Investigation of the potential analgesic, antiarthritic and cytokine modulating effects of ethanolic ginger extract in adjuvant arthritic rats

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Abstract

Background and aim of the study: Herbal medicine may form an alternative approach in treatment of polyarthritis. Previous studies reported antioxidant activities for ginger. The present study aimed at assessing the potential analgesic, anti-inflammatory, immunomodulatory activities of ethanolic ginger extract in adjuvant arthritis rats.

Methods: Ginger extract in doses of 100,200 and 400 mg/kg/d was given in two protocols (prophylactic and therapeutic) to a rat model of adjuvant-induced arthritis which was induced by the administration of Freund's adjuvant and squalene. Arthritis index, changes in ankle joints diameter and pain threshold to pressure on hind paws, were measured daily from day 0 until day 30 after adjuvant inoculation. At the end of the study, the animals have been sacrificed and blood samples have been taken for assay for TNF-alpha and IL-10 in serum.

Results: Ethanolic ginger extract in different doses significantly reduced inflammation and pain in adjuvant-induced arthritis of rats as evidenced by decreased change of ankle diameter and increased threshold of pain after mechanical pressure of both inoculated and non-inoculated hind paws of arthritic rats. Ginger extract increased significantly serum levels of the anti-inflammatory cytokine IL-10 in arthritic rats with insignificant decrease of the proinflammatory cytokine TNF-alpha.

Conclusion: Systemic use of ethanolic ginger extract significantly ameliorated inflammation and pain in adjuvant-induced arthritis of rats that may be explained by potentiating the anti-inflammatory effect of IL-10.

Keywords: Adjuvant, Analgesic, Ginger, IL-10

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Introduction

Herbal remedies Ancient Chinese and Egyptian papyrus writings describe medicinal uses for plants as early as 3,000 BC. Herbal medicine may form an alternative approach in treatment of polyarthritis patients and minimize the unwanted effects associated with the current therapies with allopathic drugs.

Ginger (Zingiber officinale Roscoe, Zingiberaceae) is one of the most commonly consumed dietary condiments that contains a number of active constituents. The active constituents of ginger are not certainly known. Gingerols and shogaols are the main potentially active constituents of the lipophilic rhizome extracts (1). Ginger is used since thousands of years for relieve of some clinical conditions e.g. nausea, headache, colds and rheumatic disorders (2). It has anti-oxidative and neuroprotective activities (3-5).

Little data in literature is available concerning the potential anti- arthritic effects of ginger or its components. Lantz et al. reported that gingerols and shogaols of ginger exhibited significant anti-inflammatory activity (6). Also, Phan et al. reported that ginger extract suppresses inflammation of rheumatoid arthritis and inhibits cytokine expression in human synoviocytes (7).

Experimental rheumatoid arthritis (RA) model, adjuvant-induced arthritis (AIA), has been used extensively to test new drugs for inflammatory arthritis and in studying the roles of

autoimmunity and inflammation in the pathogenesis of joint disease. Furthermore, this model has been used (8). The present study aimed at assessing the potential anti-inflammatory, immunomodulatory and analgesic activities of ginger extract. It studied the effect of ginger extract pretreatment on diameter of inflamed ankle joints, pain threshold and serum levels of tumor necrosis factor –alpha(TNF-alpha) and interleukin- 10 (IL-10) in adjuvant arthritis rats.

Materials and Methods

Materials

Complete Freund's adjuvant (CFA) was purchased from Difco laboratories, Detroit, Michigan, USA. Squalene will be purchased from MP Biomedicals, Inc. dimethyl sulphoxide (DMSO) was used to dissolve ethanolic ginger extract. Ginger was obtained from the market.

