

Acute effects of ginger extract on biochemical and functional symptoms of delayed onset muscle soreness

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Abstract

Background: Inflammation and pain induced by delayed onset muscle soreness (DOMS) as a result of eccentric exercise (EE) or unaccustomed activity cause some difficulties in exercise for athletes. The purpose of this study was to survey the effect of ginger extract on biochemical and functional symptom of delayed onset muscle soreness.

Methods: In a quasi-experimental study, 36 healthy female subjects, who were recruited by intra dormitory calls, randomly divided into 3 groups, including: ginger intake 1 hour before exercise (GIBE), ginger intake immediately after exercise (GIAE) and placebo group (PL). Subjects consumed capsules contain 60 mg of ginger extract (equivalent of 2 g dried ginger powder) or placebo before and after exercise. The exercise protocol consisted of a 20 minute step test using a 46cm step at a rate of 15 steps per minute. The blood samples were taken before, 1, 24 and 48 hour after exercise to assay creatine kinase (CK) and interleukin-6 (IL-6). Muscle pain scores, isometric strength and circumference of thigh muscle, and hip range of motion were recorded at mentioned times. The analysis of variance (ANOVA) with repeated measure was used to determine the differences between groups.

Results: The results showed a significant reduction of pain in GIBE compared to GIAE after 24 and 48h of EE and GIAE compared to PL ($p < 0.05$). IL-6 changed significantly in GIBE compared to PL ($p < 0.05$) after 1, 24, and 48h after EE. The other factors didn't change meaningfully.

Conclusion: The finding of this study suggests that 2 grams of ginger may have anti-inflammation and analgesic effect on DOMS.

Keywords: muscle soreness, exercise, Ginger, Interleukin-6, Creatine kinase (CK).

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Introduction

Delayed onset muscle soreness (DOMS) is an unfavorable and unsightly feeling with pain and muscle stiffness consequence of training that can deter a beginner or even an athlete from continuing with the exercise. It frequently occurs as a result of strenuous unaccustomed physical activity chiefly eccentric exercise in which force producing increase s and lead to DOMS (1-6).

Five important signs of DOMS are acute inflammation, pain, swelling, loss of func-

tion and range of motion (7,8) and increase in Thigh circumference (5). The main mechanism of DOMS is not specified, but there are some theories about it. Inflammation theory is one of the most important of them (9). DOMS causes an increase in inflammatory cytokines like IL-6, IL-8, and TNF- α , in the working muscle, plasma, and perhaps even the brain (10-13). Numerous treatment strategies, both preventive and rehabilitative, have been suggested to help relieve the severity of DOMS. Some of the

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presented treatments including herbal remedy (14-16) pharmacological treatments using non-steroidal anti-inflammatory drugs NSAIDs (17, 18) nutritional supplements (19-21) vibration (22,23), cryotherapy have been carried out (1, 24). However, little scientific evidence exists to support the full effectiveness of any of these therapeutic interventions (12).

One of the most used treatments is non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, aspirin, ketoprofen, naproxen, etc. (12,17,19). These drugs control the generation of prostaglandins and provoke the neural terminals of afferent neural fibers and ultimately the pain will be relieved (15, 18). But NSAID's use is limited by the risk of adverse effects, particularly gastrointestinal and renal toxicity (25).

Zingiber officinale, commonly known as ginger, has been widely used in Ayurvedic and Chinese medicine for arthritis, rheumatism, sprains and muscular aches. It has shown analgesic and anti-inflammatory effects. Ginger inhibits the production of immune-system components called cytokines causing inflammation (26). Gingerols and shogaols, which are constituents of ginger, have been shown to inhibit cyclooxygenase (COX) 1 and 2. Ginger constituents inhibit arachadonic acid metabolism and thus prostaglandin synthesis. One constituent specifically (6), Shogaol, (found in semi-dry, but rarely fresh ginger), appears to interfere with the arachadonic inflammatory cascade (14,26). It is found to inhibit cyclooxygenases and prevents specific prostaglandin release and hereby interacting with the vanilloid receptor TRPV1, which is known to play a role in processing nociceptive signals (27,28). Daily consumption of raw and heat-treated ginger resulted in moderate-to-large reductions in muscle pain following exercise-induced muscle injury in horses (14). Consuming a 30-g dose of ginger has also been shown to increase recovery of the fast phase of oxygen consumption after a maximal exercise test and reduces cardiovascu-

lar recovery time but has no effect on inflammatory factors (CK and IL-6 mRNA) (16). Ginger was as effective as mefenamic acid and ibuprofen in relieving pain in women with primary dysmenorrhea (29).

