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The effect of *Dioscorea esculenta* powder on PGE_2 and COX-2 levels, menstrual pain and premenstrual syndrome in young women: a randomized double-blind controlled trial

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***Running head**: Dioscorea intake and menstrual pain in women*

This study was approved by the Human Research and Ethics Committee of the Graduate School of Human Development and Environment, Kobe University (No.592). The present study registered University hospital Medical Information Network (No. 20220622-083106) in Japan as a clinical trial.

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Abstract

Backgrounds: Diosgenin, extracted from *Dioscorea esculenta*, has reported to decrease prostaglandin E_2 (PGE_2) levels and any other inflammatory cytokine in rodents. However, it is still unclear whether *D. esculenta* intake suppressed PGE_2 production and menstrual pain and premenstrual syndrome in younger female. Aim: This study aims to investigate the effect of *D. esculenta* intake on PGE_2 and cytochrome c oxidase subunit 2 (COX-2) levels and on menstrual pain, premenstrual syndrome in young women. This is a randomized, double-blind, placebo-controlled, crossover study. Methods: Ten healthy young females were administered either a placebo or *D. esculenta* (300 mg/day) for 4 weeks, followed by a 4-week washout period. Fasting blood sample was taken from the fingertips at 2^{nd} day of menstrual cycle began and obtained 24h before last *D. esculenta* to avoid acute effects. Participants then switched treatments for 4 weeks as a second trial. Plasma PGE_2 and COX-2 levels were measured before and after each trial. The visual analog scale (VAS), McGill pain questionnaire (MPQ), and daily record of severity of problems (DRSP) were also evaluated. The study was setting and conducted through 2019 to 2020. Results: PGE_2 and COX-2 levels significantly decreased after *D. esculenta* intake compared to placebo ($P = 0.038$, $P = 0.042$ each). The VAS and DRSP scores were also significantly lower after *D. esculenta* intake ($P = 0.046$, $P = 0.035$ each). Conclusion:

Four-week *D. esculenta* intake suppressed PGE_2 and COX-2 levels, resulting in an improvement in premenstrual syndrome symptoms and menstrual pain in young women.

Keywords

PGE_2, COX-2, diosgenin, menstrual pain, premenstrual syndrome, randomized crossover trial.

Introduction

Most women suffer from menstruation-concomitant symptoms. These may be influenced by physical, mental, and social factors during the menstrual phase, leading to decreased daily living activities and quality of life (QOL). Many women with premenstrual syndrome (PMS) take painkillers or low-dose estradiol. However, symptoms may persist and continue to disrupt their activities of daily living [22]. Therefore, nutrition or dietary supplementation are also explored as possible treatments for pain and other symptoms [22], which may lead to improved QOL and social health of the women.

One of the main factors that contribute to menstruation-concomitant symptoms is increased prostaglandin (PG) secretion, which enhances uterine contraction [5]. PGs are members of a large group of hormonally active fatty acids. They are synthesized from arachidonic acid by the action of cyclooxygenases (COX), prostaglandin G (PGG) synthases, or prostaglandin H (PGH) synthases [28]. There are different types of PGs, each with its own set of functions.

Prostaglandin E_2 (PGE_2) has pro-inflammatory effects. It stimulates sensory nerves to elicit pain and acts on neurons in the preoptic area to upregulate pyrogens [28]. PGE_2 commonly crosstalks with other pro-inflammatory cytokines such as interleukin-6 (IL-6),

IL-1β, and tumor necrosis factor-α (TNF-α) [2]. It is traditionally thought to be an inflammatory mediator that links innate immunity to acute inflammation.

COX is the rate-limiting enzyme in the synthesis of PG and exists in two isoforms, COX-1 and COX-2. COX-2 is induced by inflammatory stimuli, including cytokines and growth factors [38]. While PGE_2 is mainly associated with acute inflammation alone, COX-2 is also seen in chronic inflammation such as cancer and rheumatoid arthritis. Additionally, it has been noted in individuals with severe menstrual pain [24]. Therefore, PG and COX play important roles in both acute and chronic tissue inflammation.

Dioscorea esculenta, a plant widely known as wild yam, contains high levels of diosgenin, a steroid sapogenin that can be extracted from its tubers. Diosgenin is formed from the hydrolysis of saponins by acids, strong bases, or enzymes. It has a steroid molecular structure similar to that of dehydroepiandrosterone (DHEA) [23], a precursor of sex steroid hormones that is converted to testosterone and estradiol [18].

