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Ginger (*Zingiber officinale*) Reduces Muscle Pain Caused by Eccentric Exercise

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Abstract: Ginger has been shown to exert anti-inflammatory effects in rodents, but its effect on human muscle pain is uncertain. Heat treatment of ginger has been suggested to enhance its hypoalgesic effects. The purpose of this study was to examine the effects of 11 days of raw (study 1) and heat-treated (study 2) ginger supplementation on muscle pain. Study 1 and 2 were identical double-blind, placebo controlled, randomized experiments with 34 and 40 volunteers, respectively. Participants consumed 2 grams of either raw (study 1) or heated (study 2) ginger or placebo for 11 consecutive days. Participants performed 18 eccentric actions of the elbow flexors to induce pain and inflammation. Pain intensity, perceived effort, plasma prostaglandin E_2, arm volume, range-of-motion and isometric strength were assessed prior to and for 3 days after exercise. Results Raw (25%, –.78 SD, *P* = .041) and heat-treated (23%, –.57 SD, *P* = .049) ginger resulted in similar pain reductions 24 hours after eccentric exercise compared to placebo. Smaller effects were noted between both types of ginger and placebo on other measures. Daily supplementation with ginger reduced muscle pain caused by eccentric exercise, and this effect was not enhanced by heat treating the ginger.

***Perspective:** This study demonstrates that daily consumption of raw and heat-treated ginger resulted in moderate-to-large reductions in muscle pain following exercise-induced muscle injury. Our findings agree with those showing hypoalgesic effects of ginger in osteoarthritis patients and further demonstrate ginger's effectiveness as a pain reliever.*

***Key words:** DOMS, muscle injury, randomized trial, strength, PGE_2.*

Zingiber officinale, commonly known as ginger, has been used in Ayurvedic and Chinese medicine for the treatment of asthma, diabetes, nausea and pain.[1] In the United States, ~38% of adults use complementary and alternative medical (CAM) treatments,[4] often to improve or treat musculoskeletal and other pain conditions. Ginger is among the 10 most common natural products used as a CAM treatment.[5] It has been suggested that well-designed research be conducted to determine whether orally consumed botanical substances such as ginger are useful in the treatment of muscle pain.[10]

It is biologically plausible that orally consumed ginger could reduce pain. In vitro investigations show that ginger and several of its chemical constituents, including gingerols, shogaols, paradols, and zingerone, inhibit the activity of cyclooxygenase enzymes (COX-1 and COX-2),[24,29,40] block leukotriene synthesis,[23] and block the production of interleukins (IL-1, IL-12), and TNFα in activated macrophages.[17,41] In rodents, a single dose of ginger extracts or 6-gingerol has been shown to reduce paw edema and pain behaviors in a dose-dependent manner,[30,45] while 4 weeks of daily supplementation with ginger extract resulted in a dose-dependent reduction in serum prostaglandin E_2 levels.[39] Taken together, these findings suggest ginger may have anti-inflammatory and analgesic properties akin to nonsteroidal anti-inflammatory drugs. Additionally, ginger and its constituents agonize the vallinoid receptor TRPV1,[14,21] which plays a role in the central and peripheral processing of noxious stimuli.[9,27] The efficacy of oral ginger consumption as an anti-inflammatory or pain reliever in humans has not been widely studied. Administration of a single 2-gram dose of raw ginger did not alter quadriceps muscle pain during cycling[6] or muscle

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pain following high intensity eccentric exercise (Black and O'Connor, in press). Four to 36 weeks of daily consumption of 30 to 500 mg of ginger extracts resulted in reductions in hip and/or knee pain in osteoarthritis patients.[2,18,44]

To our knowledge, the efficacy of multiple days of ginger supplementation on experimentally induced muscle pain has not been examined in humans. Thus, one purpose of the experiments described here was to examine the effects of 11 days of raw ginger supplementation on arm-muscle pain induced by eccentric exercise (Study 1). The manner in which ginger is processed has also been suggested to play a role in its effectiveness as a pain reliever.[37] Heating ginger has been shown to reduce its gingerol concentration while increasing the concentration of shogaols, the dehydrated form of gingerols.[22] Shogaols have been shown to more strongly activate TRPV1 receptors,[21] thus increasing their concentration in a ginger supplement could lead to greater analgesia. Consequently, we performed a second, identical experiment examining the effects of 11 days of supplementation with heat-treated ginger on arm-muscle pain (Study 2). For both studies, we hypothesized that pain ratings after eccentric exercise would be lower in the group receiving ginger compared to a group receiving a placebo.

Methods

The research design and methods for study 1 and study 2 were identical except for the treatments. In study 1, raw ginger or yellow corn flower (placebo) was administered in white opaque gelatin capsules made by Hawkins Pharmaceutical Group (Minneapolis, MN). In study 2, powdered brown sugar (placebo) or heat-treated ginger was administered in green opaque hypromellose capsules made by Qualicaps (Whitsett, NC). Brown sugar was used as the placebo in study 2 because it was more similar in color to ginger than yellow corn flower. For heat treatment, ginger rhizomes were ground, hydrated with deionized water, placed in a media bottle which was then tightly capped and heated in a water bath for 3 hours and 15 minutes at 100°C. The ginger was then dried at room temperature for approximately 12 hours and placed in the capsules. All the ginger samples were from the McCormick Science Institute's Characterized Sample Program. Samples from the same lot of ginger used in the studies reported here are available to qualified researchers wishing to reproduce the experiments. High performance liquid chromatography analysis on samples from study 1 and study 2 revealed that gingerols and shogaols were not detected in placebo capsules used in either study. The raw ginger used in study 1 was found to contain (in mg/g) 4.1 6-gingerol, 1.3 8-gingerol, 1.9 10-gingerol and 2.2 6-shogaol. The heat treated ginger used in study 2 was found to contain 2.8 6-gingerol, 1.0 8-gingerol, 1.6 10-gingerol and 2.6 6-shogaol.