The purpose of current study was to determine if consumption of 2-g oral doses of ginger one hour before and immediately after exercise would inhibit or decrease signs of DOMS.

Methods

Subjects

Forty untrained college students (women, age between 21 and 24 year) volunteered to participate in the study. Risks and benefits were explained to the subjects. Four of them were excluded from participation because of the blood testing. The rest were given a written informed consent and health questionnaire. All participants were screened for medical and orthopedic conditions that would preclude performance of strenuous step test. To control subject's diet, they were asked to feed from the dormitory dietary program, refrain from caffeine derivatives, medications and supplements, alcohol and didn't train at least ten days before and during testing days. Height and weight were taken for BMI assaying.

Procedures

A double-blind, randomized placebo-controlled design was used for this study. Participants divided randomly into three groups including: GIBE (Ginger Intake Before Eccentric exercise, n=12), GIAE (Ginger Intake After Eccentric exercise, n=12), and PL (placebo, n=12). Participants managed to eat 60 mg ginger extract (equivalent 2 grams dried ginger) in the form of capsule. All subjects received a specific code to show their groups and just the physician of the project knew if it is a ginger group or placebo. She revealed the codes after the statistical analyze. Table 1 shows time course of ginger using. The subjects were asked to keep their nose while eating capsule because the smelling of ginger didn't make them to prejudge

Table 1. Time course of ginger consumption.

Group	1 hour before exercise	Immediately after exercise
GIBE	Ginger capsule	Placebo
GIAE	Placebo	Ginger capsule
PL	Placebo	Placebo

about their feeling of pain when they report it in the following steps of test.

Plant material and preparation of extract

Fresh rhizome of ginger (*Zingiber officinale* Rosce) was purchased from a local market in India and authenticated by a botanist (Institute of Medicinal Plants, Jahade-Daneshgahi). The plant was dried in the shade. The dried rhizome was powdered mechanically and extracted by cold percolation with 95% ethanol for 24 hr. The extract was recovered and 95% ethanol was further added to the plant material and the extraction continued. The process was repeated three times. The three extracts were pooled together and the combined extract was concentrated under reduced pressure (22 – 26 mm Hg) at 45 – 60°C. Thirty gram of solvent-free extract was equivalent to one kilogram of the dried ginger (W/W) powder. The concentrate was weighed and combined with the necessary excipients, and then filled into 500-mg capsules, each containing 60 mg of the ginger extract equivalent 2 g ginger powder. The same capsules were filled with lactose (70%), starch (20%) and talk (10%) as placebo. All of the above-mentioned procedures were undertaken in the industrial pharmacy department of the Faculty of Pharmacy, Tehran University of Medical Sciences (TUMS).

Protocol design

The exercise consisted of a 20 minute step test using a 46cm step at a rate of 15 steps per minute. All subjects go up with right leg and go down with left leg and do this with beep sounds of the metronome. Every 5 minutes they took a rest for 1 minute in a standing position. This exercise intensity has been demonstrated to stimulate mild to moderate quadriceps muscle

pain(19,30).

Testing days

During the exercise, heart rate, respiration, pulse and pain of subjects were controlled by a physician. None of the subjects presented any problem. 5cc of blood was taken from brachial vein before the test to measure plasma levels of creatine kinase and interleukine-6. Then subjects consumed one capsule containing either 60 mg of ginger extract (equivalent 2 g dried ginger powder) or 2 g of lactose (placebo) with 250 ml of water. The 2-g dose was chosen because 1- to 2-g doses have been shown to induce central nervous system effects (15, 32, 33). One hour later, subjects performed step protocol in 25 minutes as described before. Subjects ingested second capsules immediately after exercise. 1 hour after exercise, 24 and 48 hour later blood samples were taken again.

Measurement

Pain was measured using a self-reporting visual analog scale (VAS) including a horizontal line, 100 mm in length, anchored by word descriptors at each end “no pain” and “severe pain” (2,31). Subjects were asked to perform one squat and then draw a line on the scale corresponding to their level of soreness (9). Range of motion (ROM) of hip was taken by a Jamar goniometer while subject was laying and the low back and sacrum was flat. Researcher placed the center of the goniometer on the greater trochanter of hip (32). The stationary arm was parallel to the trunk and movable arm was parallel to the femur. Subject flexed knee and hip as she had felt no pain. Data were recorded for an average of three times. Thigh muscle circumference was measured using a Gulick anthropometric tape (measured 15 cm above the superior border of the

patella). A mark was placed on each participant's thigh for the next measurement (33). Subjects completed the assessments at 1, 24 and 48 hour after the test again. Blood samples centrifuged at the test performance place to prevent changing in serum enzymes. Human IL-6 kit (Canada, ID Lab Company) and creatine kinas kit CK-MM ELISA Kit were used in the laboratory.