Plasma DHEA levels gradually decrease with age, and it was reported that they were also lower in individuals with obesity and type 2 diabetes. Studies have demonstrated that *D. esculenta* administration alleviates allergies, inflammation [21], hyperlipidemia [16], and osteoporosis [7]. It has also been shown to improve neuroimmunological function [40]. However, it is still unclear whether daily intake of *D. esculenta* downregulates PGE_2

and COX-2 during the menstrual phase. Its effects on menstrual pain and premenstrual syndrome in young females are yet to be clarified. Therefore, the present study aimed to investigate the effect of chronic *D. esculenta* intake on PGE_2 and COX-2 levels during the menstrual phase, as well as menstrual pain and premenstrual syndrome.

Materials and Methods

Participants

Participants were recruited from the students in University at May to July 2019 that included normal menstruation about 21 days to 35 days as well as has symptoms for PMS and menstrual pain. Firstly, fourteen young women recruited the study, and excluded four participants because they were not matched inclusion criteria, so ten healthy young women (aged 21.2 ± 0.4 years) comprised the study cohort, and participants with a history of smoking, medication use, and dietary nutritional supplementation were excluded from this study. Participants were examined by a physician to confirm the absence of medical problems that might preclude participation or affect the study findings, and confirmed they all had primary dysmenorrhea. Room temperature was maintained at 22–24 °C throughout the experiment. This was a double-blind, randomized, crossover study (n=10). Participants were administered *D. esculenta* powder within capsules (300

mg/day) or placebo every day for 4 weeks during the first trial and, after a 4-week washout period, the *D. esculenta* and placebo groups exchanged their assigned treatments for the second trial. This methodology was performed as described in a previous study [34]. The both *D. esculenta* and placebo was saved in the morning for 4 weeks, and participants were supplied *D. esculenta* or placebo each week. An experimenter who mainly handed *D. esculenta* and placebo to participants was blinded throughout the experiment. Height, body weight and body fat (BC-760, Tanita, Tokyo, Japan) was measured when participants visited lab at 2nd day of menstrual period each trial.

This study was approved by the Human Research and Ethics Committee of the Graduate School of Human Development and Environment, Kobe University (No.592). Participants provided written informed consent before the commencement of the study, which conformed to the principles embodied in the *Declaration of Helsinki*. The present study registered University hospital Medical Information Network (No. 20220622-083106) in Japan. Moreover, the experiments have been followed by CONSORT Guidelines.

Blood sampling

Blood samples were obtained to avoid the acute effect of *D. esculenta* intake, blood sampling was conducted 24h after last *D. esculenta* intake as well as to avoid food

consumption fasting blood sample was obtained in accordance with our previous studies [32, 33]. Upon arrival at the laboratory, a blood sample was taken from the fingertips and stored using the MBS Capillary Tube (Micro Blood Science Inc., Tokyo, Japan), which included EDTA-2K. Blood samples were collected before and after each trial; blood sampling during both trials were conducted on the 2nd day of the menstrual phase. Plasma samples were immediately centrifuged at 1500 × *g* at 4 °C for 15 min. The supernatant was immediately transferred to polypropylene tubes and stored at –30 °C until analysis.

Sandwich enzyme immunoassay

The levels of estradiol, progesterone, PGE_2, and COX-2 in the plasma were determined using a sandwich enzyme immunoassay kit. Immobilized polyclonal antibodies against estradiol (Thermo Fisher Scientific, Waltham, MA, USA), progesterone (Novus Biologicals, LLC, Centennial, CO, USA), PGE_2 (Cayman Chemical, Ann Arbor, MI, USA) and COX-2 (Thermo Fisher Scientific, Waltham, MA, USA) were used, along with monoclonal secondary horseradish peroxidase-coupled antibodies. A microplate reader was used to measure the optical density at 412 nm for estradiol and progesterone, and 450 nm for PGE_2 and COX-2 (Thermo Fisher Scientific, Multiskan FC, Yokohama, Japan). All samples were assayed in duplicates.

Questionnaires and Visual analog scale (VAS)

The Japanese versions of the VAS and McGill Pain Questionnaire (MPQ) were used to assess menstrual pain in accordance with a previous study [19, 20]. The Japanese version of the Daily Record of Severity of Problems (J-DRSP) was also used to evaluate PMS symptoms [13]. The questionnaires were utilized during each menstrual phase, at the same time during each trial. VAS was asked 4 times which were from 1^{st} day to 4^{th} day when menstrual phase started. The scores of 1^{st} day to 4^{th} day each trial were averaged.