Subjects

Participants were recruited for both studies via campus classroom announcements, listservs and flyers, and screened for medical or orthopedic conditions that would preclude performance of strenuous exercise of the elbow extensors. Potential participants who reported performing moderate-to-high-intensity weight training of the biceps brachii muscle during the previous 9 months were excluded, as were individuals who reported taking prescription pain and/or psychiatric medication. Participants were asked to refrain from taking pain medication during the study period. We sought a minimum sample size of 17 per condition because it would provide statistical power to detect a true effect of $\geq$.75 SD given the study design, an alpha value of .05, and a correlation between repeated trials of $\geq$.75 on the primary outcome measure.[31] The methods were reviewed and approved by the University of Georgia Institutional Review Board, and all volunteers read and signed an informed consent prior to participating.

The flow of participants through both study 1 and study 2 can be seen in Fig 1. In study 1, 36 individuals volunteered to participate. One participant in the raw-ginger group dropped out after the first day because of symptoms of dizziness and nausea. One participant in the placebo group exhibited little decline in maximal isometric force following the eccentric exercise protocol (–2% compared to a mean $\pm$SD decline of –40% $\pm$ 14%). Thus it was decided that data from this outlier would not be analyzed because of the inadequate muscle injury. The final analyses involved a total of 34 participants with 17 in both conditions (14 women and 3 men in each condition).

In study 2, 42 individuals volunteered to participate. One individual was dropped from the study after participating for 1 day because psychiatric medication use was revealed. Additionally, 1 individual elected to stop participation after 8 days because she developed a case of hives. The final analyses involved a total of 40 participants with 20 in both conditions (13 women and 7 men in each condition). No other side effects were found in either study.

Testing Protocol

Participants were tested on 11 consecutive days, at roughly the same time of day (within 90 minutes). On testing day 1, participants were screened and consent was obtained. Next, blood was drawn from the antecubital vein of the dominant arm, isometric force of nondominant elbow flexors was measured, and ginger or placebo capsules were consumed. On testing days 2 to 7, participants reported to the lab for supervised capsule consumption. On days 3 and 5, the isometric-force testing procedure was practiced to minimize potential learning effects that could confound the effect of eccentric exercise on isometric strength. On testing day 8, capsules were consumed and a blood sample was again obtained. Elbow range-of-motion (ROM), arm volume, and isometric force of the elbow flexors were then assessed in the nondominant arm to establish baseline values. Baseline one-repetition maximal concentric strength (1-RM) of the nondominant elbow flexors was then determined. Participants then performed 18 eccentric actions of the

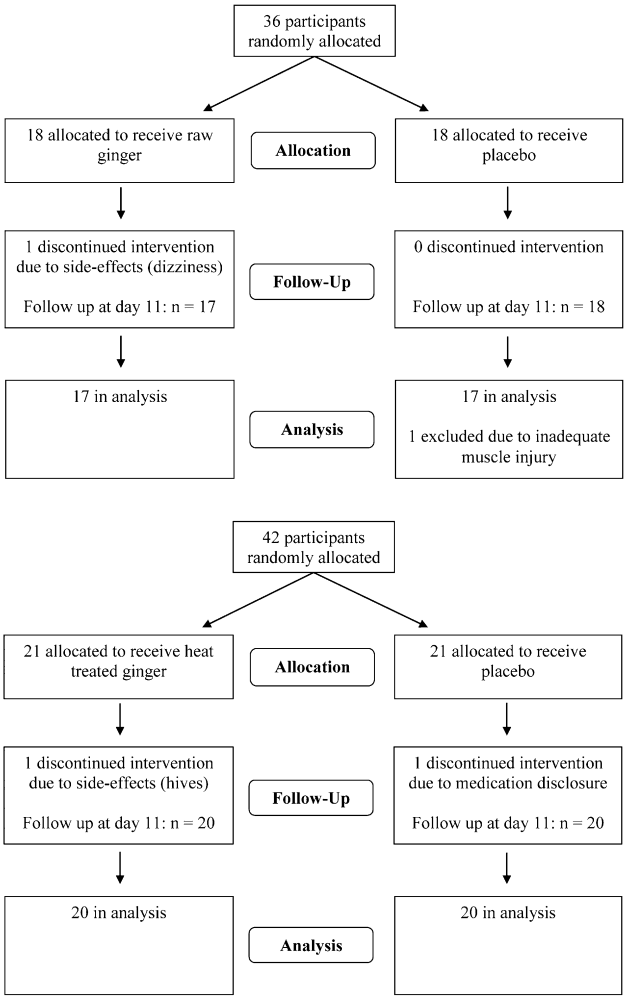

Figure 1. CONSORT diagram demonstrating the flow of participants through each stage of the randomized trials of raw and heat-treated ginger.

nondominant elbow flexors at an intensity of 120% of their concentric 1-RM.