Statistical Analysis

ANOVA was used for checking the differences within groups in different times and Repeated Measure and Bonferroni post hoc were used for checking the differences between groups. Moreover, to compare the results in different measurement between groups. The interaction effect of time and group was also measured. All statistical analysis were performed using SPSS 20. The significant level was considered at $p \leq 0.05$.

Results

In our quasi-experimental study, 36 subjects were participated. IL-6, CPK thigh circumference, hip range of motion and pain

rate of subjects were measured. The mean and standard deviation of participants are provided in Table 2.

The descriptive indexes (Mean \pm SD) of thigh circumference, hip range of motion and pain rate of subjects has been shown in Table 3.

The interaction effect of group and time was just significant for thigh muscle pain.

According to Tables 3 and 4, the interaction effect of group and time is just significant for thigh muscle pain. Table 3 shows that there is no significant difference between groups in right thigh circumference. Nevertheless the result of ANOVA with repeated measurements and Bonferroni post hoc for each group showed significant difference between right thigh circumference in pre-test and after 1h of EE with after 24h values in placebo group. About the left thigh circumference values, there is no significant difference between groups. Within group analysis showed significant difference between left thigh circumference in pre-test and after 1h of EE with 24h and 48h after EE in GIBE. Within group analysis showed significant difference in range

Table 2. Characteristics of participants.

Characteristic	Mean \pm SD	Min.	Max.
Age (year)	22.0 \pm 2.48	18	29
Height (cm)	159.3 \pm 5.67	147	171
Weight (kg)	57.1 \pm 8.00	41.6	74.6
BMI (kg/m ²)	22.5 \pm 2.99	17.95	31.53

Table 3. Mean \pm SD of thigh circumference, hip range of motion and pain.

Variable	Group	Pre-test	After 1h	After 24h	After 48h
Right thigh circumference	GIBE	54.5 \pm 4.52	54.6 \pm 4.62	54.7 \pm 4.51	54.9 \pm 4.15
	GIAE	57.2 \pm 4.65	57.5 \pm 5.01	57.7 \pm 11.53	57.7 \pm 5.03
	PL	54.2 \pm 3.43	54.9 \pm 3.41	55 \pm 3.58*	54.7 \pm 3.69
Left thigh circumference	GIBE	54.3 \pm 4.58	54.2 \pm 4.48	54.8 \pm 4.38*!	54.2 \pm 4.19*
	GIAE	57 \pm 4.65	56.8 \pm 4.67	57.3 \pm 4.95	57.4 \pm 4.74
	PL	54.1 \pm 2.96	53.7 \pm 3.14	54.4 \pm 3.47	54.2 \pm 3.37
Right Hip Range Of Motion	GIBE	108 \pm 8.77	101.7 \pm 9.64	98.5 \pm 8.44*	97.7 \pm 10.3
	GIAE	105.7 \pm 7.09	101.5 \pm 7.01*	97 \pm 11.78	98.6 \pm 9.34
	PL	105.8 \pm 6.81	100.3 \pm 10.81	99.3 \pm 11.91	97.3 \pm 11.52
Left Hip Range Of Motion	GIBE	106.3 \pm 10.49	101.1 \pm 11.58	93.5 \pm 7.44*	93 \pm 11.08
	GIAE	105.7 \pm 8.41	108.8 \pm 12.02	91.3 \pm 19.65!	98.8 \pm 14.46
	PL	110.9 \pm 9.73	99.7 \pm 7.53*	93.6 \pm 8.05*	93 \pm 11.19*
Thigh muscle pain	GIBE	0	7.9 \pm 6.56*	57.9 \pm 10.76 \ddagger *!	53.7 \pm 9.32 \ddagger *
	GIAE	0	3.0 \pm 3.06*	40.0 \pm 11.28 \ddagger *!	33.3 \pm 9.85 \ddagger *!
	PL	0	6.8 \pm 5.81*	65.0 \pm 14.30*!	58.75 \pm 8.82*!