Preparation of ethanolic extract of ginger

Smaller pieces of the Zingiber officinale rhizomes were dried under shade for 10-day duration and then pulverized by using a manual blenderto form a coarse powder. According to the method described by Giriraju and Yunus, 500grams of ginger were minced into fine pieces and then suspended in 1000 ml of 70% ethanol. The suspended minced ginger wascontinuously shacked for 48 hoursat constant intervals of time and then, by a sterile muslin cloth, undergone filtration so a residue of ginger and a filtrate will be obtained. To obtain the ethanolic extract, the filtrate was placed over steam bath apparatus for 5 days so thatenhancing evaporation of ethanol content from the filtrate. The dried extractwas obtained after 5 days and then, by using a mortar and pestle, was pulverized into fine powder (9). Ten grams of ethanolic ginger extract powder werethen being dissolved in 100 ml of DMSO to obtain 10% ethanolic ginger extract stock solution.

Animals

The experimental study was carried out using adult female albino rats of the Sprague-Dawely strain weighing between 160-200 grams. The animals will be acclimatized in a light- and

temperature- controlled room (23±1°C) with a 12-12 hrs. dark-light cycle. The rats were fed with commercial pelleted rat feed and water was given *ad libitum*. Food was placed on the floor of the cage to facilitate access, as the pain which accompanies adjuvant-induced arthritis renders the rats immobile and unable to use their hind limbs to obtain food from the cover mesh of the cage. The experimental protocol was approved by the local ethical committee.

Experimental Induction of arthritis

Rat model of adjuvant-induced arthritis (AIA), was induced by the administration of Freund's adjuvant, and has been used extensively in studying the roles of autoimmunity and inflammation in the pathogenesis of joint disease. It exhibits several pathological changes similar to those occurring in RA (8).

Each animal in all groups was injected with 0.1ml squalene and 0.1 ml CFA except animals of control non-adjuvant group. The day of inoculation was regarded as day 0 while day 16 was the day in which edema in the contralateral, non-injected, hind paw will be observed.

Arthritis index, changes in ankle joints diameter and pain threshold to pressure on hind paws, were measured daily from day 0 until day 30 after adjuvant inoculation. At the end of the study, the animals have been sacrificed and the blood was collected. Blood samples have been immediately centrifuged at 3000 rpm for 10 minutes and serum samples were stored at -80°C until assayed for TNF-alpha and IL-10.

Investigation of the effect of ginger extract on adjuvant arthritis in rats

Two groups (I&II) of 6 animals were served as control non-adjuvant and adjuvant non-treated arthritic rats respectively and received saline intraperitoneally (i.p.) daily. Other animals were randomly allocated into two treatment protocols (prophylactic or therapeutic). Each treatment protocol contained 6 groups of 6 animals each. Drug treatment have been started on day 5 till day 14 in prophylactic protocol and on day 16 till day 25 in therapeutic protocol. Animals of group III were given i.p. diluted 1% DMSO. Groups IV, V and VI in each protocol received i.p. ginger extract in doses of 100,200 and 400 mg/kg/d respectively.

Experimental measures

For each rat in the previously described experimental groups, the following evaluation parameters have been daily measured till day 30 after disease induction:

Arthritis Index

Rats were evaluated daily for arthritis. The physical signs of arthritis were judged by the following grading system (10) for each paw: 0= normal paw;1= erythema of toes; 2 = erythema and swelling of paw ; 3 = swelling of ankle joint ;4 = complete swelling of the whole leg and inability to bend it. The maximum achievable score is thus 8 (as swelling appeared only in both hind paws). Arthritis index for each rat was calculated by adding the scores of both hind paws. A sensitized animal was considered to have arthritis when at least one non-injected paw was inflamed (11).

Measurement of ankle diameter

Changes in the ankle diameter of both ipsilateral (injected) and contralateral (non-injected) hind paws, from the height on day 0, have been daily assessed using a Vernier scale (12).