On testing days 9 to 11 (24, 48, and 72 hours after eccentric exercise) ginger/ placebo capsules were consumed, followed by assessments of ROM, arm volume, isometric force, and muscle pain in the exercised arm. All assessments were completed within 20 to 30 minutes of ingestion of ginger/placebo capsules. Blood was drawn on testing day 10 following capsule consumption, but prior to all other assessments. On testing days 2 through 11, the participants were asked to indicate whether the capsules they consumed on the prior day contained ginger or placebo and to indicate their degree of certainty (0 to 100% certain).

Ginger/Placebo Consumption

Ginger plants (*Zingiber officinale)* were shipped from India to Baltimore, Maryland. Ginger rhizomes were ground and placed in capsules (study 1) or ground, heated and then placed in capsules (study 2). The capsules were shipped overnight to Athens, Georgia in light-impenetrable containers and refrigerated at 8°C until used. Ginger and placebo capsules to be consumed by each subject on each experimental day were placed into separate coded envelops and sealed by an investigator not involved in day-to-day testing. Participants were assigned to 1 of the 2 conditions using block randomization (in blocks of 2) to avoid a large inequality in the number of ginger and placebo participants. Randomization was performed using Research Randomizer (www.randomizer.org).

Six capsules were ingested on each testing day (all within 1 minute) and the mean weight of the capsules was .33 (±.018) grams. The capsules were administered in a double-blind manner to minimize participant and researcher-expectancy effects. To aid in blinding, participants were blindfolded and wore a nose clip while consuming the capsules in order to minimize taste, odor, and appearance cues. Ginger and placebo consumption was confirmed through direct observation by the investigators. In the few instances when an observation was not made (eg, because of weekend travel) the participants phoned an investigator and verbally confirmed that the capsules had been taken.

The 2 gram per day dose of ginger was chosen based upon the small amount of relevant, available literature in humans. Relief of musculoskeletal pain has been reported in association with the consumption of large (3 to 7 grams per day) daily doses of ginger in uncontrolled studies.[36] Three of 4 randomized controlled trials with osteoarthritis patients have demonstrated reductions in pain compared to placebo with 30 to 500 mg daily doses of ginger extracts.[2,7,18,44] Oral administration of 1 to 2 grams of ginger has been shown to reduce postoperative and motion-sickness-induced vomiting, potentially by acting on the central nervous system.[15,25] In the absence of compelling evidence about the amount of ginger to use to optimize bioavailability of ginger constituents, a 2-gram dose was chosen in an attempt to both minimize potential side effects and maximize the likelihood of producing a true hypoalgesic effect.

Maximal Concentric Strength

Maximal voluntary concentric strength (1-RM) of the nondominant elbow flexors was used to ensure that all participants were given approximately the same injury stimulus. The 1-RM was determined using a seated preacher-curl bench and adjustable dumbbell. The height of the bench was adjusted to fit each participant. Participants first performed a set of 8 to 10 concentric/eccentric repetitions using a "light" weight (5 to 15 pounds, depending on the size of the participant) as a warm-up. Following 2 minutes of rest, participants placed their upper arm on the bench with the elbow at full extension. Researchers then placed the dumbbell in the participant's hand with a weight estimated to be 80 to 90% of maximal. Participants were then instructed to perform a single elbow flexion with the dumbbell. Participants were instructed on proper lifting form (feet on the ground, upper arm maintaining contact with the bench, and maintaining a seated position). Four seconds were allowed to move the dumbbell through a complete range of motion. Researchers lowered the weight

following each attempt to ensure only concentric elbow flexion was performed. If a lift was completed with proper form in the prescribed time period, then weight was added to the dumbbell and the lift was repeated until participants could not complete the lift. The heaviest weight lifted in the prescribed time period with proper form was judged to be the participants 1-RM. Ratings of perceived exertion (RPE) were obtained following each lift using Borg's 6 to 20 scale[8] to aid in determining how much weight to add to the dumbbell and determine if participants gave a maximal effort. Three to 5 attempts, separated by 2 minutes of rest, were usually required to determine a participant's 1-RM.

Eccentric Exercise

Eighteen eccentric muscle actions (3 sets of 6 repetitions) were performed in the nondominant elbow flexors with at an initial weight of 120% of concentric 1-RM. Participants lowered the weight in a controlled manner (a duration of ~3 seconds) and a researcher returned the weight to the starting position (full elbow flexion). Approximately 3 minutes of rest was provided between each set and the participant provided a rating of perceived exertion following each set with the 6 to 20 RPE scale.[8] If participants were no longer able to lower the weight in a controlled fashion, the weight was decreased by ~5% and the set continued until completion. The next set was begun using this lower weight, and exercise continued until completion of all 3 sets.