* ($p \leq 0.05$), (mean \pm SD)

\ddagger Significant difference between GIBE and GIAE

\ddagger Significant difference between GIAE and PL

* Significant difference in comparison with pre-test

! Significant difference in comparison with previous phase of measurement

Table 4. The interaction effect of group and time on indexes of the study * (P<0.05)

Variable	Factor	F+	p
IL-6	Group × Time	1.048	0.349
CPK	Group × Time	1.325	0.263
Thigh muscle pain	Group × Time	12.481	*0.0001
Right thigh circumference	Group × Time	0.221	0.302
Left thigh circumference	Group × Time	1.267	0.280
Right Hip Range of Motion	Group × Time	0.252	0.933
Left Hip Range of Motion	Group × Time	1.597	0.180
Isometric strength of thigh	Group × Time	0.433	0.787

of motion (ROM) of right and left hip in pre-test and after 24h of EE in GIBE. There were significant differences in right hip ROM in 1h after EE in GIAE and in 24h in GIBE in both right and left hip ROM compared to pre-test values. In PL, there was significant difference in left hip ROM in pre-test values compared to 1, 24 and 48h after EE.

According to table 3, there is significant difference between GIBE and PL with GIAE in pain after 24 and 48h of EE. The results of repeated measurements show that in all of the groups, rate of the pain increased significantly after 1, 24 and 48h of EE in comparison with pre-test. In all of the

three groups, in comparison with 1h after EE, rate of the pain at 24h after EE, had significant difference. Also, in GIAE and PL, rate of the pain at 48h after EE had significant difference compared with 24h, but not in GIBE.

According to analysis of variances outputs (ANOVA) it has been shown that there is significant difference between GIBE and GIAE ($p \leq 0.001$) and also between GIBE and PL ($p = 0.01$) at 1h after EE (Fig. 1). This difference is significant at 24h after EE (between GIBE and GIAE, $p = 0.001$) and 48h after EE (between GIBE and GIAE, $p = 0.001$ and GIBE and PL, $p = 0.05$). The result of ANOVA with repeated meas-

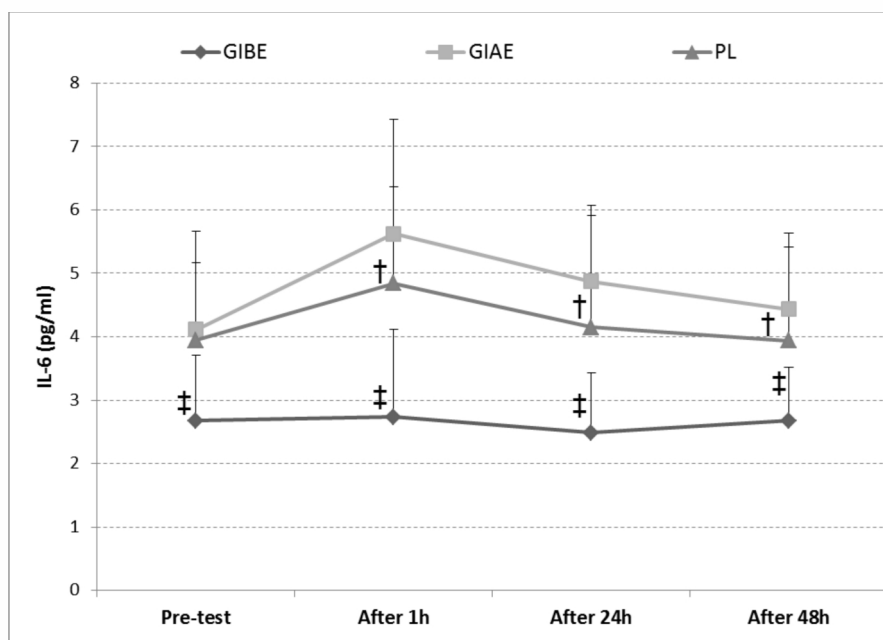


Fig. 1. The changes of IL-6

- ‡ Significant difference between GIBE and GIAE
- † Significant difference between GIBE and PL
- †† Significant difference between GIAE and PL
- * Significant difference in comparison with pre-test
- ! Significant difference in comparison with previous phase of measurement