Statistical analysis

Data are presented as mean ± standard deviation of the mean. Differences were analyzed using a two-way analysis of variance. Post-hoc tests were used for multiple comparisons (Tukey's test) of data with significant differences. Statistical significance was set at $P < 0.05$. All statistical analyses were conducted by StatView version 5.0 (SAS Institute Inc., Tokyo, Japan).

Results

There are no significant differences between after placebo and *D. esculenta* intake in physical characteristics (Table 1).

Estradiol and progesterone concentrations

There were no significant differences before and after the interventions in both estradiol (pre placebo; 20.8 ± 8.3 pg/mL, post placebo; 23.2 ± 7.8 pg/mL, pre *D. esculenta* intake; 22.1 ± 7.2 pg/mL, post *D. esculenta* intake; 25.6 ± 9.6 pg/mL) and progesterone levels (pre placebo; 0.53 ± 0.12 pg/mL, post placebo; 0.58 ± 0.08 pg/mL, pre *D. esculenta* intake; 0.54 ± 0.10 pg/mL, post *D. esculenta* intake; 0.63 ± 0.14 pg/mL). Likewise, no significant changes were seen in the *D. esculenta* group compared to placebo intake.

PGE_2 and COX-2 levels

PGE_2 levels before intervention were not significantly different between the two groups. There were also no significant changes seen in the placebo group before and after the intervention. However, significant suppression of PGE_2 levels was observed after chronic *D. esculenta* intake compared to that in the placebo group ($P < 0.05$; Fig 1A). In terms of COX-2 levels, significant increases were seen after intervention in both placebo and *D. esculenta* intake groups compared to baseline. However, the increase in COX-2 levels was significantly suppressed by *D. esculenta* intake compared to the placebo ($P < 0.05$; Fig 1B).

VAS

The average of the VAS scores from the 1st to 4th day of the menstrual phase was evaluated. There was no significant difference between the two groups at baseline.

However, the mean VAS score of the *D. esculenta* intake group was significantly lower after the intervention than at baseline ($P < 0.05$; Table2).

DRSP and MPQ

The average MPQ score was not significantly different before and after *D. esculenta* intake. No significant difference was observed between the placebo and *D. esculenta* groups; however, the *D. esculenta* group had relatively lower MPQ scores after the intervention than the placebo group ($P = 0.059$; Table 2). The average of DRSP score was significantly lower than that in the placebo group, and a significant change was observed after *D. esculenta* intake compared to baseline ($P < 0.05$; Table 2).

Discussion

In the present study, chronic *D. esculenta* intake significantly decreased VAS and DRSP scores compared to placebo intake. Therefore, chronic oral intake of *D. esculenta* alleviated menstrual pain and PMS symptoms in young, healthy women. The decrease in VAS and DRSP scores may be attributable to increased testosterone levels. Aizawa et al. reported that DHEA administration in rodents increased estradiol levels in males and testosterone levels in females [1]. According to previous studies, low testosterone levels cause fatigue, anxiety, depression, and irritability [4]. Testosterone has also been used for pain treatment, as it contributes to healing and pain reduction in long-term pain care [8].

Therefore, the increase in DHEA and testosterone in young women after *D. esculenta* intake likely led to the reduction in VAS and DRSP scores. However, total testosterone and free testosterone levels were not measured in the present study. Thus, further studies should focus on the effect of *D. esculenta* intake on testosterone levels, apart from menstrual pain and PMS symptoms. Additionally, MPQ, VAS was generally used for evaluation of menstrual pain and, these have higher validity and reliability [3], and DRSP conducted for determination of PMS and higher validity and reliability according to previous study [14]. The average of the VAS scores from the 1st to 4th day of the menstrual phase in the present study because large difference among participants were seen, such as higher only 1^{st} and/or 2^{nd} day or higher score throughout 1^{st} to 4^{th} day of the menstrual phase. It needs further investigation for evaluation method or biomarker of menstrual pain during menstrual pain

In the present study, four-week oral *D. esculenta* intake is postulated to have caused a decrease in PG secretion. The suppression of the menstruation-induced increase in PGE_2 and COX-2 results in decreased uterine muscle contraction and alleviated pain during the menstrual phase. Although women with severe menstrual pain or PMS take painkillers or low-dose estradiol, symptoms may persist and continue to disrupt their activities of daily living. Therefore, these results suggest that *D. esculenta* supplementation are explored as

possible treatments for pain and other symptoms, which may lead to improved QOL and social health of the women without any side-effects. As mentioned, COX is the enzyme catalyzing the rate-limiting step for the secretion of prostaglandins. COX expression may be induced by lipopolysaccharides (LPS) or other inflammatory stimuli. A study reported that *D. esculenta* supplementation reduced PGE_2 and COX-2 levels by more than 60% in rodents [37]. Moreover, *D. esculenta* intake was found to improve the symptoms of rheumatoid arthritis [6], and asthma [26].