Assessment of Muscle Pain Intensity and Perceived Exertion

Pain intensity experienced in the elbow flexors was rated using a visual analog scale (VAS) during a series of 3, concentric/eccentric actions (~3 seconds "up", ~3 seconds "down") of the nondominant elbow flexors with a weight equal to 50% of concentric 1-RM. The VAS scale consisted of a 100-mm line with 2 verbal anchors. "No pain" was printed just to the left of the left edge of the line and "most intense pain imaginable" was printed just to the right of the right edge of line. Participants were instructed to place a vertical line on the scale at the point that best described the intensity of the pain they felt in their arm while performing the eccentric portion of the contraction. Substantial evidence indicates the VAS scale can be used to obtain both valid and reliable pain-intensity responses to noxious stimuli.[34] In addition to providing ratings of muscle pain, participants provided separate local (arm) ratings of perceived exertion for each of the concentric/eccentric actions using the 6 to 20 RPE scale.[8] The participants were instructed to report the intensity of the effort required to complete each concentric/ eccentric action of the elbow flexors. Three ratings were performed and averaged to obtain criterion values for muscle pain and RPE.

Isometric Force

Isometric force was used to document the presence of muscle injury immediately after eccentric exercise, and assess muscle function in the days following eccentric exercise. Force was assessed at 90 degrees of elbow flexion (full flexion = 180 degrees) using a modified preacher curl bench attached to a force transducer (model 2000A; Rice Lake Weighing Systems, Rice Lake, WI) via a high-tension cable. Participants were seated on the bench with feet flat on the floor. Participants placed their upper arm on the pad of the preacher bench such that the shoulder was fixed at approximately 45° of flexion. The arm was then secured at approximately 90 degrees of elbow flexion via placement of a rigid, padded brace, secured via inelastic straps to the forearm and upper arm. Three maximal voluntary isometric contractions (MVIC) were performed with 2 minutes of rest between trials by having participants grasp a wooden bar connected to the force transducer via a cable. Force was recorded from the transducer using a MacLab analog-to-digital converter (model ML 400; ADInstruments, Milford, MA) with a sampling rate of 100 Hz. Values were transferred to a portable computer for storage and analysis (Apple Computer, Cupertino, CA). Subjects were given verbal encouragement to maintain their effort for 3 to 5 seconds to ensure a plateau in the force tracing. For each effort, force was measured from this plateau region of the tracing. The average of the 3 trials was taken as the criterion measure of force.

Arm Volume

Arm volume was used as a marker of inflammation.[32] The volume of the nondominant arm was measured via water displacement using a volumeter consisting of a plastic rectangular tank with a spout at the top to allow the displaced water to drain. The volumeter was placed on a level surface and filled with tepid (32–34°C) tap water to the level of the spout. A mark was placed on each participant's upper arm half the distance between the acromium process and the lateral epicondyle of the humerus. While standing with the arm fully extended, participants then slowly submerged their arm into the volumeter until the mark was at the same position as the overflow. Displaced water was collected in a pitcher and then weighed to the nearest mg on an electronic scale. Three to 5 consecutive measures were made with the participants drying their arms to remove excess water between each measure. The water weights were converted to volume (mL) and the average of 3 measures that differed by ≤1% was used as the criterion measure.

Elbow Range of Motion

Elbow range of motion was used to assess stiffness and function of the elbow flexors. Relaxed arm angle of the elbow joint was measured using a goniometer and defined as the angle between the midpoint of the wrist, the lateral humeral epicondyle, and the acromion process. Measurements were made while participants stood with their arms hanging in a relaxed position by their sides with the palms facing medially. Flexed arm angle was measured using the same anatomical landmarks while participants flexed their arm to the point where mechanical interference prohibited further voluntary

Table 1. Subject Characteristics for Study 1 and Study 2

	Raw ginger (14 women / 3 men)	*Placebo (14 women / 3 men)*	*Heated ginger (13 women / 7 men)*	*Placebo (13 women / 7 men)*
Age (yr)	21.1 ± 0.7	20.9 ± 0.6	20.6 ± 0.6	21.4 ± 0.8
Weight (Kg)	70.3 ± 3.8	62.3 ± 1.7	71.1 ± 3.0	65.6 ± 2.7
Height (cm)	171.5 ± 2.2	166.2 ± 1.6	173.3 ± 1.9	170.3 ± 2.5
1-RM (lbs)	25.9 ± 2.5	26.5 ± 2.8	35.9 ± 3.0	33.6 ± 2.9
MVIC (lbs)	16.1 ± 1.5	14.8 ± 1.3	16.2 ± 1.2	15.8 ± 1.5

Abbreviations: 1-RM, 1 repetition maximal concentric strength; MVIC, maximal voluntary isometric contraction.
NOTE. Values are mean ± SE.

flexion. Three consecutive measures of relaxed and flexed angles were made. Range of motion about the elbow joint was determined by subtracting flexed arm angle from relaxed arm angle and the average of the 3 measurements was used as the criterion for ROM.

Prostaglandin E_2 Assay

Venous blood samples were obtained from an antecubital vein and collected in 7-mL vacutainer tubes containing EDTA (Becton Dickinson, Rutherford, NJ). The samples were placed on ice for 10 minutes, after which 70 μL of a 100-μM solution of meclofenamic acid (Sigma, St. Louis, MO) was added to each tube and the tubes were gently mixed by hand (final concentration 1 μM meclofenamic acid$\cdot$mL^{-1} of whole blood). Samples were then returned to ice for an additional 10 minutes. The samples were centrifuged at 1,800 rpm for 10 minutes at 4°C. The plasma was harvested into sterile microcentrifuge tubes and stored frozen at −80°C until analysis. On the day the assay was performed, 100 μL of plasma was added to 900 μL of methanol, vortexed for 30 seconds, and the ethanol was removed by evaporation in an evacuated centrifuge (Centravap; Labconco, Kansas City, MO). Concentrations of prostaglandin E_2 were determined using the ACETM Competitive Enzyme Immunoassay (Cayman Chemical, Ann Arbor, MI) and the concentrations of samples were determined relative to the standards provided in the kit.