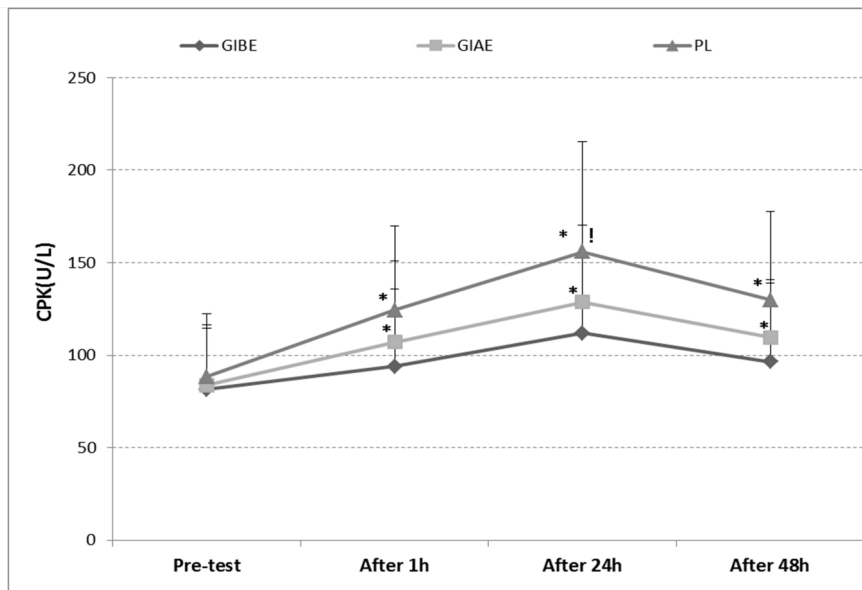


Fig. 2. The changes of CPK

‡ Significant difference between GIBE and GIAE

† Significant difference between GIBE and PL

†† Significant difference between GIAE and PL

* Significant difference in comparison with pre-test

! Significant difference in comparison with previous phase of measurement

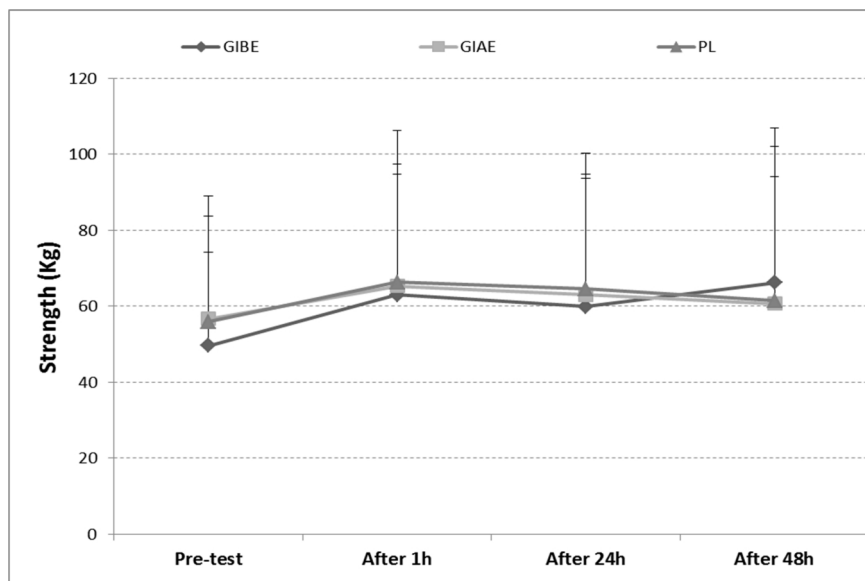


Fig. 3. The isometric strength of thigh

‡ Significant difference between GIBE and GIAE

† Significant difference between GIBE and PL

†† Significant difference between GIAE and PL

* Significant difference in comparison with pre-test

! Significant difference in comparison with previous phase of measurement

measurements for each group didn't show any significant difference between the phases of measurement within groups.

As it is shown in Figure 2, there is no significant difference between groups in CPK levels ($p > 0.05$). But ANOVA with

repeated measurements for within group showed significant difference in changes of CPK in pre-test than to 24 and 48 h after exercise in GIAE and PL ($p \leq 0.05$). In PL, there is significant difference in the changes of CPK at 1 and 24 h after EE. There is

no significant difference in all of the phases of measurement in GIBE ($p>0.05$). As it is shown in Figure 3, there isn't significant difference in isometric strength of thigh between and within groups after EE in none of the phases of measurement.

Discussion

The purpose of the current study was to examine the acute effect of oral consumption of 2-g dose of ginger extract on some biochemical and functional factors of delayed onset muscle soreness after one session step test as an eccentric exercise. Right and left thigh muscle circumference, ROM of right and left hip, isometric strength of thigh and CPK after step test did not differ between ginger and placebo conditions but the ratio of pain and IL-6 were significantly different between groups. Ginger exhibited hypoalgesic effect on quadriceps pain intensity in GIBE and GIAE compared with PL.