Assessment of pain threshold by analgesimeter

A crescent pressure (in grams) using a Ugobasile analgesimeter (UgoBasile Biological Research Apparatus, Italy), has beenapplied separately to the posterior paws until the animal displayed a reaction that consisted of withdrawing the paw and/or vocalizing (13). The slide of the device moved at the speed of 16mm per second. The force on the paw was at rate of 16 grams per second, so a distance of 11.5 mm means 115 grams. The pain threshold to pressure (gm.) on hind paws of rats have been measured. The percentage of change of pressure (gm.) on hind paws on day 30 for each anima, was calculated by using the following formula:

$$\frac{\text{(Pressure on day 30 – pressure before adjuvant injection on day 0) X 100}}{\text{Pressure before adjuvant injection on day 0}}$$

Measurement of TNF-alpha and IL-10

Animals have been sacrificed on day 30 after disease induction and samples of blood have beentaken to separate sera from control ,adjuvant non-treated and ginger extract-treated arthritic rats .Serum levels of TNF- alpha and IL-10 have beendetermined using enzyme-linked immunosorbent assay (ELISA) kits from (Bender Medsystems,Vienna, Austria). Antibodies specific for rat TNF- alpha and IL-10 have been coated onto the wells of the microtiter strips and the samples including standards of known rat TNF-alpha and IL-10 have beenpipetted into the wells, incubated and washed. Intensity of the color has been determined at (450) nm with a correction wave length of (630) nm.

Statistical Analysis

The results have been presented as the mean ±standard error. Arthritis scores, body weight, temperature, changes of ankle joints diameters, hind paws volumes, percentage of change of pressure (gm.) on hind paws and serum levels of cytokines, that have been measured in different treatment groups, were compared with control groups by one way analysis of variance (ANOVA) and Student's t-tests for significance (by use of SPSS version 22).

Results

Effect of ginger extract on arthritis index of adjuvant arthritic rats

After induction of arthritis in the positive control non-treated group (group II), the injected hind paw (right one) showed, on day 1, obvious swelling of the ankle and small joints of the foot with marked redness of the inflamed joints while the left non-injected hind paw showed swelling and redness on day 16 after adjuvant inoculation. On day 1 after adjuvant inoculation, arthritis index was 2.5±0.22. Arthritis index peaked on day 18 (6.17±0.17) and slightly decreased on the subsequent days until the end of experiments on day 30 (5.67±0.21). Prophylactic administration of ethanolic ginger extract significantly decreased the arthritic scores in a dose-dependent manner. The maximum effect of ginger was recorded in day 30. The arthritic scores of animals treated with 400, 200, and 100 mg/kg/d on day 30 were

0.17±0.02, 0.6±0.01 and 0.83±0.17 respectively compared to 1.33±0.2 of DMSO-treated arthritic rats.

Effect of ginger extract on ankle diameter of adjuvant arthritic rats

On day 3 after induction of adjuvant arthritis, increase in diameter of ankle joint of the injected right hind paw with redness wereobserved in control non-treated arthritic rats. There was a significant increase in the change of diameter of right ankle joint on the fifth day followed bya slight decrease on the following days till day 16. There was a second peak for ankle diameter change on the 20th day (0.43±0.01 mm) then there was insignificant further change until 30th day after adjuvant inoculation. Regarding the ankle joint of the contralateral non-injected left hind paw, the swelling was observed on the 15th day. There was a significant increase ($P<0.05$) inthe change of left ankle diameter on the 20th day (0.54±0.01 mm) followed by a decrease on the subsequent days.

Intraperitoneal administration of ginger ethanolic extract either prophylactically or therapeutically (groups IV, V and VI) inhibited significantly ($P<0.05$) the observed increase of right ankle diameter in adjuvant arthritic rats (positive control group). Ginger extract in 400 mg exhibited the maximum effect (0.08±0.001 and 0.1±0.01mm respectively). There was also a lesser significant decrease ($P<0.05$) inDMSO-treated arthritic rats (0.23±0.04 and 0.22±0.03mm). Prophylactic administration of ginger ethanolic extract in 100, 200 and 400 mg, prevented completely the increase of left ankle joints diameters observed in arthritic positive control arthritic rats. Therapeutic administration of gingerin the aforementioned doses, and its vehicle DMSO, inhibitedsignificantly (($P<0.05$), but fail to completely abolish the increase of left ankle joint diameter (see tables 1&2).

Effect of pretreatment of adjuvant arthritic rats with ethanolic ginger extract on pain threshold

Following administration of complete Freund's adjuvant with squalene to the subplantar surface of hind paws of rats, hyperalgesia manifested by lowering of the pain threshold to pressure (gm.) on hind paws, was observed. There was a reduction of pain threshold until the30thday after adjuvant inoculation. The percentage of reduction of pressure(in grams) on

both right and left hind paws were 52.8 ±0.2 and 59.8±0.3 respectively compared with pressure before adjuvant injection.