Statistical Analysis

Prior to breaking the blind in each study, data were entered into a spreadsheet, checked for errors, and analyzed using SPSS v15.0 (SPSS Inc., Chicago, IL). The reliability of repeated measurements of the outcome measures was calculated from 3 assessments of each variable at each measurement time using intraclass correlation coefficients (2-way mixed, ICC 3,3) with participants as random effects and trials as fixed effects. The average of the 3 measures was used as the criterion score in the primary analysis for muscle pain, RPE, and PGE_2, while the mean percent change from baseline was used for arm volume, elbow ROM, and isometric force. Data are presented as mean ±standard error (SE). Glass's delta effect size (Δ) is reported to provide a standardized measure of the magnitude of the difference between the ginger and placebo groups for each of the dependent variables. This effect size was computed by subtracting the mean score in the placebo condition from the mean for the ginger condition and dividing by the associated standard deviation for the placebo condition. As a general guideline, effect sizes between .50 and .79 standard deviations (SD) can be described as moderate sized while those greater than .80 SD can be described as large.[12] Mann-Whitney U planned comparisons were used for hypothesis testing.[35] A 2 (ginger vs. placebo) × 4 (time: pre, 24, 48, and 72 hours postexercise) mixed model ANOVA with repeated measures was used to test differences in the mean values for elbow range of motion, arm volume, isometric force, and RPE. When significant effects were found, *t*-tests with a bonferonni alpha correction were used to compare individual time points.

Results

Preliminary Analysis

Baseline measures of ratings of muscle pain and perceived exertion, arm volume, range of motion, and isometric force were all highly reliable in both study 1 and 2 (ICC's ranging from 0.96 to 1.00). Demographic, elbow flexor concentric one repetition maximum, and baseline maximal voluntary isometric contraction force data are presented in Table 1.

Muscle-Pain Intensity

Muscle-pain data for the 3 days following eccentric exercise in study 1 and 2 are presented in Fig 2. As expected, the exercise protocol induced mild-intensity pain (<40 mm) for the placebo groups. Pain-intensity ratings were significantly lower in the ginger group 24 hours after eccentric exercise in both study 1 (Glass's Δ = .78 SD, 25.3%, U = 85, P = .041) and study 2 (Δ = .57 SD, 22.5%, U = 127, P = .049).

Blinding

In study 1, participants correctly indicated the type of capsules they consumed on the previous day 66 ± 8% and 58 ± 10% of the time in the raw-ginger and placebo groups, respectively. In study 2, participants correctly indicated the type of capsules they had consumed on the previous day 48 ± 7% and 67 ± 9% of the time in the heated ginger and placebo groups, respectively. In study 1, the raw-ginger group reported being 54 ± 6% certain of their indication while the

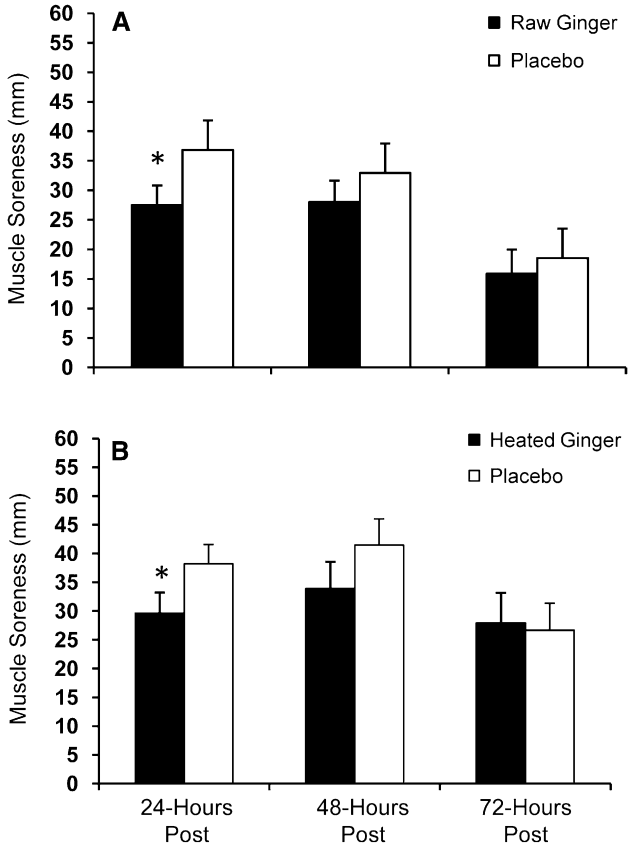

Figure 2. Ratings of arm muscle pain intensity 24, 48, and 72 hours after eccentric exercise. Preexercise muscle pain was "0" on a 0 to 100 VAS scale and is therefore not included. *Indicates a significant ($P < .05$) difference from placebo. Values are mean ± SE.

placebo group was 37 ± 6% certain of their indication. In study 2, the heat treated ginger group reported being 41 ± 4% certain of their indication while the placebo group was 47 ± 5% certain of their indication. Of the 17 participants in the ginger group in study 1, those who guessed their condition correctly (>50% correct) and reported a high certainty (>50% certainty) of having consumed ginger (n = 10) did not have lower pain-intensity ratings 24 hours after exercise than those (n = 7) who were uncertain about whether they had consumed ginger (mean pain of 27.1 mm vs 28.0 mm, respectively). In study 2, none of the 8 participants who guessed their condition correctly (>50% correct) reported a high certainty of having consumed ginger (ie, 51% certainty or lower).

