits of the randomized, placebo-controlled treatment with PFP extract, showing that PFP supplementation resulted in a relevant improvement of WOMAC subscales, with the exception of stiffness. Values are presented as means ± SD.

* P < .05 compared with the control group (analyzed by Student t test).
** P < .001 compared with the control group (analyzed by Student t test).

supplementation by the quercetin, luteolin, cyanidin 3-O-glucoside, and other flavonoids, which resulted in the improvement in hypertension [13]. In OA, the same processes could support the reduction in the pathologic condition of OA. Nitric oxide and reactive oxygen species have multiple activities that promote the degradation of articular cartilage via actions on chondrocytes in patients with OA and those susceptible to develop OA [17]. Passion fruit peel may also act as a protective agent against OA because of its ability to reduce nitric oxide production, as this would lead to the reduction in the potential for articular cartilage degeneration [6,13,17]. The ability for PFP to moderate nitric oxide production was observed in a study looking at PFP and hypertension [13]. Hypertension development was slowed in SR rats when treated with PFP, which modulated nitric oxide production.

The PFP extract with its unique mixture of bioflavonoids with antioxidant and inflammatory activity shown previously [10,13], as predicted, reduced symptoms of knee OA, which is known to be caused, in part, by oxidation and inflammation. This may have occurred via regulation of proinflammatory mediator production by human chondrocytes, modulated by some of the flavonoids in PFP. Genistein is a component of soy shown to reduce symptoms of OA [14]. Genistein, a selective estrogen receptor modulator, suppressed nitric oxide and cyclooxygenase production by human chondrocytes activated in tissue culture [16]. Some flavonoids may act similarly to estrogen with antiinflammatory effects [16], reducing inflammatory mediator release. Such actions would play a pivotal role in OA pathogenesis. Flavonoids, such as those in PFP, attenuate inflammation by inhibition of important regulatory enzymes involved in arachidonic acid metabolism via suppression of cyclooxygenase activity [15,18,19] and could also directly regulate chondrocytes.

In summary, PFP supplementation should help patients to reduce their reliance upon NSAIDs without undesirable side effects because PFP mediates OA symptoms. An increasing number of people in the United States are using dietary supplements as alternatives to pharmaceutical drugs. This is especially found with supplements such as PFP that have a scientific basis for clinical benefits and appear to have no toxicity compared to NSAIDs that may have significant side effects. Overall, the ability for PFP to act as an antiinflammatory agent, antioxidant, and MMP inhibitor may explain its reduction in OA pathology in the patients studied in this double-blinded, placebo-controlled study. The PFP supplementation should help patients to reduce their reliance upon NSAIDs that may have undesirable side effects in the treatment of OA symptoms.

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References