Administration of ginger extract by both protocols (i.e. prophylactic andtherapeutic), significantly (P<0.05)decreased the percentage of reduction of pressure on both hind paws (i.e. increased the pain threshold to pressure). On the 30th day after adjuvant inoculation, the percentages of decrease of pressure on right hind paws in arthritic rats treated with 100,200 and 400mg ginger extract were 3.3±0.1, 4.3±0.1 and 5.9±0.1in prophylactic protocol and 3.9±0.02, 6.9±0.1 and 7.8±0.01 in therapeutic protocol respectively (see table 3).Therapeutic and prophylactic ginger extract treatmentsin the aforementioned doses were effective in ameliorating hyperalgesia of left hind paw. Percentages of decrease of pressure were4.9±0.01, 5.8±0.04, 8.1±0.02. Diluted DMSO pretreatment also reduced hyperalgesia of right and left hind paws of arthritic rats compared with adjuvant arthritic group (see tables 3&4).

Effect of ginger ethanolic extract on serum levels of TNF-alpha and IL-10 in adjuvant arthritic rats

On the 30th day after adjuvant inoculation, serum TNF-alpha levels were insignificantly higher(P>0.05)in adjuvant arthritic positive control rats (30.02±1.2picograms) compared with negative control saline-treated non arthritic animals (29.8 ±2.3 picograms). With regard to serum IL-10 level, it was significantly lower (P<0.05) in arthritic positive control rats (170.7±33picograms) compared with 335.7±63.2 in negative control rats.

As shown in table (5), Administration of ethanolic ginger extract either prophylactically or therapeutically in dose of 400 mg/kg produced insignificant change(P>0.05) in TNF-alpha serum levels compared with either non arthritic or arthritic non-treated groups. TNF-alpha levels were29.8 ±2.3, 30.2±1.2, 28.6±2.8 and 29.04±1.2picogramsin groups I, II and VI respectively. Regarding serum levels of IL-10, it was significantly higher (P<0.05) in rats given either prophylactic ethanolic ginger extract in dose of 400mg/kg (475.9±247.4)or therapeutically (428±128.6) compared with IL-10 level in adjuvant arthritic rats (group II).

Table (1): Effect of prophylactic ginger ethanolic extract on the change of left ankle diameter (mm) of adjuvant arthritic rats

Drug treatment	change of left ankle diameter (mm)			
	Day 5	Day 9	Day 14	Day 30
Saline-treated rats (negative control =group I)	0	0	0	0
Adjuvant arthritic rats (positive control = group II)	0	0.05±0.001	0.08±0.01	0.35±0..01
DMSO-treatedarthritic rats (group III)	0	0	0*	0*
Ethanolic ginger extract-treated (100 mg/kg/d) arthritic rats (group IV)	0	0	0*	0*
Ethanolic ginger extract -treated (200 mg/kg/d) arthritic rats (group V)	0	0	0*	0*
Ethanolic ginger extract -treated (400 mg/kg/d) arthritic rats (group VI)	0	0	0*	0*

Values represent the mean±SE.* p<0.05 vs. groups II, ANOVA.

Table (2): Effect of therapeuticginger ethanolic extract on the change of left ankle diameter (mm) of adjuvant arthritic rats

Drug treatment	change of left ankle diameter (mm)			
	Day 15	Day 20	Day 25	Day 30
Saline-treated rats (negative control =group I)	0	0	0	0
Adjuvant arthritic rats (positive control = group II)	0.28±0.01	0.54±0.01	0.45±0.02	0.42±0.01
DMSO-treatedarthritic rats (group III)	0.15±0.01	0.13±0.01	0.11±0.01*	0.09±0.01*
Ethanolic ginger extract-treated (100 mg/kg/d) arthritic rats (group IV)	0.14±0.01	0.09±0.01	0.05±0.001*	0.02±0.001*
Ethanolic ginger extract -treated (200 mg/kg/d) arthritic rats (group V)	0.15±0.02	0.12±0.01	0.11±0.03*	0.08±0.002*
Ethanolic ginger extract -treated (400 mg/kg/d) arthritic rats (group VI)	0.14±0.01	0.13±0.01	0.12±0.01*	0.06±0.001*

Values represent the mean±SE.* p<0.05 vs. groups II, ANOVA.