Secondary Dependent Measures

Mean absolute values for elbow range of motion, arm volume, isometric force, and plasma PGE_2 concentration as well as mean percent change in range of motion (ΔROM), percent change in arm volume (ΔVOL), and percent change in isometric force (ΔForce) for the ginger and placebo conditions on each testing day are presented in Table 2 (raw ginger; study 1) and table 3 (heated ginger; study 2).

Table 2. Selected Responses to Eccentric Exercise Following 11 Days of Supplementation With Raw Ginger or Placebo (Study 1)

	Time	Raw ginger	Placebo	Effect size (SD)
ROM (°)	Pre	119 ± 3	123 ± 2	
	24-post	110 ± 3*	110 ± 2*	
	48-post	111 ± 3*	110 ± 3*	
	72-post	112 ± 3*	114 ± 3*	
Arm volume (mL)	Pre	2,399 ± 165	2,012 ± 82†	
	24-post	2,438 ± 168*	2,041 ± 83*,†	
	48-post	2,438 ± 169*	2,042 ± 85*,†	
	72-post	2,429 ± 169*	2,051 ± 87*,†	
Isometric force (lbs)	Pre	16.7 ± 1.6	15.4 ± 1.4	
	24-post	11.8 ± 1.1*	10.4 ± 0.7*	
	48-post	12.5 ± 1.5*	10.8 ± 1.1*	
	72-post	13.1 ± 1.3*	12.4 ± 1.2*	
ΔROM (%)	24-post	−7.3 ± 1.1	−10.7 ± 1.3	0.64
	48-post	−6.6 ± 1.6	−10.5 ± 1.3	0.74
	72-post	−5.5 ± 1.6	−7.6 ± 1.5	0.32
ΔVolume (%)	24-post	1.6 ± 0.3	1.5 ± 0.2	0.11
	48-post	1.6 ± 0.4	1.5 ± 1.2	0.06
	72-post	1.2 ± 0.4	1.9 ± 0.4	−0.40
ΔForce (%)	24-post	−30.0 ± 3.8	−33.4 ± 2.9	0.29
	48-post	−25.8 ± 4.1	−29.5 ± 3.0	0.30
	72-post	−20.1 ± 3.7	−19.3 ± 3.6	−0.06
PGE_2(pg/mL)	Pre 1	154 ± 26	185 ± 43	−0.17
	Pre 2	153 ± 32	173 ± 23	−0.21
	48-post	145 ± 27	180 ± 19	−0.41

Abbreviations: ΔROM, mean change in range of motion from pre; ΔVolume, mean change in arm volume from pre; ΔForce, mean change in isometric force from pre; PGE_2, Plasma prosteglandin E_2.
NOTE. Values are Mean ± SE. Effect Size: Glass's delta (SD's).
*Indicates a significant difference ($P < .05$) from pre.
†Indicates a significant main effect ($P = .046$) for group.

No significant group × time interactions were found in either study when comparing raw or heated ginger to placebo for elbow ROM, arm volume, isometric force, or PGE_2 concentration ($P > .14$ or higher). A significant main effect for time (days postexercise) was found elbow ROM in both study 1 ($P < .001$) and study 2 ($P < .001$) with ROM being significantly reduced at 24, 48, and 72 hours postexercise time points compared to pre values ($P < .001$ for each time point in both study 1 and 2). A significant main effect for time was also found for arm volume in both study 1 ($P < .001$) and study 2 ($P < .001$) with arm volume being significantly elevated at 24, 48, and 72 hours postexercise compared to pre ($P < .001$ for each time point in both study 1 and 2). In study 1, a significant ($P = .046$; table 2) main effect for group was also found, with the raw-ginger group having larger arm volumes than the placebo groups at all time points. A significant main effect for time in isomeric force was also found in both study 1 ($P < .001$) and study 2 ($P < .001$) with force production being significantly reduced at 24, 48, and 72 hours postexercise compared to pre ($P < .001$ for each time point in both study 1 and 2). Plasma PGE_2 concentrations did not differ between ginger or placebo groups

Table 3. Selected Responses to Eccentric Exercise Following 11 Days of Supplementation With Heat-Treated Ginger or Placebo (Study 2)