The finding that ginger reduced muscle pain as a result of delayed onset muscle soreness caused by eccentric exercise is consisted with previous studies demonstrating that 2-g use of raw or heated ginger can reduce arm pain in human after eccentric elbow action (14). One study showed that administration of 1500 mg ginger powder daily for three days produce analgesia in students with primary dysmenorrhea (34). Ginger act as a pain relief in patients with osteoarthritis of the knee (35) and have more effect than ibuprofen (25). But ingesting 2-grams of ginger doesn't have any effect on quadriceps muscle pain during and after moderate-intensity cycling exercise (15) and this may be because of the severity of the protocol was used. 6-Shogaol is one of the major biologically active compounds found in the rhizome of *Zingiber officinale*/ginger that have analgesic effects (26). To explain the effects of ginger on pain relief, it has been reported that ginger inhibits cyclooxygenase and lipoxygenase pathways in prostaglandin and leukotriene synthesis and the anti-inflammatory property of ginger has been attributed to inhibition of

prostaglandin synthesis (26, 36). Inflammatory response ends up in autacoid leukotriene synthesis. PGE₂ directly causes pain by sensitizing types III and IV pain receptors. In the current study, perception of pain in GIBE was less than GIAE and PL and this may be due to the inhibitory effect of ginger on prostaglandin's release. It seems that consumption of ginger before exercise could cease the cascade of inflammatory factors and thereby caused a lesser pain report. Ginger also showed an inhibitory effect on IL-6 in GIBE compared with GIAE and PL; but within groups there was no difference. According to the results of some in vitro studies, rhizome of ginger and its main components, gingerols and shogaols, can inhibit synthesis of pro-inflammatory cytokines including IL-1, TNF- α and IL-8 along with inhibiting prostaglandin and leukotriene synthesis enzymes (37). The systemic response to inflammation rapidly becomes anti-inflammatory as plasma levels of IL-6, IL-10, IL-1ra and soluble TNF- α receptors rise in direct proportion to the intensity and duration of exercise (38, 39). The release of the pro-inflammatory cytokines into the circulation is inhibited by IL-6, which stimulates the production of the anti-inflammatory cytokines (40). Nieman et al. (2005) tested the relationship between plasma CPK, DOMS and various plasma cytokines. These researchers found that muscle damage, post-race DOMS and IL-6, IL-10 were positively correlated. The increase in the cytokines was greatest for IL-6 (125-fold), corresponding with a 112-fold increase in CPK (13). In our study increase in IL-6 in GIBE in comparison with the other groups was less and this may be related to the anti-inflammatory effect of ginger. It seems that one hour, was enough for ginger to affect on cytokine's release. After muscular damaged, the sarcolemma disruption allows muscle proteins such as CK to be released from the fiber into the blood stream (41, 42). The increased level of CPK confirmed occurrence of DOMS. After eccentric exercise, CPK changed significantly in GIAE and PL but not in GIBE

that was similar to previous studies (43-45). The main symptoms of DOMS are pain, decrease in range of motion, decrease in muscle strength and swelling (13,15). Swelling is often associated with acute inflammation. Many studies using humans to investigate an association between DOMS and swelling. Loss of function and strength is associated with loss of force generating capacity (12). Our findings of increased thigh muscle volume and decreases hip ROM and isometric strength, clearly showed that the exercise protocol resulted in muscle damage, but ginger couldn't ameliorate these symptoms. Ginger and DHA (docosahexaenoic acid) (15, 46), and vitamin C (45) didn't change arm volume and elbow ROM after EE. The increase in isometric strength of thigh 1 hour after exercise may be due to better use of dynamometer. Similar to Drager et al. study, the decrease in ROM was associated with decrease in isometric strength and this suggests that muscular tightness can impair maximum isometric force production (46). Although the changes in these variables weren't statistically significance, but it showed that ginger had a positive effect on GBE in comparison with GIAE and PL. In summery the results of the present study suggest that ginger extract could reduce pain and inflammation caused by eccentric exercise. It could be used as an effective herbal in healing DOMS.