Table (3): Effect of prophylactic administration of ginger ethanolic extract on the change of left hind paw volume (ml) of adjuvant arthritic rats

Drug treatment	% of change to pressure (gm) on the right hind paw			
	Day 5	Day 9	Day 14	Day 30
Saline-treated rats (negative control =group I)	4.7±0.01	0	3.4±0.1	2.2±0.1
Adjuvant arthritic rats (positive control = group II)	38.4±0.2	32.8±0.3	25.7±0.4	53.9±0.3
DMSO-treatedarthritic rats (group III)	42.3±0.1	28.7±0.1	18.5±0.1	7.3±0.1*
Ethanolic ginger extract-treated (100 mg/kg/d) arthritic rats (group IV)	37.6±0.1	12.4±0.1	11.8±0.1* º	3.3±0.1* º
Ethanolic ginger extract -treated (200 mg/kg/d) arthritic rats (group V)	36.5±0.3	21.3±0.1	13.2±0.2* º	4.3±0.1* º
Ethanolic ginger extract -treated (400 mg/kg/d) arthritic rats (group VI)	40.4±0.1	27.3±0.2	16.2±0.1*	5.9±0.1*

Values represent the mean±SE.* p<0.05 vs. groups II, º p<0.05 vs. groups III, ANOVA.

Table (4): Effect of prophylactic administration of ginger ethanolic extract on the % of change to pressure (gm.) on the left hind paw of adjuvant arthritic rats

Drug treatment	% of change to pressure (gm) on the right hind paw			
	Day 15	Day 20	Day 25	Day 30
Saline-treated rats (negative control =group I)	3.4±0.1	4.4±0.1	7.9±0.1	2.2±0.1
Adjuvant arthritic rats (positive control = group II)	28.9±0.4	43.8±0.2	45.8±0.2	53.9±0.3
DMSO-treatedarthritic rats (group III)	7.9±0.1	3.9±0.1	18.2±0.1	12.1±0.1*
Ethanolic ginger extract-treated (100 mg/kg/d) arthritic rats (group IV)	23±0.1	13.5±0.2	10.9±0.1* º	3.9±0.02* º
Ethanolic ginger extract -treated (200 mg/kg/d) arthritic rats (group V)	18.8±0.1	14.9±0.1	13.1±0.1* º	6.9±0.1* º
Ethanolic ginger extract -treated (400 mg/kg/d) arthritic rats (group VI)	20.2±0.1	15.8±0.1	13.9±0.1* º	7.8±0.01* º

Values represent the mean±SE.* p<0.05 vs. groups II, º p<0.05 vs. groups III, ANOVA.

Table (5): Effect of ethanolic ginger extract on serum levels of TNF-α and IL-10 of adjuvant arthritic rats

Drug treatment	Serum levels (picograms)	
	TNF- α	IL-10
Negative control (Non-arthritic)	29.8±2.3	335.7±63.2
Positive control (Adjuvant arthritic)	30.02±1.2	170.7±33†
Prophylactic DMSO-treated arthritic	27.5±1.5	382±97.04
Therapeutic DMSO -treated arthritic	30.1±1.8	453.2±149.1*
ProphylacticEthanolic ginger extract -treated (400 mg/kg/d) arthritic rats	28.6±2.8	475.9±247.4*
TherapeuticEthanolic ginger extract -treated (400 mg/kg/d) arthritic rats	29.04±1.2	428±128.6*

Values represent the mean±SE. * P <0.05 vs. positive control, † P <0.05 vs. negative control, ANOVA.