	Time	Raw ginger	Placebo	Effect size (SD)
ROM (°)	Pre	120 ± 2	122 ± 2	
	24-post	104 ± 3*	110 ± 2*	
	48-post	105 ± 3*	112 ± 2*	
	72-post	107 ± 3*	113 ± 2*	
Arm volume (mL)	Pre	2398 ± 126	2166 ± 111	
	24-post	2430 ± 127*	2192 ± 112*	
	48-post	2436 ± 127*	2207 ± 114*	
	72-post	2438 ± 126*	2207 ± 115*	
Isometric force (lbs)	Pre	16.8 ± 1.2	16.4 ± 1.5	
	24-post	11.5 ± 1.1*	11.5 ± 1.1*	
	48-post	12.3 ± 1.1*	12.0 ± 1.0*	
	72-post	13.3 ± 1.3*	12.5 ± 1.1*	
ΔROM (%)	24-post	−12.9 ± 2.2	−11.5 ± 1.4	−0.22
	48-post	−12.0 ± 2.3	−10.3 ± 1.3	−0.30
	72-post	−10.7 ± 2.5	−9.3 ± 1.3	−0.23
ΔVolume (%)	24-post	1.4 ± 0.3	1.2 ± 0.4	0.09
	48-post	1.6 ± 0.5	1.9 ± 0.3	−0.19
	72-post	1.8 ± 0.6	1.8 ± 0.4	−0.03
ΔForce (%)	24-post	−32.7 ± 3.8	−29.8 ± 3.1	−0.21
	48-post	−27.9 ± 4.1	−24.0 ± 4.2	−0.21
	72-post	−21.5 ± 4.2	−22.3 ± 3.0	0.06
PGE_2(pg/mL)	Prel	59.1 ±6.1	59.9 ± 6.8	−0.03
	Pre 2	51.5 ±8.2	62.6 ± 9.9	−0.25
	48-post	51.9 ± 0.6	60.4 ± 6.4	−0.29

Abbreviations: ΔROM, mean change in range of motion from pre; ΔVolume, mean change in arm volume from pre; ΔForce, mean change in isometric force from pre; PGE_2, Plasma prosteglandin E_2.
NOTE. Values are Mean ± SE.
Effect Size: Glass's delta (SD's).
*Indicates a significant difference ($P < 0.05$) from pre.

(main effect for group; $P = .585$ for study 1, $P = .261$ for study 2).

Ratings of perceived exertion were 13.1 ± .6, 13.2 ± .6, 12.7. ± .7, and 11.0 ± .6 in the raw-ginger group pre, 24, 48, 72 hours postexercise, respectively. Mean values in the placebo group were 13.7 ± 1.0, 14.7 ± .6, 14.0. ± .7, and 12.6 ± .8 at pre, 24, 48, 72 hours postexercise, respectively. Despite the moderate sized differences (glass's delta = −.59 at 24 hours post, −.45 at 48 hours post, and −.46 at 72 hours post) they did not reach statistical significance ($P = .30$). In study 2 RPE values were 13.0 ± .7, 14.7 ± .5, 14.6. ± .5, and 13.5 ± .6 in the heated-ginger group pre, 24, 48, 72 hours postexercise, respectively. Mean values in the placebo group were 11.8 ± 1. 16.2 ± .6, 15.4 ± .5, and 13.4 ± .6 at pre, 24, 48, 72 hours postexercise, respectively. Despite the moderate-sized differences (glass's delta = −.57 at 24 hours post, −.35 at 48 hours post) the differences did not reach statistical significance ($P = .57$)

Discussion

This experiment was designed to determine whether 11 consecutive days of dietary supplementation with 2 grams of raw or heat-treated ginger would influence delayed onset muscle pain caused by eccentric exercise. The primary novel finding was that supplementation with both raw and heat-treated ginger attenuated muscle pain intensity 24 hours after eccentric exercise. Consumption of raw ginger resulted in a 25% reduction (9.3 VAS units) while heat-treated ginger resulted in a 23% reduction (8.6 VAS units) in muscle-pain intensity 24 hours postexercise. These findings are consistent with data from randomized controlled trials showing a reduction in knee or hip pain during movement in osteoarthritis patients after longer term (4 to 36 weeks) daily consumption of smaller doses (30 to 510 $mg \cdot day^{-1}$) of ginger extracts.[2,18,44] Considerable evidence supports the biological plausibility of ginger possessing hypoalgesic effects. Ginger and its constituents, specifically 6-gingerol and 6-shogaol, have been shown to inhibit COX 1 and 2 enzymes,[24,29,40] leukotriene synthesis,[23] and the release of proinflammatory cytokines[17,41] in vitro. These established biological actions suggest that ingested ginger could blunt the increase in mechanical hypersensitivity of muscle tissue via a reduction in direct activation of type III and type IV afferent nerve fibers by substances such as bradykinin and sensitization of afferent fibers by prostaglandins and cytokines such as IL-1 and IL-6. In addition to its potential to act at peripheral sites, ginger may also act centrally. Gingerols, shogaols and zingerone are known TRPV1 receptor agonists.[14,21] TRPV1 receptors are expressed in peripheral (dorsal root ganglion) and central neural tissue and are thought to play a role in nociception and pain processing.[9,27] A recent study demonstrated the role TRPV1 receptors play in mechanical hyperalgesia following eccentric exercise in rodents.[16] Activation of TRPV1 receptors by agonists such as capsaicin can initially be painful. However, large doses or longer-term administration has been shown to desensitize nociceptive afferents to mechanical and chemical stimuli[20] plausibly via the depletion of substance p.[38] Thus, it is possible ginger consumption decreased muscle-pain intensity in the present study in part by desensitizing peripheral and/or central TRPV1 receptors.[42]