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References

1. Pournot H, Bieuzen F, Louis J, Fillard JR, Barbiche E, Hausswirth C. Time-course of changes in inflammatory response after whole-body cryotherapy multi exposures following severe exercise. *PLoS One* 2011;6(7):e22748.
2. Arent SM, Senso M, Golem DL, McKeever KH. The effects of theaflavin-enriched black tea extract on muscle soreness, oxidative stress, inflammation, and endocrine responses to acute anaerobic interval training: a randomized, double-blind, crossover study. *Journal of the International Society of Sports Nutrition* 2010;7(1):11.
3. Kanda K, Sugama K, Hayashida H, Sakuma J, Kawakami Y, Miura S, et al. Eccentric exercise-induced delayed-onset muscle soreness and changes in markers of muscle damage and inflammation. *Exerc Immunol Rev* 2013;19:72-85.
4. Frost DR, Grant T, Faivovich J, Bain RH, Haas A, Haddad CF, et al. The amphibian tree of life. *Bulletin of the American Museum of natural History* 2006:1-291.
5. Martel GF, Harmer ML, Logan JM, Parker CB. Aquatic plyometric training increases vertical jump in female volleyball players. *Medicine and science in sports and exercise* 2005;37(10):1814-9.
6. Jamurtas Az, Fatouros Ig, Buckenmeyer P, Kokkinidis E, Taxildaris K, Kambas A, et al. Effects of plyometric exercise on muscle soreness and plasma creatine kinase levels and its comparison with eccentric and concentric exercise. *The Journal of Strength & Conditioning Research* 2000;14(1):68-74.
7. Jordaan DP. TRAUMEEL S. The sportsman's answer to enhanced exercise performance and the overtraining syndrome? : University of Pretoria; 2006.
8. Byrne C, Twist C, Eston R. Neuromuscular function after exercise-induced muscle damage. *Sports medicine* 2004;34(1):49-69.
9. Rahnama N, Rahmani-Nia F, Ebrahim K. The isolated and combined effects of selected physical activity and ibuprofen on delayed-onset muscle soreness. *Journal of sports sciences* 2005;23(8):843-50.
10. Davis JM, Murphy EA, Carmichael MD, Zielinski MR, Groschwitz CM, Brown AS, et al. Curcumin effects on inflammation and performance recovery following eccentric exercise-induced muscle damage. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 2007;292(6):R2168-R73.
11. Veqar Z. Causes and Management of Delayed Onset Muscle Soreness: A Review. 2013.
12. Connolly DA, SAYERS SE, McHugh MP. Treatment and prevention of delayed onset muscle soreness. *The Journal of Strength & Conditioning Research* 2003;17(1):197-208.
13. Montgomery PG, Pyne DB, Cox AJ, Hopkins WG, Minahan CL, Hunt PH. Muscle damage, inflammation, and recovery interventions during a 3-day basketball tournament. *European Journal of Sport Science* 2008;8(5):241-50.
14. Black CD, Herring MP, Hurley DJ, O'Connor PJ. Ginger (*Zingiber officinale*) Reduces Muscle Pain Caused by Eccentric Exercise. *The Journal of Pain* 2010;11(9):894-903.
15. Black CD, O'Connor PJ. Acute effects of dietary ginger on quadriceps muscle pain during moderate-intensity cycling exercise. *International*

journal of sport nutrition & exercise metabolism 2008;18(6).

16. Liburt N, McKeever K, Streltsova J, Franke W, Gordon ME, Manso Filho H, et al. Effects of ginger and cranberry extracts on the physiological response to exercise and markers of inflammation in horses. *Comparative Exercise Physiology* 2009; 6(04):157-69.

17. Hyldahl RD, Keadle J, Rouzier PA, Pearl D, Clarkson PM. Effects of ibuprofen topical gel on muscle soreness. *Medicine and science in sports and exercise* 2010;42(3):614-21.

18. Tartibian B, AZIZ BBK. The effect of taking naproxen drug on the level of perceived pain and changes of CPK serum after eccentric exercise. *HARAKAT* 2008;37(77):9.

19. Tartibian B, Maleki BH, Abbasi A. Omega-3 fatty acids supplementation attenuates inflammatory markers after eccentric exercise in untrained men. *Clinical Journal of Sport Medicine* 2011;21(2):131-7.

20. Koikawa N, Nakamura A, Ngaoka I, Aoki K, Sawaki K, Suzuki Y. Delayed-onset muscle injury and its modification by wheat gluten hydrolysate. *Nutrition* 2009;25(5):493-8.

21. Sugiyama K, Sakakibara R, Tachimoto H, Kishi M, Kaga T, Tabata I. Effects of Acetic Acid Bacteria Supplementation on Muscle Damage After Moderate-Intensity Exercise. *circulation* 2009;9:10.

22. Kamandani R, Ghazalian F, Ebrahim K, Ghassembaglou N, Piraghaj MS, Khorram A. The Effect of Acute Vibration Training on Delayed Onset Muscle Soreness in Young Non-Athlete Women 2013.

23. Bakhtiary AH, Safavi-Farokhi Z, Aminian-Far A. Influence of vibration on delayed onset of muscle soreness following eccentric exercise. *British journal of sports medicine*. 2007;41(3):145-8.

24. Day M, Ploen E. The effectiveness of cryotherapy in the treatment of exercise-induced muscle soreness. *UW-L J Undergrad Res* 2010;13:1-6.

25. Khalvat A. Comparing the effects of ginger (*Zingiber officinale*) extract and ibuprofen on patients with osteoarthritis. *Archives of Iranian medicine* 2005;8(4):267-71.

26. Ali BH, Blunden G, Tanira MO, Nemmar A. Some phytochemical, pharmacological and toxicological properties of ginger (*Zingiber officinale* Roscoe): A review of recent research. *Food and chemical Toxicology* 2008;46(2):409-20.