Discussion

Currently, Ginger is a focus for many research studies and staring to become a potential therapeutic approach for many clinical disorders like diabetes atherosclerosis, hypertension, cancer and gastrointestinal disorders as constipation, vomiting and peptic ulcer. It is reported in literature that it possesses anti-inflammatory (14) neuroprotective and anti-oxidative activities (3-5).

The present work observed that ethanolic ginger extract in all doses used showed a dramatic inhibitory effect on joint inflammation induced by complete Freund's adjuvant and squalene as manifested by the significant inhibition of ankle joint diameter in both inoculated hind paw (right one) and the contralateral non-inoculated paw (the left one). These results are in line with the study of Sharma et al. who mentioned that oral ginger oil caused a significant amelioration of severe chronic adjuvant arthritis (15). A study by Funk et al. also showed

that ginger extract inhibited streptococcal cell wall-induced arthritis animal model of rheumatoid arthritis (16).

Previous studies are conflicting with regard to the potential antiarthritic effect of ginger. Reginster et al. have been suggested that ginger is effective against osteoarthritis and rheumatism (17). On the contrary Marcus and Suarez-Almazor reported debate in its effectiveness and safety as an antiarthritic (18). Our results in this study agree with the observation of a previous study by Bliddal et al. on human patients with osteoarthritis of the hip or knee showed that ginger has the same effects as placebo (19). Contrarily, a study by Altman and Marcussen 2001 reported that ginger extract exhibited a good response in patients with osteoarthritis of the knee (20).

The present work demonstrated that DMSO, in which ginger was dissolved, reduced also joint inflammation however; ginger's effect was significantly higher. This is in line with the observation of Santos and Tipping, 1994 that DMSO inhibited all indices of arthritis in a dose-dependent fashion providing an evidence for ROS scavenging as the mechanism of attenuation of injury in adjuvant arthritis of rats (21). Colucci et al. reported that oral administration of DMSO produced anti-inflammatory effects on zymosan-induced edema in the mouse paw, whereas local administration potentiated the inflammatory action exerted by zymosan (22). Also, Simons et al. showed that topical diclofenac in DMSO vehicle was an effective treatment option for knee osteoarthritis with efficacy similar to, but tolerability better than oral diclofenac (23).

On the other hand, the present study revealed an anti-nociceptive effect for ethanolic ginger extract as evidenced by increasing the pain threshold to mechanical pressure on both the inoculated and non-inoculated hind paws of arthritic rats. Previously, Srivastava and Mustafa reported that powdered ginger as a dietary supplement for 3 months to 2 years relieved pain and swelling in patients of rheumatoid arthritis, osteoarthritis (24). Other studies as Ozgoli et al. reported an analgesic effect of ginger in other modalities of pain e.g. painof primary dysmenorrhea(25). On the contrary a study by Black and Oconnor showed that ginger consumption before cycling exercise had no effect on muscle pain.The present work also demonstrated that DMSO treatment, prophylactic or therapeutic, alleviated hyperalgesia of arthritic rats to mechanical pressure on hind paws (26). This observation is consistent with the study of Colucci et al. who reported that orally administered DMSO displayed anti-

nociceptive effects but to thermal (hot plate and tail-flick test) and chemical (formalin test) stimuli (22).

Ginger administration to arthritis rats prophylactically or therapeutically did not significantly change the serum level of the proinflammatory cytokine, TNF-α. On the other hand, our study demonstrated that ginger increased significantly serum levels of IL-10, the anti-inflammatory. This observation is in agreement with other previous studies. Hisadome et al. reported that a novel antirheumatic drug, Y-39041, has an anti-arthritic effect through not only TNF- α and interlukin-6 suppression but also interleukin-10 augmentation (27). A very recent studyobserved that ginger extract reduced TNF-alpha and increased IL-10 but in acetic-acid induced ulcerative colitis model (28). A study by Sepideet al. reported thatginger supplementation significantly lowered TNF- α in type 2 diabetic patients (29).

Conclusion

In conclusion, our results presented in this study revealed that systemic use of ethanolic ginger extract significantly ameliorated inflammation and pain in adjuvant-induced arthritis of rats that may be explained by potentiating the anti-inflammatory effect of IL-10.

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