Improvements in pain symptoms of at least one-half standard deviation are thought to have clinical or practical importance.[28] By this criterion, the finding of a .77 SD (raw ginger) and .57 SD (heated ginger) reduction of muscle pain compared to placebo can be described as having practical importance. Another potential indicator of the usefulness of a treatment is how it compares to other therapies. Although not directly tested, data from the present study imply that ginger consumption is potentially more efficacious as a therapy for exercise-induced muscle pain than nonsteroidal anti-inflammatory drugs (NSAIDS). The efficacy of NSAIDS, such as aspirin, ibuprofen, naproxen, and diclofenac, as a therapy for muscle pain associated with eccentric exercise has been inconsistent.[13] Only a few experiments have demonstrated a hypoalgesic effect on muscle pain of .50 SD or greater, and those with the best results have involved chronic NSAID administration over several days.[13] Many previous studies examining the efficacy of

NSAIDS and other therapeutic interventions on muscle pain following eccentric exercise have used severe exercise protocols designed to produce high levels of pain (>50 on a 0 to 100 VAS scale). This amount of pain may be too intense to be effectively treated with the typical over-the-counter dose of medications given in the studies. The magnitude of the hypoalgesic effect found in the present studies was roughly similar to that of Maridakis et al,[26] who demonstrated a large (Cohen's d = −.88) reduction in muscle pain following eccentric exercise when a 5 mg/kg dose of caffeine was administered. As in the present study, a more moderate amount of pain was induced in the study by Maridakiset al.[26] Low-to-moderate pain intensity may better approximate the level of pain experienced in daily life by individuals during activities of daily living, sports, and other recreational activities. Future studies should consider examining the effects of NSAIDS on low-to-moderate pain intensity following eccentric exercise to determine if this improves their efficacy.

Inflammation and muscle dysfunction often accompany muscle pain following eccentric exercise and are often used as markers of muscle injury.[11,43] Our findings of increased arm volume, and decreases in elbow ROM and isometric strength, clearly indicate that the exercise protocol resulted in muscle damage, as expected. Neither raw nor heated-ginger supplementation resulted in large (effect sizes >.80 SD) differences in arm swelling, plasma PGE_2 concentrations, ROM impairment, or reductions in isometric-force production compared to placebo in the 72 hours following eccentric exercise. However, in humans, little change has been observed in plasma levels of PGE_2 48 hours after eccentric exercise,[19] and treatment of muscle injury with NSAIDS has not been shown to result in improvements in ROM,[33] large improvements in isometric strength,[13] or attenuation of muscle swelling assessed by MRI.[3] Thus, our findings that raw and heat-treated ginger supplementation resulted in only small-to-moderate differences from placebo in arm swelling, plasma PGE_2, ROM impairment, or force loss was not surprising.

Perceptions of exercise intensity paralleled the pain-intensity results in both studies. This was not surprising because pain and effort perceptions during exercise are known to covary at moderate-to-high exercise intensities. Caution should be taken in comparing the pain and effort effect sizes because different scales were used to obtain the data. The categories in the 6 to 20 scale used for perceived exertion often promote reduced variation compared to the visual analog scale used to obtain the pain ratings because people tend to use whole numbers and they were instructed to use not less than one-half a number in making a rating (eg, 13.5 was acceptable but 13.25 was not). The question of whether ginger has larger effects on pain or effort will be best addressed by future studies that use the same scale to assess effort and pain perceptions.

A novel and interesting finding was that heat treating ginger did not produce greater hypoalgesic effects as had been previously hypothesized.[37] Heat treatment of ginger has been shown to increase the concentration of shogaols, while decreasing the gingerol concentration.[22] Shogaols activate TRPV1 receptors more strongly than gingeols;[21] thus, increasing their concentration could potentially lead to greater pain-relieving effects. In the present study, 6-shogaol content increased by 18% from 2.2 mg/g of ginger to 2.6 mg/g following heat treatment, but differences in muscle-pain intensity between the ginger and placebo groups were similar for raw and heat-treated ginger. These data suggest that a larger increase in shogaols content is needed to enhance the analgesic effect of ginger in our model of pain.

The findings of the present investigation are strengthened by having avoided several common limitations of prior studies examining the efficacy of supplements as potential treatments for pain. First, rather than only requesting that the ginger capsules be taken each day, the participants in this investigation were observed ingesting the capsules. Because of this approach, we have full confidence that both ginger and placebo capsules were ingested as prescribed in both studies. Second, most of the dependent variables (pain intensity, ROM, arm volume, MVIC, and RPE) were measured 3 times at each trial so as to determine the reliability of their assessment. The high observed reliability of these measures strongly discounts the possibility that the results of the present study were biased by a lack of reliability of the measures. Third, the participants indicated each day whether they had consumed ginger or placebo on the previous day and how certain they were of this indication. These data help to rule out the possibility that the results might be explained by ineffective blinding or experimental artifact (ie, demand characteristics, or participants recognizing they were ingesting ginger, recognizing the purpose of the experiment, and giving low pain ratings to help the investigators "find what they were looking for"). For these reasons, and the use of a randomized, placebo-controlled experimental design in which muscle injury and arm-muscle pain were induced in a laboratory, results of the experiment summarized here provide strong evidence that the lower pain ratings in each study were the result of ginger consumption.

In summary, the present investigation demonstrated that 11 consecutive days of dietary supplementation with 2 grams of raw and heat-treated ginger reduces muscle pain caused by eccentric exercise, and raw ginger is as effective as heat-treated ginger in achieving this effect.

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