27. Kárai LJ, Russell JT, Iadarola MJ, Oláh Z. Vanilloid receptor 1 regulates multiple calcium compartments and contributes to Ca²⁺-induced Ca²⁺ release in sensory neurons. *Journal of Biological Chemistry* 2004;279(16):16377-87.

28. Zaccaro L, García-López MT, González-Muñiz R, García-Martínez C, Ferrer-Montiel A, Albericio F, et al. TRPV1 modulators: Structure-activity relationships using a rational combinatorial

approach. *Bioorganic & medicinal chemistry letters* 2011;21(12):3541-5.

29. Ozgoli G, Goli M, Moattar F. Comparison of effects of ginger, mefenamic acid, and ibuprofen on pain in women with primary dysmenorrhea. *The journal of alternative and complementary medicine* 2009;15(2):129-32.

30. Hindell P, Poole K, Robinson E, Reynolds L, Mason H. Induction of DNA damage by a step-test exercise protocol. *Biochemical Society Transactions* 2001;29(5):115-.

31. Akif Seriken M, Cençoğlu C, Muammer Kayatekin B. The Effect of Eccentric Exercise-Induced Delayed-Onset Muscle Soreness on Positioning Sense and Shooting Percentage in Wheelchair Basketball Players. *Balkan Medical Journal* 2013;30(4).

32. Clarkson HM. Joint motion and function assessment: a research-based practical guide: Lippincott Williams & Wilkins; 2005.

33. Rainsford K. Drug Derivatives and Formulations. Ibuprofen: Pharmacology, Therapeutics and Side Effects: Springer; 2012. p. 77-90.

34. Rahnama P, Montazeri A, Huseini HF, Kianbakht S, Naseri M. Effect of *Zingiber officinale* R. rhizomes (ginger) on pain relief in primary dysmenorrhea: a placebo randomized trial. *BMC complementary and alternative medicine* 2012; 12(1):92.

35. Altman R, Marcussen K. Effects of a ginger extract on knee pain in patients with osteoarthritis. *Arthritis & Rheumatism* 2001;44(11):2531-8.

36. Levy AS, Simon O, Shelly J, Gardener M. 6-Shogaol reduced chronic inflammatory response in the knees of rats treated with complete Freund's adjuvant. *BMC pharmacology* 2006;6(1):12.

37. Mahluji S, Ostadrahimi A, Mobasser M, Attari VE, Payahoo L. Anti-Inflammatory Effects of *Zingiber Officinale* in Type 2 Diabetic Patients. *Advanced pharmaceutical bulletin* 2013;3(2):273.

38. Nieman DC, Dumke CL, Henson DA, McNulty SR, Gross SJ, Lind RH. Muscle damage is linked to cytokine changes following a 160-km race. *Brain, behavior, and immunity* 2005; 19(5):398-403.

39. Peake JM, Suzuki K, Hordern M, Wilson G, Nosaka K, Coombes JS. Plasma cytokine changes in relation to exercise intensity and muscle damage. *European journal of applied physiology* 2005;95(5-6):514-21.

40. Radtke S, Wüller S, Yang X-p, Lippok BE, Mütze B, Mais C, et al. Cross-regulation of cytokine signalling: pro-inflammatory cytokines restrict IL-6 signalling through receptor internalisation and degradation. *Journal of cell science* 2010; 123(6):947-59.

41. Brancaccio P, Maffulli N, Limongelli FM. Creatine kinase monitoring in sport medicine. *British Medical Bulletin* 2007;81(1):209-30.

42. Sietsema KE, Meng F, Yates NA, Hendrickson RC, Liaw A, Song Q, et al. Potential biomarkers of muscle injury after eccentric exercise. *Biomarkers* 2010;15(3):249-58.

43. Jordan SL. The effects of green tea extract supplementation on delayed onset muscle soreness and oxidative stress: Texas Tech University; 2007.

44. Van Someren KA, Edwards AJ, Howatson G. Supplementation with B-Hydroxy-B-Methylbutyrate (HMB) and α -Ketoisocaproic Acid (KIC) Reduces Signs and Symptoms of Exercise-Induced Muscle

Damage in Man. *International journal of sport nutrition & exercise metabolism* 2005;15(4).

45. Rahmani Nf, Talebi E, Nakhostin B, Ebrahim K. Effect of two regimes of vitamin c on delayed onset muscle soreness. *Journal of Movement Science*. 2008.

46. Drager CJ. Effect of DHA supplementation on muscle damage and inflammation during the first two weeks of a novice resistance training program: Virginia Polytechnic Institute and State University; 2012.