Our previous studies also reported that *D. esculenta* supplementation caused an increase in the levels of DHEA [29, 30], which is converted to testosterone and estradiol in peripheral tissues. Generally, DHEA has potent anti-inflammatory properties, and many chronic inflammatory diseases are associated with lower serum DHEA levels [35]. Additionally, DHEA administration suppressed PGE_2 secretion and COX-2 gene expression. It also reduced the secretion of other pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 [36]. The mechanism of the anti-inflammatory action of DHEA seems to involve the direct inhibition of the transfer of nuclear factor kappa B (NF-κB) to the nucleus. This occurs through the activation of peroxisome proliferator-activated receptor alpha (PPARα), which inhibits the binding of the nuclear factor activator protein 1 (AP-1) to DNA [15]. Therefore, the *D. esculenta*-induced increase in DHEA levels may

suppress PGE_2 and COX-2 levels, resulting in the mitigation of menstrual pain in the present study.

The symptoms of dysmenorrhea include abdominal pain, headache, nausea, diarrhea, depression, frustration, and anorexia [27] Physical symptoms mainly manifest due to uterine contractions induced by PGE_2 secretion [27]. In contrast, psychological symptoms may be caused by fluctuations in hormone levels such as estradiol and progesterone, which change according to the menstrual cycle [39]. Estradiol modifies the function of the serotonergic system, resulting in the suppression of frustration and anxiety [10]. It has been reported that isoflavone, which has an estrogenic function, improves symptoms of PMS such as abdominal pain, headache, and anxiety [9]. In a previous study, 8-week administration of *D. esculenta* (2000 mg/day) to young sprint athletes resulted in increased serum DHEA and free testosterone levels [12]. Another study investigated the effect of *D. esculenta* in ovariectomized rats. *D. esculenta* was administered at varied dosages (250, 750, 1500 mg/kg/day) for 27 days, and the results showed that a 250 mg/kg dose of *D. esculenta* reduced interleukin-2 (IL-2) levels and anxiety [11]. Moreover, single doses of *D. esculenta* (200–800 mg/kg) resulted in a reduction in fasting blood glucose levels in diabetic rats [17]. Many existing studies also investigated the effects of higher doses of *D. esculenta* on both humans and rodents [11, 12, 17]. They involved a

large amount of diosgenin, which increased DHEA levels and enhanced steroidogenesis in peripheral tissues. The net effect of this process is increased testosterone or estradiol levels, especially in older and diabetic patients who generally have lower sex steroid hormones [29, 30]. However, *D. esculenta* administration and higher levels of DHEA did not increase sex steroid hormone levels in individuals with sufficient sex steroid hormones, such as young, healthy rodents [31].

In the present study, the dose of *D. esculenta* was 300 mg/day for 4 weeks. Fluctuations in the hormonal balance between progesterone and estradiol were not observed. Although further studies are needed to optimize the dosage for young and healthy adults, the dosage used in the present study was noted to reduce menstrual pain and inflammation-related biomarkers. The results suggested that chronic oral intake of *D. esculenta* suppressed the increase in PGE_2 and COX-2 levels, resulting in the alleviation of menstrual pain and PMS in young, healthy females. Thus, *D. esculenta* supplementation may be a new therapeutic candidate for treatment and prevention of PMS or severe menstrual pain without side-effect. Moreover, the *D. esculenta* supplementation induced improvement for menstrual pain or PMS would lead to improvement of QOL and social health of the women.

Study limitation

Prostaglandin F2 alpha (PGF_2) also related to dysmenorrhea [41] and PGF_2 level increased in women with dysmenorrhea and was directly related to the menstrual pain [25]. Therefore, it should focus on PGF_2 level for future study. Moreover, the number of participants in the present study was less and need a greater number of participants.

Conflict of interests

The authors declare that they have no conflict of interest concerning this article. All authors have been given the opportunity to comment on the content of this manuscript and have approved its submission.

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Figure legends

Figure 1: Effect of *Dioscorea esculenta* intake on plasma prostaglandin E_2 (PGE_2 :A) and cytochrome c oxidase subunit 2 (COX-2 : B) levels. Data are presented as means ± SD. Dio: *D. esculenta* intake. * $P < 0.05$ compared with placebo intake. † $P < 0.05$ compared with baseline.

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